Universidade de Aveiro Escola Superior de Saúde

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Sons respiratórios adventícios em crianças com infeção respiratória

Adventitious respiratory sounds in children with respiratory infection

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia, realizada sob a orientação científica da Doutora Alda Marques, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro.

O júri

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Palavras-chave Sons respiratórios adventícios, pediatria, saudáveis, IRTI

Sumário

Enquadramento: As infeções respiratórias do tracto inferior (IRTI) são a principal causa de visitas/admissões hospitalares em crianças com idade inferior a 5 anos. Desta forma, verifica-se uma urgente necessidade de desenvolver medidas de avaliação respiratória pediátricas que sejam objetivas, fiáveis e de rápida aplicação. Os sons respiratórios adventícios (SRA) computorizados têm-se revelado objetivos e fiáveis na avaliação/monitorização de doenças respiratórias; contudo a sua aplicação em pediatria é desconhecida.

Objetivos: Caracterizar/comparar os SRA em crianças saudáveis e com IRTI.

Métodos: Um estudo transversal descritivo-comparativo foi realizado em três instituições de saúde. As crianças foram diagnosticadas pelo pediatra como saudáveis ou com IRTI e agrupadas de acordo com a sua idade (i.e., 0-2 anos ou 3-5 anos). Dados antropométricos, sócio-demográficos, cardio-respiratório e tipo/severidade da IRTI foram recolhidos. Os sons respiratórios foram foram recolhidos no tórax com um estetoscópio digital, de acordo com as orientações internacionais. A localização, número médio, tipo, frequência e taxa de ocupação das sibilâncias e a localização número médio, tipo, frequência, initial deflection width, two cycle duration, e largest deflection width dos fervores foram analizados por fase respiratória.

Resultados: Quarenta crianças participaram neste estudo: 22 com idades entre is 0-2 anos (G1: 11 saudáveis; G2: 11 com IRTI) e 18 com idades entre os 3-5 anos (G3: 9 saudáveis; G4: 9 com IRTI). Poucas crianças de ambos os grupos apresentaram sibilâncias. Para ambas as faixas etárias as crianças com IRTI apresentaram uma maior percentagem da expiração ocupada por sibilâncias (G1: M 2.15 IQR 1.45 vs. G2: M 4.73 IQR 6.72 p=0.001; G3: M 2.80 IQR 3.27 vs. G4: M 5.17 IQR 15.99 p=0.07). Todas as crianças apresentaram fervores em pelo menos um local de auscultação. Em ambas as faixas etárias, aqueles com IRTI apresentaram mais fervores inspiratórios (G1: M 0.25 IQR 0.31 vs. G2: M 0.52 IQR 0.70; p<0.001; G3: M 0.50 IQR 0.49 vs. G4: M 0.70 IQR 0.21 p=0.03), especialmente fervores crepitantes , (G1: M 0.07 IQR 0.13 vs. G2: M 0.18 IQR 0.42 p=0.001; G3: M 0.11 IQR 0.21 vs. G4: M 0.17 IQR 0.23 p=0.001). Os fervores expiratórios subcrepitantes foram os mais comuns entre todas as crianças (G1: M 0.33 IQR 0.56; G2: M 0.33 IQR 0.56; G3: M 0.56 IQR 0.99; G4: M 1.14 IQR 1.38).Não foram encontradas diferenças relativamente aos restantes parâmetros avaliados.

Conclusão: Crianças saudáveis e com IRTI de diferentes faixas etárias apresentam SRA (i.e., sibilâncias e fervores). A taxa de ocupação das sibilâncias e o número de fervores foram as características que apresentaram mais diferenças entre os participantes saudáveis e os participantes com IRTI. Desta forma, conclui-se que estas características dos SRA poderão constituir os melhores critérios de discriminação entre os grupos.

Keywords Adventitious respiratory sounds; Paediatrics; Healthy; LRTI

Abstract

Background: Lower respiratory tract infections (LRTI) are the leading cause of hospital visits in children under 5 years old. Therefore, there is an urgent and unmet need to develop objective, reliable and quick measures for respiratory paediatric assessment. Computerised adventitious respiratory sounds (ARS) have shown to be objective and reliable to assess/monitor respiratory diseases; however its application in children with LRTI is unknown.

Aim: To characterise/compare ARS in healthy children and children with LRTI.

Methods: A cross-sectional descriptive-comparative study was conducted in three healthcare institutions. Children were diagnosed by the paediatrician as healthy or with a LRTI and grouped according to their age (i.e, 0-2 years old or 3-5 years old). Socio-demographic and anthropometric data, type and severity of LRTI and cardio-respiratory parameters were collected. Respiratory sounds were recorded from the chest with a digital stethoscope following the Computerised Respiratory Sound Analysis guidelines. Wheezes' location, mean number, type, frequency and occupation rate and crackles' location, mean number, type, frequency, initial deflection width, two cycle duration, and largest deflection width were analysed per breathing phase.

Results: Forty children enrolled in this study: 22 aged 0-2 years old (G1: 11 healthy; G2: 11 with LRTI) and 18 aged 3-5 years old (G3: 9 healthy; G4: 9 with LRTI). Few children, both healthy and with LRTI presented wheezes. In both age ranges, children with LRTI presented a higher percentage of the expiratory phase occupied by wheezes (G1: M 2.15 IQR 1.45 vs. G2: M 4.73 IQR 6.72 p=0.001; G3: M 2.80 IQR 3.27 vs. G4: M 5.17 IQR 15.99 p=0.07). Crackles were found in all children in at least one chest location. In both age ranges, children with LRTI presented more inspiratory crackles (G1: M 0.25 IQR 0.31 vs. G2: M 0.52 IQR 0.70; p<0.001; G3: M 0.50 IQR 0.49 vs. G4: M 0.70 IQR 0.21 p=0.03), especially fine crackles than healthy children (G1: M 0.07 IQR 0.13 vs. G2: M 0.18 IQR 0.42 p=0.001; G3: M 0.11 IQR 0.21 vs. G4: M 0.17 IQR 0.23 p=0.001). Coarse expiratory crackles were the most common type of crackle found in both healthy children (G1: M 0.33 IQR 0.56; G3: M 0.56 IQR 0.99) and children with LRTI (G2: M 0.33 IQR 0.56; G4: M 1.14 IQR 1.38). No differences were found for the remaining parameters.

Conclusion: Healthy children and children with LRTI of different ages present ARS (i.e., crackles and wheezes). The occupation rate of wheezes and the mean number of crackles were the parameters that most differed between healthy children and children with LRTI in both age ranges. Therefore these ARS' parameters may be the best criteria to discriminate the groups.

Abbreviations and/or acronyms

ARS – adventitious respiratory sounds

BMI – body mass index

CORSA – computerised respiratory sound analysis

F – frequency

IDW – initial deflection width

LDW – largest deflection width

LRTI – lower respiratory tract infection

RSAT – Respiratory Sound Annotation Software

SpO_2 – peripheral oxygen saturation

Wh%: – wheeze occupation rate

WHO– World Health Organization

2CD – two cycle duration

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1. INTRODUCTION

Lower respiratory tract infections (LRTI) are the worldwide leading cause of hospital visits, hospitalizations, morbidity and death in children under the age of 5 years old (1, 2). In Portugal, 300 children died and 3005 were hospitalised in 2012, a number that suffered a tremendous increase since 2003 (n=85) (3). It has also been suggested that the incidence of LRTI in children may potentiate the development of chronic respiratory diseases in adulthood (4).

Lower respiratory tract infection covers a wide range of diseases from mild mucosal colonisation/infection (bronchiolitis) to an overwhelming parenchymal infection, such as community acquired pneumonia (5). Essentially, LRTI is characterised by an inflammation of the airways/pulmonary tissue, due to a viral or bacterial infection, from the trachea to the lung parenchyma (6). As a result, patients experience cough as the main symptom, and at least one other lower respiratory tract symptom, such as sputum production, respiratory discomfort/dyspnoea, wheeze or chest discomfort/pain (5, 7). Currently, chest X-ray is the gold standard for detecting and monitoring respiratory infections (8). However, this method presents several limitations, as it is not always available in all clinical settings, non-portable, expensive, presents high levels of inter-observer subjectivity (9) and involves considerable doses of radiation. All these factors prevent the monitoring of patients with the required frequency.

Additionally to X-ray, health professionals also base their diagnosis on clinical rationale but, at this point in time, there is no clinical algorithm to accurately diagnose LRTI in children. The World Health Organization (WHO) developed a management algorithm for diagnosing paediatric pneumonia which relies on symptoms of respiratory discomfort/dyspnoea or cough, elevated respiratory rate (>50 cycles/min) and chest indrawing (7). Although this algorithm is extremely valuable for the diagnosis of pneumonia, it has only moderate sensitivity (from 49% for non-severe pneumonia to 95% for very severe pneumonia) (10), poor specificity (from 16% to 20% for children presenting wheeze) (11) and does not address other respiratory diseases of high prevalence in children, such as bronchiolitis (12).

A promising alternative for diagnosis and monitoring respiratory diseases in children is computerised respiratory auscultation. The sounds generated from the lungs have the potential to provide useful information as they relate directly to movement of air and changes within the lungs and secretions (13). Research of the acoustic properties of paediatric respiratory sounds has shown that the presence of a respiratory disease is often marked by changes in the frequency and intensity of respiratory sounds (14). This highlights the usefulness of adventitious respiratory sounds (ARS) to detect and inform the clinical course of respiratory diseases and treatments. However, standard

auscultation is too subjective to provide a useful outcome measure (15) and it has been progressively replaced by computerised respiratory sound analysis (CORSA), a simple, objective and non-invasive method to detect, characterise and place ARS within the respiratory cycle (16, 17). Through the use of CORSA, ARS have been found to be a more sensitive indicator, detecting and characterising the severity of the respiratory disease before any other measure (16).

Adventitious respiratory sounds, i.e., wheezes and crackles, are sounds superimposed to the normal respiratory sound. Wheezes have been the most used ARS in the diagnosis and monitoring of respiratory diseases in children (18), however it should be noticed that wheezes only occur when there is a flow limitation (but flow limitation is not necessarily accompanied by wheezes), that reaches a critical value, called flutter velocity (19, 20). Thus, when there is not enough flow to generate wheezing, wheezes parameters will not be useful despite the presence of a respiratory condition. Therefore, the information provided by crackles is also crucial to proper diagnose and monitor children's respiratory diseases. Crackles are related with the sudden opening or closing of airways due to a pathological process in pulmonary tissue/airways or presence of secretions (19, 21-23), and their parameters provide essential information about the function and structure of the tracheobronchial tree (24). Currently, it has also been recognised that ARS can be present in healthy subjects (25), but reference values of ARS in healthy children and in those with LRTI have not been established. In the absence of these reference values, health professionals do not know when changes in the respiratory sounds should be considered clinically relevant.

The lack of information on respiratory sounds and the limitations presented by the other respiratory measures (e.g., X-ray and WHO algorithm) may lead to imprecise diagnosis and affect paediatric treatment/monitoring, which will ultimately increase the length of hospitalisation and cause additional costs to health care systems. Therefore, this study aimed to characterise and compare ARS in healthy children and children with LRTI.

2. METHODS

2.1. Ethics

Ethical approval was previously obtained from the Ethics Committee of the Research Unit of Health Sciences at the School of Nursing in Coimbra, Portugal (P186-10/2013) and from the private hospital Cliria, SA (12/02/2014). Prior to any data collection, written informed consents were collected from children's legal representatives (26).

2.2. Design and Participants

A cross-sectional descriptive-comparative study was conducted in the north and central regions of Portugal (27). Two hospitals and 17 clinical practices were contacted, from which two hospitals and one clinical practice accepted to participate. A meeting was then arranged with each of the institutions where the aims of the study were explained. In the meeting, written permission to conduct the study was obtained from the Hospital/Clinical Practices' administration and from the consultant of the paediatric department. Children with LRTI were recruited when attending the casualties of the Hospital Santa Maria (Porto, Portugal), Cliria SA and the clinical practice Estrela Esteves, Unip., Lda (Aveiro, Portugal). Children were eligible if i) aged 0 to 5 years old; ii) diagnosed, by the paediatrician, with a LRTI; and ii) presented cough plus at least one of the following symptoms: sputum production, respiratory distress/dyspnea, chest pain/discomfort, wheezing and/or fever (5, 28). Exclusion criteria were the presence of chronic respiratory diseases, cardiac diseases, neurological impairment, current/previous history of pulmonary lobectomy, neoplasic disease or immunological disease and/or significant musculoskeletal disorders (e.g., kyphoescoliosis) that could affect respiratory acoustics. Healthy volunteers were recruited from these three institutions, whilst attending paediatrics' routine appointments, and from the Music School of Ovar after written permission from the institution's director. Criteria for exclusion were presence of one or more of the following conditions: acute (within the last month) or chronic respiratory disease, cardiac diseases, cognitive impairment, history of neoplasic or immunological disease and/or significant musculoskeletal disorders (e.g., kyphoescoliosis).

2.3. Measures

A structured questionnaire was used to collect socio-demographic and anthropometric data, as they are known to affect respiratory sounds (29). Socio-demographic data included gender, date of birth, exposure to environmental risk factors, personal and family history of respiratory diseases. Anthropometric data involved weight and height measurements to calculate the body mass index.

A cardio-respiratory assessment was performed to collect data on respiratory common symptoms (presence and type of cough, fever, wheezing and dyspnea/respiratory distress), body inspection (cyanosis, changes in face, neck, limbs and chest; tracheal deviations, intercostal, infracostal, suprasternal, supraclavicular and global indrawing, nasal flutter and weeping), peripheral oxygen saturation levels (SpO_2), heart and respiratory rates and blood pressure (30).

Dyspnoea is the perception of an unpleasant and/or uncomfortable sensation of breathing that can only be described by the subject (31), however, accurate verbalisation of the perception of laboured breathing is difficult to obtain from small children (32). Thus, in infants and children, dyspnoea describes the physical signs of respiratory distress rather than the expressed perception of breathlessness (32). In this study, dyspnoea/respiratory distress was assessed through the modified Wang Score (33). The modified Wang Score is an assessment scoring system which evaluates the presence of five clinical signs (wheezing, retractions, peripheral oxygen saturation, respiratory rate and heart rate). Each category is scored as "0" for normal, "1" for moderate impairment, "2" for mild impairment or "3" for severe impairment. Normally functioning children should have a cumulative score of 0, whereas critically ill and severely distressed children will have scores closer to 15 (34). This score has been used in the evaluation of neonates and infants (34, 35) and shows a good inter-observer agreement among caregivers (36, 37).

Respiratory sounds were collected with a digital stethoscope (Welch Allyn Master Elite Plus Stethoscope Model 5079-400, New York, USA) connected to an external sound card (Cakewalk UA-25EX UA-25, Boston, USA). The signal was converted with a 24-bit resolution at a sample rate of 44100 samples per second (38) and recorded in .wav format on a laptop computer with the "LungSounds@UA" interface developed to collect respiratory sounds (39).

2.4. Procedures

Socio-demographic data, anthropometric data and cardio-respiratory parameters were collected in the presented order to characterise the sample and complement the respiratory assessment. This assessment followed WHO recommendations, which advocate the capture of a holistic perspective of the person (40). This information composed a structured questionnaire, which was fulfilled by the researcher using information from the clinical notes, parental information and through individually assessment of each participant.

Respiratory sounds were collected from older children while they were sat in a chair ensuring a 90º angle between the spinal column and the lower limbs (41) (Figures 1 and 2). For infants and newborns, legal representatives were instructed to hold them in the upright position (28). Six anatomical sites were recorded: anterior (at the second intercostal space in mid-clavicular, right and left), lateral (at the fourth or fifth intercostal space on the mid-axillary line, right and left) and posterior (laterally from the paravertebral line and below the scapular angle, right and left) areas, using reference points to ensure that the stethoscope was placed on the same anatomical sites in

each child. Tracheal sounds were not recorded in this study as it has been reported that respiratory sounds from the trachea are differently filtered than those from other respiratory morphological sites (42). In addition, health professionals rarely use this anatomical site for assessing chest conditions (43) as it is difficult to be obtained in paediatric populations given the size of the neck and constant movement of the head/neck. Each sound recording was performed with children breathing at tidal breathing during 20 seconds (to ensure that 7 to 10 respiratory cycles were recorded) following the CORSA short-term acquisition guidelines (41).

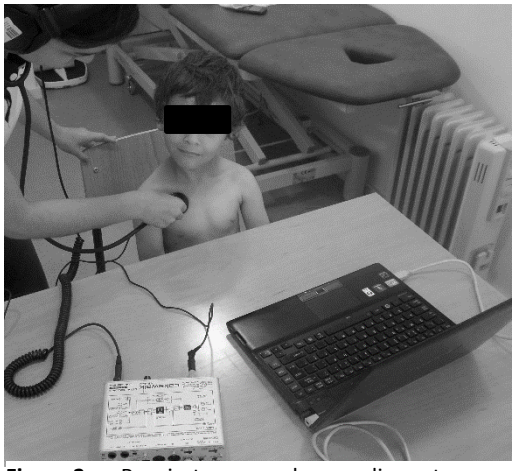


Figure 2 - – Respiratory sounds recordings at anterior right site.

Figure 1 – Respiratory sounds recordings at posterior right site.

2.5. Data Analysis

Children's data were grouped according to the maturity of their respiratory system. The development of the respiratory system can be divided in three stages which are closely related with the chronological age: i) exponential growing of the number of alveoli's, from 20 to approximately 300 million (0-2 years old); ii) development of the collateral ventilation through the formation of the pores of Kohn and Lambert's canal (3-6 years old); and iii) deposition of elastin in the lung which decreases the resistance of respiratory airways (7-8 years old) (44, 45). Respiratory sounds are direct related with the lung tissue changes and consequently with children's age (29, 46), therefore four subgroups resulted from this division: G1) healthy children aged 0 to 2 years old; G2) children with LRTI aged 0 to 2 years old; G3) healthy children aged between 3 and 5 years old; and G4) children with LRTI aged between 3 and 5 years old.

Descriptive statistics were applied to characterise each group (i.e., socio-demographic and anthropometric data, cardio-respiratory parameters and respiratory sounds). Then, the distribution

of the data was tested with Shapiro-Wilk tests and inferential statistics were used to compare groups from the same age-range (i.e., G1 vs. G2; G3 vs. G4). Independent sample t-tests were used to compare age, body mass index (BMI) and cardio-respiratory parameters, namely SpO_2, heart rate, respiratory rate and body temperature, between groups. Mann-Whitney U tests were used to compare BMI percentiles and Wang Score between groups and Fisher's exact tests to analyse group differences on categorical data (i.e., gender, environmental risk factors, comorbidities, family comorbidities and parental smoking) (47).

Sound files were processed based on published algorithms (48-51) implemented in Matlab 2009 (The MathWorks, Inc, Natick, MA, USA). Crackles and wheezes found in the sound files were characterised in terms of their number, type, frequency, and duration per respiratory phase. All statistical analysis was conducted in the PASW Statistics version 19.0 for Windows (SPSS Inc., Chicago, Illinois). The level of significance considered was set at $p< 0.05$.

2.5.1. Wheezes Analysis

The mean number of wheezes was studied as it provides information on the possible presence of obstructive lung disease. The fundamental frequency and type of wheeze was analysed as it is an important characterisation parameter which provides information on the source of the wheeze (52, 53). The wheeze's ratio was studied because the proportion of the respiratory cycle occupied by wheezing is associated with the degree of bronchial obstruction (54).

Wheezes were automatically detected using Respiratory Sound Annotation Software – RSAT, an interface developed by Dinis et al. (55). The interface uses the algorithm of Taplidou and Hadjileontiadis (48), which is based on a time-frequency analysis technique, the Short-time Fourier transform, proposed by Gabor (56). This algorithm has demonstrated a sensitivity of 99.2%, a specificity of 72.5% and a performance of 84.8% in the automatic detection of wheezes in adult patients with LRTI (57). Visual and hearing inspection of the sound spectrum was performed by the researcher to confirm algorithms' annotation.

First, the number of children with wheezes in each group was calculated and then descriptive statistics were used to assess and characterise number, type (i.e., monophonic or polyphonic), frequency (*F*) and occupation rate (Wh%) of wheezes, per respiratory phase, in those presenting this ARS. Fisher's exact test was used to investigate the groups' differences on the number of children presenting wheezes and Mann Whitney U tests were applied to compare wheezes characteristics between groups.

2.5.2. Crackles Analysis

The variable "mean number" was studied as the number of crackles reflects the severity of the disease process (58). The variable frequency was also chosen as it allows identification of crackles' source (52, 59). The type (i.e., fine or coarse), initial deflection width (IDW), two cycle duration (2CD), and largest deflection width (LDW) were collected because these parameters allow crackle's characterisation (52). Both IDW and 2CD have reference values which classify crackles in fine (mean IDW of 0.7ms; 2CD<10 ms) or coarse (mean IDW of 1.5ms; 2CD>10 ms) (52, 60) and 2CD has also been consider a more stable and reliable parameter (43, 61). LDW was studied as it was considered a good parameter to classify crackles (62) for diagnostic (23) and monitoring purposes (18).

Crackles were also automatically detected using the RSAT interface (55), which contains an algorithm based on the combination of fractal dimension (49-51), box filtering (63) techniques, and the crackle established criteria (52, 64), i.e., crackle complexes contain 5 to 16 baseline crossings, their amplitude is greater, than twice of the background signal, the beginning of the event has a sharp deflection and crossings of the baseline after the initial deflection are progressively wider. Visual and hearing inspection of the sound spectrum was performed by the researcher to confirm algorithms' annotation.

First, the number of children with crackles in each group was calculated. Then descriptive statistics were used to calculate the mean number, type, *F*, IDW, 2CD, and LDW of crackles per respiratory phase (i.e., early, mid and late inspiration; early, mid and late expiration) in children presenting crackles. Fisher's exact test was used to investigate differences on the number of children presenting crackles and Mann Whitney U tests were applied to establish comparisons between the crackle parameters of healthy children and children with LRTI. Comparisons were performed per respiratory phase and cycle.

3. RESULTS

Sixty children met the criteria to be included in the study. Nineteen legal representatives refused the participation of their child due to: time constrictions (n=11) and children's agitation (n=8). One participant was posteriorly excluded from the data analysis due to the poor quality of the sound recording (i.e., movement artefacts and voice sounds). In total 40 children were enrolled in this study: 11 healthy (G1) and 11 with LRTI (G2) aged 0 to 2 years old; 9 healthy (G3) and 9 with LRTI (G4) aged 3 to 5 years old (Figure 3).

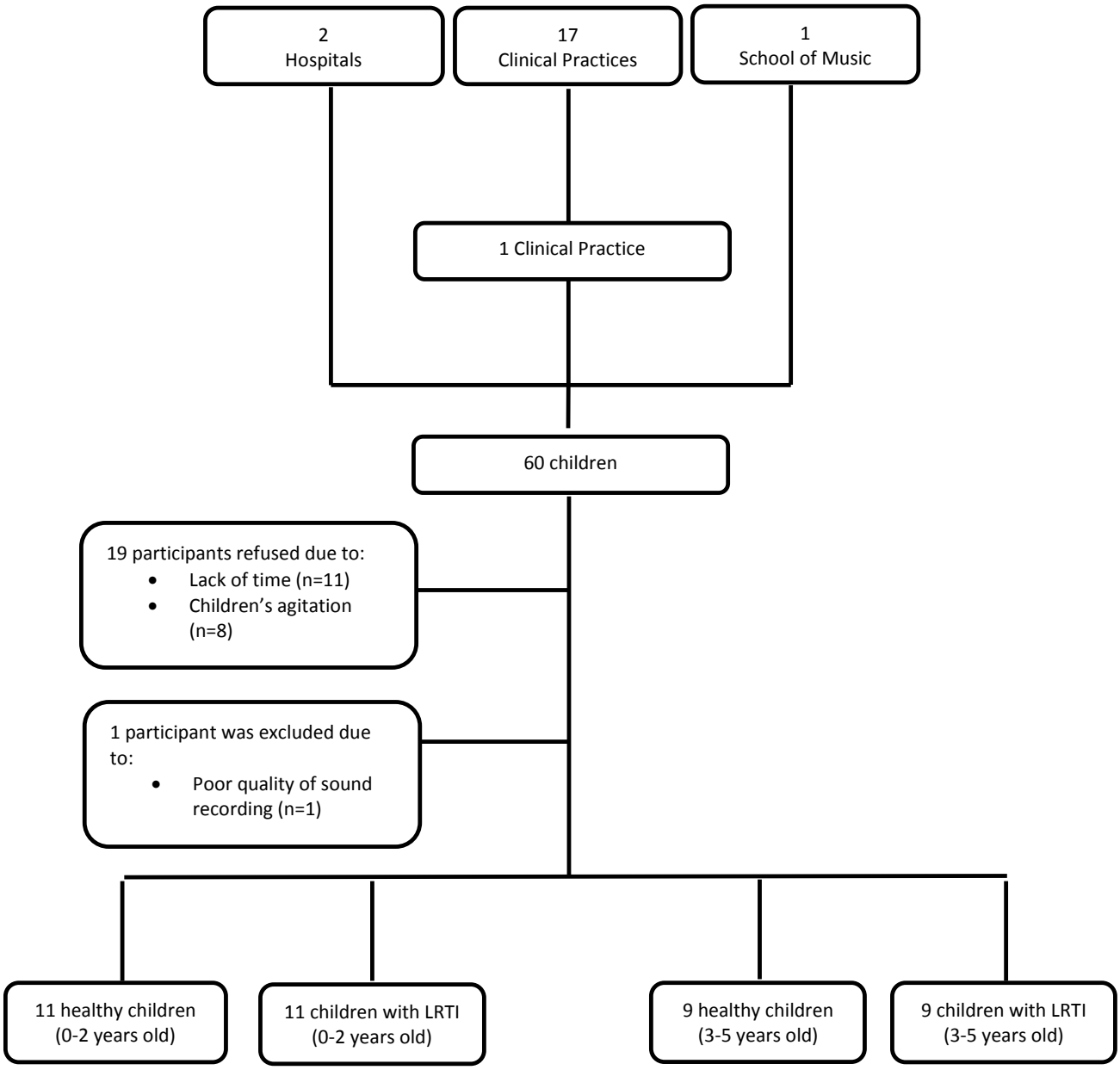


Figure 3 - Sample recruitment process.

3.1. Sample characterisation

Groups were mainly composed by males (G1: n=7, 63.6%; G2: n=8, 72.7%; G3: n=6, 66.7%; G4: n=6, 66.7%). Children's mean age was 16.5±10.4 months (G1: 15.1±3.6 vs. G2: 17.8±2.7 months) in the group aged 0 to 2 years old and 52.7±9.5 months (G3: 56.2.1±3.0 vs. G4: 41.1±3.0 months) in those aged 3 to 5 years old. Body mass index, calculated according to children's age, was between percentile 50 (G2, G3 and G4) and 75 (G1). Most children with LRTI had non-specified LRTI (G1: n=5,

45.5%; G3: n=4, 44.4%), followed by bronchiolitis (G1: n=5, 45.5%; G3: n=2, 22.2%) and pneumonia (G1: n=1, 9.1%; G3: n=3, 33.3%) (Table 1).

Healthy children tended to present more exposure to risk factors then children with LRTI (G1: n=7, 63.6% vs. G2: n=4, 36.4%; G3: n=6, 66.7% vs. G4: n=4, 44.4%). Also, healthy children presented more history of parental smoking, namely in the older age group (G3: n=4, 44.5% vs. G4: n=2, 22.2%). Conversely, children with LRTI were the ones with higher history of recurrent LRTI (65) (G1: n=1, 9.1% vs. G2: n=3, 27.3%; G3: n=0, 0% vs. G4: n=1, 11.1%) and family co-morbidities (G1: n=4, 36.4% vs. G2: n=6, 54.5%; G3: n=4, 44.4%; vs. G4: n=5, 55.6%) (Table 1).

There were no differences between groups for those variables reported above (Table 1).

Table 1 – Sample characterisation.

GROUPS / VARIABLES	0-2				3-5			
	G1 Healthy (n=11)	G2 LRTI (n=11)	Test Value	ρ-value	G3 Healthy (n=9)	G4 LRTI (n=9)	Test Value	ρ-value
Gender (n, %)				1.00				1.00
Female	4 36.4	3 27.3			3 33.3	3 33.3		
Male	7 63.6	8 72.7			6 66.7	6 66.7		
Age (months)	15.1±3.6	17.8±2.7	T=-0.61	0.55	56.2±3.0	41.1±3.0	T=1.67	0.12
BMI (kg/m²)	16.9±1.7	18.0±5.0	T=-0.71	0.49	16.37±2.9	15.56±0.9	T=0.90	0.39
BMI for age/percentiles (M, (IQR]	75 (60)	50 (65)	U=45.0	0.51	50 (82)	50 (43.8)	U=33.0	0.81
Diagnosis (n, %)	N/A				N/A			
LRTI (non-specified)		5 45.5				4 44.4		
Pneumonia		1 9.1				3 33.3		
Bronchiolitis		5 45.5				2 22.2		
Environmental Risk Factors (n, %)	7 63.6	4 36.4		0.36	6 66.7	4 44.4		0.67
Carpet	3	4			2	3		
Animals (cats, dogs and birds)	5	2			3	1		
Smoke	0	0			1	1		
House humidity	0	1			0	0		
Recurrent LRTI (≥3/year) (n, %)	1 9.1	3 27.3		0.59	0 0	1 11.1		1.00
Family Comorbidities (n, %)	4 36.4	6 54.5		0.67	4 44.4	5 55.6		1.00
COPD (grandparents)	1 25	0 0			1 25	1 20		
Rhinitis (parents)	2 50	3 50			1 25	1 20		
Sinusitis (parents)	0 0	3 50			0 0	1 20		
Asthma (parents)	0 0	1 16.7			0 0	0 0		
Asthma (grandparents)	2 50	2 33.3			1 25	3 60		
Atopy (parents)	0 0	0 0			1 25	0 0		
Parental Smoking (n, %)	0 0	0 0		1.00	4 44.5	2 22.2		0.62

Results are mean ± standard deviation, unless otherwise stated.

LRTI: lower respiratory tract infection; BMI: body mass index; N/A: not applicable; COPD: chronic obstructive pulmonary disease; M: median; IQR: inter-quartile range; T: Independent samples t-test; U: Mann Whitney test.

3.2. Cardio-respiratory assessment

Similar results between groups were found for SpO_2 (G1: 96.0±0.8% vs. G2: 97.3±0.6%; G3: 98.7±0.3%; vs. G4: 97.3±0.6%), respiratory rate (G1: 38.6±12.4 cpm vs. G2: 43.8±11.0 cpm; G3: 25.7±6.9 cpm; vs. G4: 30.7±5.6 cpm) and body temperature (G1: 36.2±0.1ºC vs. G2: 36.5±0.4ºC; G3: 36.3±0.3 ºC; vs. G4: 36.3±0.2 ºC) (Table 2). Children with LRTI with age between 0 and 2 years old had significantly higher heart rate than healthy children (G1: 119.8±11.0 bpm vs. G2: 140.8±20.8 bpm ρ=0.01). Both groups composed by children with LRTI showed more dyspnoea/respiratory distress than healthy peers (G1: M 0 IQR 3 vs. G2: M 4 IQR 3; p=0.01; G3: M 0 IQR 0.5 vs. G4: M 1 IQR 2; p= 0.03) (Table 2).

Among children with LRTI, the most common sign/symptom was productive cough (G2: n=11, 100% ; G4: n=6, 66.7%), followed by fever (G2: n=9, 81.8%; G4: n=6, 66.7%), wheezing (G2: n=8, 72.7%; G4: n=3, 33.3%), dry cough (G2: n=1, 9.1%; G4: n=4, 44.4%), increased respiratory rate (G2: n=3, 27.3%; G4: n=0, 0%), poor feeding (G2: n=2, 18.2%; G4: n=0, 0%) and rhinorrhoea (G2: n=1, 9.1%; G4: n=1, 11.1%) (Table 2).

Table 2 – Sample's cardio-respiratory assessment.

GROUPS / VARIABLES	0-2				3-5			
	G1 Healthy (n=11)	G2 LRTI (n=11)	Test Value	ρ-value	G3 Healthy (n=9)	G4 LRTI (n=9)	Test Value	ρ-value
SpO_2(%)	96.0±0.8	97.3±0.6	T=-1.28	0.21	98.7±0.3	97.3±0.6	T=1.89	0.08
Heart rate (bpm)	119.8±11.0	140.8±20.8	T=-2.96	0.01*	113.9±16.1	121.0±19.0	T=-0.86	0.40
Respiratory rate (cpm)	38.6±12.4	43.8±11.0	T=-2.96	0.30	25.7±6.9	30.7±5.6	T=-1.69	0.11
Body temperature (ºC)	36.2±0.1	36.5±0.4	T=-1.04	0.32	36.3±0.3	36.3±0.2	T=0.12	0.91
Signs/Symptoms (n, %)	N/A	11 100			N/A	9 100		
Cough (dry)		1 9.1				4 44.4		
Cough (productive)		11 100				6 66.7		
Fever		9 81.8				6 66.7		
Increased RR		3 27.3				0 0		
Poor feeding		2 18.2				0 0		
Wheezing		8 72.7				3 33.3		
Rhinorrhea		1 9.1				1 11.1		
Days with symptoms [M (IQR)]	N/A	5.5(23)			N/A	3(2)		
Wang Score [M (IQR)]	0 (3)	4 (3)	U=21.5	0.01*	0 (0.5)	1 (2)	U=18.5	0.03*

Results are mean ± standard deviation, unless otherwise stated.

LRTI: lower respiratory tract infection; SpO_2: peripheral oxygen saturation; beats per minute; cpm: cycles per minute; N/A: not applicable M: median; IQR: inter-quartile range; T: Independent samples t-test; U: Mann Whitney test; * ρ<0.05

3.3. Adventitious respiratory sounds

To simplify the reading and understanding of the results on ARS, two sub-sections have been created (i.e., "wheezes" and "crackles") and results will be presented per age ranges within each subsection: i) children aged 0 to 2 years old (G1 and G2) and ii) children aged 3 to 5 years old (G3 and G4).

3.3.1. Wheezes

Few participants presented this type of ARS. Significant differences were not found between G1 and G2 (aged 0-2 years old) for the number of children with wheezes. Considering all chest sites of auscultation, children with LRTI had a higher number of inspiratory (G1: M 0.10 IQR 0.05 vs. G2: M 0.14 IQR 0.48 p=0.03) and expiratory wheezes (G1: M 0.11 IQR 0.03 vs. G2: M 0.20 IQR 0.32 p=0.003) than healthy peers. They also presented a higher expiratory Wh% (G1: M 2.15 IQR 1.45 vs. G2: M 4.73 IQR 6.72 p=0.001), especially monophonic wheezes (G1: M 0.09 IQR 0.07 vs. G2: M 0.14 IQR 0.16 p=0.003) (Table 3).

The individual analysis of the six chest locations revealed only differences in the expiratory Wh% at the lateral right site (G1: M 2.03 IQR 1.30 vs. G2: M 4.62 IQR 5.03 p=0.03). Comparisons for the wheezes' parameters were not possible to perform at the lateral left site for inspiration, as no healthy participant presented wheezes in this site (Table 3).

Monophonic wheezes were the most common type of wheezes founded in both healthy children and children with LRTI (Table 3).

Table 3- Wheezes' parameters during inspiration and expiration in children aged 0 to 2 years old.

Chest Locations	Position in the BC	GROUPS / VARIABLES	0-2 G1 Healthy (n=11)	0-2 G2 LRTI (n=11)	Test Value	ρ-value
All Locations	**Inspiration**	**No. of children with Wh (n)**	3	3		1.00
		No. of Wh	0.10 (0.05)	0.14 (0.48)	U= 11.50	0.03*
		No. of monophonic Wh	0.10 (0.05)	0.14 (0.45)	U= 15.00	0.91
		No. of polyphonic Wh	0.00 (0.00)	0.00 (0.10)	U= 25.00	0.30
		Wh%	3.04 (2.79)	6.51 (10.33)	U=24.00	0.41
		F	223.39 (265.48)	265.32 (363.73)	U= 31.00	1.00
	Expiration	**No. of children with Wh (n)**	5	8		0.15
		No. of Wh	0.11 (0.03)	0.20 (0.32)	U= 185.50	0.03*
		No. of monophonic Wh	0.09 (0.07)	0.14 (0.16)	U= 142.50	0.003*
		No. of polyphonic Wh	0.00 (0.06)	0.00 (0.08)	U= 287.00	0.94
		Wh%	2.15 (1.45)	4.73 (6.71)	U=130.00	0.001*
		F	198.73 (213.76)	250.37 (504.39)	U= 336.00	0.27

Anterior Right	**Inspiration**	**No. of children with Wh (n)**	3	1		0.59
		No. of Wh	0.10 (0.00)	0.67	U= 0.00	0.50
		No. of monophonic Wh	0.10 (0.00)	0.08	U= 0.00	0.50
		No. of polyphonic Wh	0.00 (0.00)	0.58	U= 0.00	0.50
		Wh%	3.04 (0.00)	14.05	U=0.00	0.50
		F	456.59 (0.00)	269.84	U= 1.00	1
	Expiration	**No. of children with Wh (n)**	1	5		0.15
		No. of Wh	0.04	0.30 (0.28)	U= 0.00	0.50
		No. of monophonic Wh	0.04	0.20 (0.28)	U= 0.00	0.50
		No. of polyphonic Wh	0.00	0.00 (0.05)	U= 0.00	1.00
		Wh%	1.21	5.63 (6.37)	U=0.00	0.50
		F	113.05	250.37 (762.01)	U= 0.00	1.00
Anterior Left	**Inspiration**	**No. of children with Wh (n)**	1	2		1.00
		No. of Wh	0.12	0.12 (0.00)	U= 1.00	1.00
		No. of monophonic Wh	0.12	0.12 (0.00)	U= 1.00	1.00
		No. of polyphonic Wh	0.00	0.00 (0.00)	U= 1.00	1.00
		Wh%	2.29	2.24 (0.00)	U=1.00	1.00
		F	129.20	161.49 (107.66)	U= 1.00	1.00
	Expiration	**No. of children with Wh (n)**	5	4		1.00
		No. of Wh	0.11 (0.04)	0.08 (0.03)	U= 3.50	0.11
		No. of monophonic Wh	0.00 (0.11)	0.08 (0.07)	U= 9.50	0.90
		No. of polyphonic Wh	0.06 (0.11)	0.00 (0.04)	U= 5.50	0.29
		Wh%	1.90 (1.92)	2.28 (3.26)	U= 9.00	0.90
		F	166.88 (359.60)	310.56 (570.82)	U= 9.00	0.90
Lateral Right	**Inspiration**	**No. of children with Wh (n)**	1	1		1.00
		No. of Wh	0.13	0.09	U= 0.00	1.00
		No. of monophonic Wh	0.13	0.09	U= 0.00	1.00
		No. of polyphonic Wh	0.00 (0.00)	0.00 (0.00)	U= 0.50	1.00
		Wh%	3.91	1.74	U= 0.00	1.00
		F	223.39	215.33	U= 0.00	1.00
	Expiration	**No. of children with Wh (n)**	4	4		1.00
		No. of Wh	0.10 (0.03)	0.20 (0.30)	U= 3.00	0.20
		No. of monophonic Wh	0.10 (0.03)	0.20 (0.30)	U= 3.00	0.20
		No. of polyphonic Wh	0.00 (0.00)	0.00 (0.00)	U= 8.00	1.00
		Wh%	2.03 (1.30)	4.62 (5.03)	U=0.00	0.03*
		F	308.28 (217.51)	661. 08 (876.33)	U= 3.00	0.20
Lateral Left	**Inspiration**	**No. of children with Wh (n)**	0	2		0.48
		No. of Wh	N/A	0.32 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.32 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.00 (0.00)	N/A	N/A
		Wh%	N/A	6.49 (0.00)	N/A	N/A
		F	N/A	760.61 (0.00)	N/A	N/A
	Expiration	**No. of children with Wh (n)**	5	7		0.67
		No. of Wh	0.10 (0.10)	0.14 (0.12)	U= 13.50	0.53
		No. of monophonic Wh	0.10 (0.10)	0.14 (0.11)	U= 15.00	0.76
		No. of polyphonic Wh	0.00 (0.00)	0.00 (0.10)	U= 12.50	0.43
		Wh%	2.78 (1.22)	2.7 (3.78)	U=14.00	0.64
		F	193.78 (384.52)	286.49 (888.18)	U= 15.00	0.76
Posterior Right	**Inspiration**	**No. of children with Wh (n)**	1	2		1.00
		No. of Wh	0.13	0.5 (0.00)	U= 1.00	1.00
		No. of monophonic Wh	0.67	0.31 (0.00)	U= 1.00	1.00
		No. of polyphonic Wh	0.66	0.19 (0.00)	U= 0.00	0.67

		Wh%	7.17	14.13 (0.00)	U=0.00	0.67
		F	218.12	533.80 (0.00)	U= 0.00	0.67
	Expiration	**No. of children with Wh (n)**	2	5		0.36
		No. of Wh	0.13 (0.00)	0.25 (0.31)	U= 2.00	0.38
		No. of monophonic Wh	0.09 (0.00)	0.25 (0.25)	U= 1.00	0.19
		No. of polyphonic Wh	0.05 (0.00)	0.00 (0.06)	U= 4.00	0.86
		Wh%	2.42 (0.00)	6.29 (15.24)	U=2.00	0.38
		F	249.99 (0.00)	249.99 (259.01)	U= 4.00	0.86
Posterior Left	**Inspiration**	**No. of children with Wh (n)**	1	1		1.00
		No. of Wh	0.04	0.25	U= 0.00	1.00
		No. of monophonic Wh	0.04	0.25	U= 0.00	1.00
		No. of polyphonic Wh	0.00	0.00	U= 0.00	1.00
		Wh%	2.74	6.52	U= 0.00	1.00
		F	301.11	164.19	U= 0.00	1.00
	Expiration	**No. of children with Wh (n)**	3	4		1.00
		No. of Wh	0.11 (0.00)	0.50 (0.38)	U= 3.00	0.40
		No. of monophonic Wh	0.05 (0.00)	0.16 (0.29)	U= 2.50	0.16
		No. of polyphonic Wh	0.05 (0.00)	0.22 (0.32)	U= 3.00	0.29
		Wh%	3.59 (0.00)	16.22 (8.90)	U=0.00	0.06
		F	193.78 (0.00)	182.98 (319.72)	U= 4.00	0.63

Results are median (inter-quartile range), unless otherwise stated.

[1]Mann Whitney U test; LRTI: lower respiratory tract infection; N/A: not applicable; Wh: Wheezes; Wh%: wheeze occupation rate; *F*; frequency; * ρ<0.05

In the age range of 3 to 5 years old, the number of children with wheezes was not significantly different between the healthy group (G3) and the group with LRTI (G4). No differences were found between groups for wheezes' parameters, both at chest sites pooled together and analysed individually. However, the expiratory Wh% tended to be increased in the LRTI group (G3: M 2.80 IQR 3.27 vs. G4: M 5.17 IQR 15.99 p=0.07) (Table 4).

Healthy children did not present wheezes at the anterior and posterior sites; therefore the parameters of wheezes in these sites could not be compared with children with LRTI. Low frequency monophonic expiratory wheezes were the most common type of wheezes founded in both healthy children and children with LRTI (Table 4).

Table 4- Wheezes' parameters during inspiration and expiration in children aged 3 to 5 years old.

Chest Locations	Position in the BC	**GROUPS** / **VARIABLES**	3-5 G3 Healthy (n=9)	3-5 G4 LRTI (n=9)	Test Value	ρ-value
All Locations	**Inspiration**	**No. of children with Wh (n)**	3	6		0.16
		No. of Wh	0.15 (0.10)	0.13 (0.21)	U= 26.50	0.88
		No. of monophonic Wh	0.12 (0.17)	0.13 (0.16)	U= 21.00	0.51
		No. of polyphonic Wh	0.00 (0.09)	0.00 (0.00)	U= 24.50	0.72
		WH%	4.23 (1.89)	3.95 (2.82)	U=27.00	0.96
		F	261.79 (852.11)	207.57 (420.51)	U= 27.00	0.96

	Expiration	**No. of children with Wh (n)**	6	9		0.15
		No. of Wh	0.16 (0.11)	0.24 (0.40)	U= 64.50	0.28
		No. of monophonic Wh	0.17 (0.09)	0.13 (0.33)	U= 83.50	0.84
		No. of polyphonic Wh	0.00(0.19)	0.11 (0.18)	U= 55.00	0.13
		WH%	2.80 (3.27)	5.17 (15.99)	U=49.00	0.07
		F	326.93 (489.86)	477.93 (489.86)	U= 74.00	0.53
Anterior Right	**Inspiration**	**No. of children with Wh (n)**	0	2		0.47
		No. of Wh	N/A	0.34 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.27 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.06 (0.00)	N/A	N/A
		WH%	N/A	5.99 (0.00)	N/A	N/A
		F	N/A	153.42 (0.00)	N/A	N/A
	Expiration	**No. of children with Wh (n)**	0	1		1.00
		No. of Wh	N/A	0.50	N/A	N/A
		No. of monophonic Wh	N/A	0.20	N/A	N/A
		No. of polyphonic Wh	N/A	0.30	N/A	N/A
		WH%	N/A	23.29	N/A	N/A
		F	N/A	133.78	N/A	N/A
Anterior Left	**Inspiration**	**No. of children with Wh (n)**	0	2		0.47
		No. of Wh	N/A	0.32 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.32 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.00 (0.00)	N/A	N/A
		WH%	N/A	6.49 (0.00)	N/A	N/A
		F	N/A	760.61 (0.00)	N/A	N/A
	Expiration	**No. of children with Wh (n)**	0	3		0.21
		No. of Wh	N/A	0.18 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.13 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.09 (0.00)	N/A	N/A
		WH%	N/A	2.71 (0.00)	N/A	N/A
		F	N/A	366.03 (0.00)	N/A	N/A
Lateral Right	**Inspiration**	**No. of children with Wh (n)**	1	3		0.57
		No. of Wh	0.08	0.11 (0.00)	U= 0.00	0.50
		No. of monophonic Wh	0.08	0.11 (0.00)	U= 0.00	0.18
		No. of polyphonic Wh	0.00	0.00 (0.00)	U= 0.00	1.00
		WH%	2.62	4.00 (0.00)	U= 0.00	0.50
		F	372.18	250.97 (0.00)	U= 1.00	1.00
	Expiration	**No. of children with Wh (n)**	2	5		0.34
		No. of Wh	0.38 (0.00)	0.25 (1.08)	U= 5.00	1.00
		No. of monophonic Wh	0.18 (0.00)	0.13 (0.63)	U= 4.50	0.86
		No. of polyphonic Wh	0.20 (0.00)	0.11 (0.46)	U= 4.00	0.70
		WH%	4.46 (0.00)	5.58 (21.99)	U=3.00	0.57
		F	181.27 (0.00)	406.36 (497.08)	U= 4.00	0.86
Lateral Left	**Inspiration**	**No. of children with Wh (n)**	3	2		1.00
		No. of Wh	0.17 (0.00)	0.15 (0.00)	U= 2.00	0.80
		No. of monophonic Wh	0.17 (0.00)	0.15 (0.00)	U= 2.50	0.80
		No. of polyphonic Wh	0.00 (0.00)	0.00 (0.00)	U= 2.00	0.80
		WH%	4.29 (0.00)	4.46 (0.00)	U=3.00	1.00
		F	151.39 (0.00)	156.36 (0.00)	U= 3.00	1.00
	Expiration	**No. of children with Wh (n)**	4	3		1.00
		No. of Wh	0.17 (0.09)	0.11 (0.00)	U= 4.00	0.63
		No. of monophonic Wh	0.17 (0.09)	0.11(0.00)	U= 4.00	0.63
		No. of polyphonic Wh	0.00 (0.00)	0.00 (0.17)	U= 4.00	0.63

		WH%	2.80 (2.95)	2.31 (0.00)	U=5.00	0.86
		F	392.65 (327.70)	305.04 (0.00)	U= 5.00	0.86
Posterior Right	**Inspiration**	**No. of children with Wh (n)**	0	3		0.21
		No. of Wh	N/A	0.11 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.11 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.00 (0.00)	N/A	N/A
		WH%	N/A	3.68 (0.00)	N/A	N/A
		F	N/A	661.49 (0.00)	N/A	N/A
	Expiration	**No. of children with Wh (n)**	0	3		0.21
		No. of Wh	N/A	0.22 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.10 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.22 (0.00)	N/A	N/A
		WH%	N/A	5.19 (0.00)	N/A	N/A
		F	N/A	361.81 (0.00)	N/A	N/A
Posterior Left	**Inspiration**	**No. of children with Wh (n)**	0	2		0.47
		No. of Wh	N/A	0.10 (0.00)	N/A	N/A
		No. of monophonic Wh	N/A	0.10 (0.00)	N/A	N/A
		No. of polyphonic Wh	N/A	0.00 (0.00)	N/A	N/A
		WH%	N/A	3.50 (0.00)	N/A	N/A
		F	N/A	207.57 (0.00)	N/A	N/A
	Expiration	**No. of children with Wh (n)**	0	4		0.08
		No. of Wh	N/A	0.33 (0.97)	N/A	N/A
		No. of monophonic Wh	N/A	0.11 (0.44)	N/A	N/A
		No. of polyphonic Wh	N/A	0.00 (0.00)	N/A	N/A
		WH%	N/A	5.72 (50.58)	N/A	N/A
		F	N/A	715.26 (679.71)	N/A	N/A

Results are median (inter-quartile range), unless otherwise stated.

[1]Mann Whitney U test; [2]value from one participant: LRTI: lower respiratory tract infection; N/A: not applicable; Wh: Wheezes; R: occupation rate; *F*; frequency; * ρ<0.05

3.3.2. Crackles

Significant differences were found between G1 and G2 (aged 0-2 years old) for the number of children with crackles and crackles' number, type, *F* and 2CD, per respiratory phase. Considering all chest sites of auscultation, children with LRTI had more inspiratory (G1: M 0.25 IQR 0.31 vs. G2: M 0.52 IQR 0.70; p<0.001) and expiratory crackles (G1: M 0.42 IQR 0.73 vs. G2: M 1.08 IQR 1.46; p<0.0001) than healthy peers (Figure 4). The inspiratory crackles of children with LRTI also presented shorter IDW (G1: M 3.81 IQR 1.97 vs. G2: M 3.15 IQR 1.38 p=0.04), LDW (G1: M 2.99 IQR 0.85 vs. G2: M 2.63 IQR 0.89 p=0.04) and 2CD (G1: M 13.29 IQR 4.20 vs. G2: M 11.82 IQR 4.36 p=0.02) (Table 5).

All children presented crackles in at least one chest location. At the anterior right sites, more children with LRTI presented inspiratory crackles (G1: n=5 vs. G2: n=11, p=0.01). However, it was on the expiration that crackles parameters varied significantly in terms of the mean number (G1: M 0.39 IQR 0.39 vs. G2: M 1.23 IQR 0.87; p<0.0001) and type (coarse crackles - G1: M 0.20 IQR 0.43

vs. G2: M 1.08 IQR 0.76; p=0.002; fine crackles - G1: M 0.10 IQR 0.10 vs. G2: M 0.31 IQR 0.24; p=0.004). Children with LRTI also presented more expiratory fine crackles at the anterior left (G1: M 0.07 IQR 0.26 vs. G2: M 0.40 IQR 0.77; p=0.03) and posterior left (G1: M 0.20 IQR 0.29 vs. G2: M 0.69 IQR 1.17; p=0.03) sites than healthy peers. At posterior left site, children with LRTI presented inspiratory crackles with higher frequency (G1: M 137.07 IQR 19.97 vs. G2: M 152.10 IQR 22.04; p=0.02) and expiratory crackles with lower 2CD (G1: M 14.92 IQR 3.25 vs. G2: M 11.19 IQR 3.24; p=0.009) (Table 5).

Coarse expiratory crackles were the most common type of crackle founded in both healthy children and children with LRTI (Table 5).

Table 5- Crackles' parameters during inspiration and expiration in children aged 0 to 2 years old.

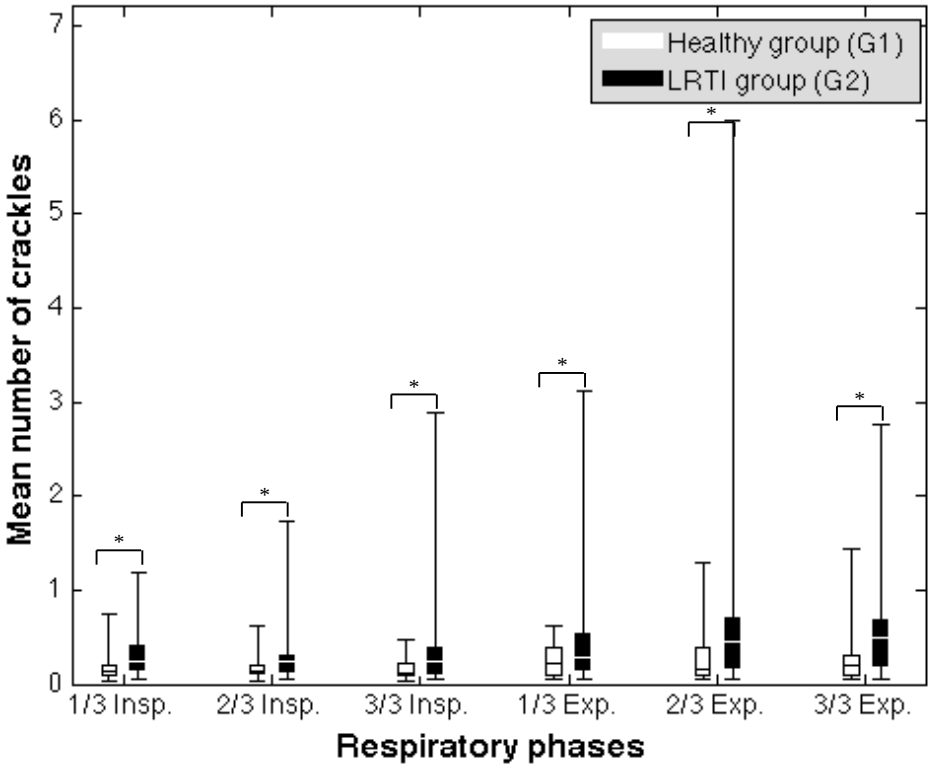
Chest Locations	Position in the BC	GROUPS / VARIABLES	0-2 G1 Healthy (n=11)	0-2 G2 LRTI (n=11)	Test Value[1]	p-value
All Locations	**Inspiration**	**No. of children with Cr (n)**	11	11		1.00
		No. of Cr	0.25 (0.31)	0.52 (0.70)	U= 781.00	<0.0001*
		No. of coarse Cr	0.16 (0.23)	0.29 (0.48)	U= 927.00	0.02*
		No. of fine Cr	0.07 (0.13)	0.18 (0.42)	U= 803.00	0.001*
		IDW	3.81 (1.97)	3.15 (1.38)	U=973.00	0.04*
		LDW	2.99 (0.85)	2.63 (0.89)	U= 959.00	0.04*
		2CD	13.29 (4.20)	11.82 (4.36)	U= 927.50	0.02*
		F	144.96 (46.68)	151.40 (78.62)	U= 998.00	0.07
	Expiration	**No. of children with Cr (n)**	11	11		1.00
		No. of Cr	0.42 (0.73)	1.08 (1.46)	U= 1024.50	<0.0001*
		No. of coarse Cr	0.33 (0.55)	0.56 (0.99)	U= 1178.00	<0.0001*
		No. of fine Cr	0.12 (0.22)	0.25 (0.45)	U= 984.00	<0.0001*
		IDW	3.42 (1.55)	3.48 (1.36)	U=1589.00	0.51
		LDW	2.74 (0.95)	2.72 (0.74)	U= 1600.50	0.55
		2CD	13.09 (3.49)	12.21 (2.99)	U= 1401.00	0.09
		F	157.12 (105.57)	171.86 (72.92)	U= 1679.50	0.87
Anterior Right	**Inspiration**	**No. of children with Cr (n)**	5	11		0.01*
		No. of Cr	0.13 (0.39)	0.38 (0.69)	U= 11.00	0.07
		No. of coarse Cr	0.09 (0.31)	0.25 (0.27)	U= 16.00	0.22
		No. of fine Cr	0.04 (0.30)	0.19 (0.38)	U= 13.00	0.12
		IDW	3.38 (3.54)	2.94 (0.78)	U= 18.00	0.32
		LDW	2.81 (1.02)	2.63 (0.53)	U= 20.00	0.41
		2CD	12.15 (6.16)	11.04 (2.1)	U= 15.00	0.18
		F	141.30 (61.88)	314.84 (45.66)	U= 15.00	0.18
	Expiration	**No. of children with Cr (n)**	10	11		1.00
		No. of Cr	0.39 (0.39)	1.23 (0.87)	U= 6.00	<0.0001*
		No. of coarse Cr	0.20 (0.43)	1.08 (0.76)	U= 12.50	0.002*
		No. of fine Cr	0.10 (0.10)	0.31 (0.24)	U= 15.50	0.004*
		IDW	2.96 (3.32)	3.43 (1.49)	U= 43.00	0.43
		LDW	2.43 (1.19)	2.86 (0.56)	U= 37.00	0.22
		2CD	12.07 (12.48)	13.07 (2.76)	U= 48.00	0.65

		F	189.77 (675.28)	159.68 (68.86)	U= 46.00	0.58
Anterior Left	**Inspiration**	**No. of children with Cr (n)**	5	10		0.06
		No. of Cr	0.22 (0.20)	0.57 (1.13)	U= 14.00	0.30
		No. of coarse Cr	0.20 (0.29)	0.40 (0.68)	U= 13.00	0.24
		No. of fine Cr	0.00 (0.12)	0.29 (0.49)	U= 14.00	0.30
		IDW	3.95 (2.08)	3.54 (1.23)	U= 15.00	0.36
		LDW	2.93 (0.91)	2.90 (0.99)	U= 17.00	0.52
		2CD	14.98 (6.24)	13.54 (3.98)	U= 22.00	1.00
		F	139.65 (37.47)	137.95 (23.6)	U= 18.00	0.61
	Expiration	**No. of children with Cr (n)**	10	9		1.00
		No. of Cr	0.23 (0.26)	1.11 (2.99)	U= 20.50	0.08
		No. of coarse Cr	0.13 (0.14)	0.63 (1.76)	U= 34.00	0.07
		No. of fine Cr	0.07 (0.16)	0.40 (0.77)	U= 39.00	0.03*
		IDW	3.61 (2.48)	3.50 (1.23)	U= 38.50	0.90
		LDW	2.61 (1.26)	2.55 (0.66)	U= 38.50	0.90
		2CD	13.03 (5.12)	12.60 (9.11)	U= 35.00	0.70
		F	144.18 (270.62)	165.68 (151.08)	U= 35.00	0.70
Lateral Right	**Inspiration**	**No. of children with Cr (n)**	10	9		1.00
		No. of Cr	0.30 (0.30)	0.58 (0.63)	U= 24.00	0.17
		No. of coarse Cr	0.12 (0.25)	0.17 (0.42)	U= 38.50	0.90
		No. of fine Cr	0.10 (0.24)	0.33 (0.63)	U= 19.00	0.07
		IDW	3.41 (2.57)	2.94 (2.14)	U= 26.00	0.24
		LDW	2.71 (1.34)	2.21 (0.77)	U= 25.50	0.20
		2CD	12.59 (7.51)	9.38 (4.41)	U= 20.00	0.08
		F	165.43 (181.38)	240.05 (276. 85)	U= 32.00	0.52
	Expiration	**No. of children with Cr (n)**	10	10		1.00
		No. of Cr	0.98 (0.91)	0.73 (1.74)	U= 39.00	0.66
		No. of coarse Cr	0.46 (0.92)	0.45 (0.68)	U= 49.50	0.97
		No. of fine Cr	0.20 (0.24)	0.25 (0.38)	U= 54.00	0.66
		IDW	3.60 (1.62)	3.19 (2.01)	U=35.00	0.45
		LDW	2.43 (1.12)	2.77 (0.84)	U= 38.00	0.60
		2CD	12.53 (4.73)	12.47 (3.73)	U= 38.00	0.60
		F	181.26 (224.07)	173.13 (67.48)	U= 35.00	0.45
Lateral Left	**Inspiration**	**No. of children with Cr (n)**	7	10		0.31
		No. of Cr	0.25 (0.51)	0.58 (0.50)	U= 15.50	0.09
		No. of coarse Cr	0.16 (0.44)	0.3 (0.44)	U= 23.50	0.40
		No. of fine Cr	0.13 (0.20)	0.08 (0.53)	U= 28.50	0.76
		IDW	3.85 (1.47)	3.87 (2.09)	U=24.50	0.47
		LDW	2.86 (1.00)	3.04 (1.19)	U= 30.00	0.92
		2CD	12.06 (5.01)	13.23 (7.35)	U= 27.00	0.68
		F	177.53 (63.93)	144.47 (176.84)	U= 31.00	1.00
	Expiration	**No. of children with Cr (n)**	11	11		1.00
		No. of Cr	0.37 (0.71)	0.65 (0.84)	U= 32.00	0.11
		No. of coarse Cr	0.29 (0.48)	0.45 (0.83)	U= 29.50	0.07
		No. of fine Cr	0.08 (0.23)	0.13 (0.21)	U= 49.50	0.71
		IDW	3.69 (2.00)	3.93 (1.08)	U=53.00	0.92
		LDW	2.85 (1.00)	2.75 (1.15)	U= 47.50	0.61
		2CD	12.15 (3.38)	12.34 (4.16)	U= 51.00	0.81
		F	157.44 (120.47)	149.34 (240.01)	U= 54.00	0.97

Posterior Right	**Inspiration**	**No. of children with Cr (n)**	9	9		1.00
		No. of Cr	0.20 (0.40)	0.28 (1.73)	U= 34.00	0.89
		No. of coarse Cr	0.14 (0.16)	0.24 (0.55)	U= 24.00	0.54
		No. of fine Cr	0.00 (0.09)	0.08 (0.81)	U= 29.50	0.28
		IDW	3.54 (1.82)	3.35 (1.83)	U=30.50	0.61
		LDW	2.81 (0.99)	2.71 (1.17)	U= 33.00	0.82
		2CD	13.58 (4.86)	12.01 (5.68)	U= 28.00	0.48
		F	137.60 (92.74)	149.90 (195.01)	U= 27.00	0.42
	Expiration	**No. of children with Cr (n)**	9	10		
		No. of Cr	0.67 (0.66)	0.79 (1.27)	U= 36.00	0.73
		No. of coarse Cr	0.60 (0.50)	0.56 (1.12)	U= 39.50	0.93
		No. of fine Cr	0.13 (0.13)	0.25 (0.35)	U= 22.00	0.11
		IDW	3.45 (0.56)	3.50 (0.98)	U=33.00	0.55
		LDW	3.09 (0.78)	2.67 (0.53)	U= 24.00	0.16
		2CD	13.47 (2.53)	10.69 (3.07)	U= 22.00	0.11
		F	145.02 (79.85)	183.18 (94.86)	U= 30.00	0.39
Posterior Left	**Inspiration**	**No. of children with Cr (n)**	11	10		1.00
		No. of Cr	0.43 (0.40)	0.71 (0.85)	U= 29.00	0.13
		No. of coarse Cr	0.22 (0.34)	0.43 (0.74)	U= 37.50	0.37
		No. of fine Cr	0.05 (0.13)	0.20 (0.38)	U= 27.00	0.09
		IDW	3.63 (2.11)	2.97 (1.57)	U=43.00	0.66
		LDW	3.27 (0.39)	2.80 (0.96)	U= 26.00	0.08
		2CD	13.88 (3.28)	12.99 (3.71)	U= 35.00	0.30
		F	137.07 (19.97)	152.10 (22.04)	U= 19.00	0.02*
	Expiration	**No. of children with Cr (n)**	10	11		1.00
		No. of Cr	0.83 (1.08)	1.55 (2.28)	U= 39.50	0.44
		No. of coarse Cr	0.68 (0.99)	0.36 (1.21)	U= 45.50	0.74
		No. of fine Cr	0.20 (0.29)	0.69 (1.17)	U= 21.50	0.03*
		IDW	3.82 (1.83)	3.25 (1.83)	U=30.00	0.14
		LDW	3.05 (0.62)	2.62 (0.63)	U= 29.00	0.12
		2CD	14.92 (3.25)	11.19 (3.24)	U= 16.00	0.009*
		F	154.54 (99.60)	175.49 (34.07)	U= 44.00	0.68

Results are median (inter-quartile range), unless otherwise stated.

[1]Mann Whitney U test; LRTI: lower respiratory tract infection; Cr: crackles; IDW: initial deflection width; LDW: largest defection width; 2CD: two cycle duration; *F*; frequency;* ρ<0.05



Legend: 1/3 Insp.: early inspiration; 2/3 Insp.: mid inspiration; 3/3 Insp.: late inspiration; 1/3 Exp.: early expiration; 2/3 Exp.: mid of expiration; 3/3 Exp.: late expiration; LRTI: lower respiratory tract infection; *p<0.05

Figure 4 - Crackles' mean number per breathing phase in children aged 0 to 2 years old (all chest sites of auscultation).

Healthy children (G3) and children with LRTI (G4) aged 3 to 5 years old presented differences in the number, type and IDW of crackles. Considering all chest sites of auscultation, children with LRTI presented a higher number of inspiratory crackles (G3: M 0.50 IQR 0.49 vs. G4: M 0.70 IQR 0.21 p=0.03), especially fine crackles (G3: M 0.11 IQR 0.21 vs. G4: M 0.17 IQR 0.23 p=0.001) than healthy children (Table 6). This phenomena was observed mainly during the 2/3 of inspiration (G3: M 0.17 IQR 0.17 vs. G4: M 0.30 IQR 0.79 p=0.06) (Figure 5).

All children presented crackles in at least one chest location. Children with LRTI had a higher number of inspiratory crackles at the anterior left (G3: M 0.25 IQR 0.48 vs. G4: M 1.53 IQR 2.61 p=0.02), lateral left (G3: M 0.50 IQR 0.58 vs. G4: M 0.83 IQR 2.09 p=0.04) and posterior left (G3: M 0.29 IQR 0.42 vs. G4: M 1.21 IQR 1.85 p=0.02) sites. At the lateral left site, children with LRTI presented more coarse crackles than healthy peers (G3: M 0.25 IQR 0.25 vs. G4: M 0.66 IQR 2.50 p=0.008); however at the posterior left site it was the mean number of fine crackles that was significantly increased (G3: M 0 IQR 0.17 vs. G4: M 0.26 IQR 0.31 p=0.006). The IDW was shorter in the children with LRTI at the anterior right site during expiration (G3: M 3.08 IQR 0.57 vs. G4: M

2.98 IQR 0.55 p=0.04) and longer at the anterior left site during inspiration (G3: M 1.90 IQR 2.04 vs. G4: M 3.34 IQR 1.27 p=0.02) (Table 6).

No differences were found for the remaining locations and parameters of crackles in both children aged 0 to 2 and 3-to 5 years old and coarse crackles were the most common type of crackle founded in both groups (Table 6).

Table 6- Crackles' parameters during inspiration and expiration in children aged 3 to 5 years old.

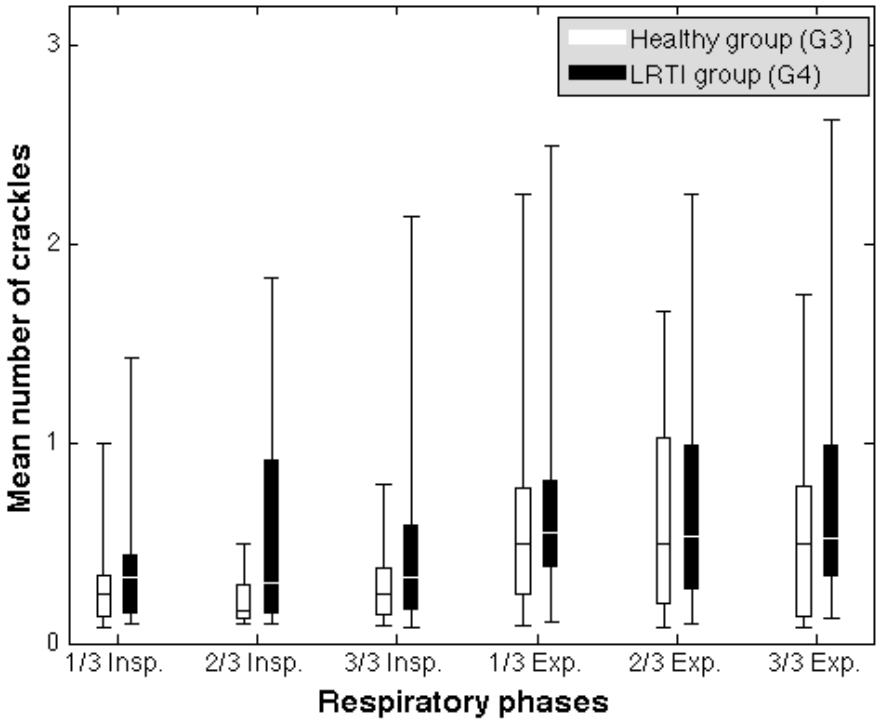
Chest Locations	Position in the BC	GROUPS / VARIABLES	3-5 G3 Healthy (n=9)	3-5 G4 LRTI (n=9)	Test Value	p-value
All Locations	**Inspiration**	**No. of children with Cr (n)**	9	9		1.00
		No. of Cr	0.50 (0.49)	0.70 (0.21)	U= 722.00	0.03*
		No. of coarse Cr	0.31 (0.48)	0.43 (0.75)	U= 765.00	0.07
		No. of fine Cr	0.11 (0.21)	017 (0.23)	U= 684.00	0.01*
		IDW	3.22 (1.81)	3.58 (1.59)	U=865.50	0.32
		LDW	2.98 (0.92)	2.84 (0.48)	U= 883.50	0.40
		2CD	12.62 (5.49)	12.43 (4.81)	U= 922.00	0.59
		F	141.65 (55.38)	151.100 (70.81)	U= 952.00	0.77
	Expiration	**No. of children with Cr (n)**	9	9		1.00
		No. of Cr	1.44 (1.97)	1.43 (1.57)	U= 1108.50	0.33
		No. of coarse Cr	1.00 (1.54)	1.14 (1.38)	U= 1098.50	0.30
		No. of fine Cr	0.17 (0.39)	0.25 (0.34)	U= 1220.00	0.37
		IDW	3.72 (1.04)	3.47 (1.16)	U=1195.00	0.71
		LDW	2.98 (0.70)	3.04 (0.45)	U= 1160.50	0.54
		2CD	13.85 (4.11)	13.62 (2.95)	U= 1227.00	0.88
		F	138.70 (95.20)	143.19 (54.94)	U= 1155.00	0.52
Anterior Right	**Inspiration**	**No. of children with Cr (n)**	7	8		1.00
		No. of Cr	0.71 (0.11)	0.78 (0.87)	U= 23.00	0.61
		No. of coarse Cr	0.63 (0.42)	0.55 (0.66)	U= 25.50	0.78
		No. of fine Cr	0.13 (0.20)	0.18 (0.38)	U= 17.00	0.23
		IDW	3.14 (1.61)	3.04 (1.86)	U=22.00	0.54
		LDW	3.05 (0.43)	2.81 (2.62)	U= 12.00	0.07
		2CD	12.86 (1.18)	11.66 (3.26)	U= 15.00	0.23
		F	167.82 (27.73)	163.52 (118.76)	U= 20.00	0.40
	Expiration	**No. of children with Cr (n)**	9	8		1.00
		No. of Cr	0.50 (1.45)	1.33 (1.21)	U= 26.50	0.37
		No. of coarse Cr	0.50 (1.20)	1.15 (0.87)	U= 32.50	0.74
		No. of fine Cr	0.18 (0.34)	0.26 (0.99)	U= 25.00	0.32
		IDW	3.72 (0.79)	2.98 (0.42)	U=14.00	0.04*
		LDW	3.08 (0.57)	2.93 (0.55)	U= 25.50	0.32
		2CD	13.67 (1.75)	12.64 (2.59)	U= 19.00	0.11
		F	145.57 (126.94)	158.13 (124.64)	U= 33.00	0.82
Anterior Left	**Inspiration**	**No. of children with Cr (n)**	7	6		1.00
		No. of Cr	0.25 (0.48)	1.53 (2.61)	U= 5.00	0.02*
		No. of coarse Cr	0.25 (0.25)	0.66 (2.50)	U= 3.00	0.008*
		No. of fine Cr	0.10 (0.25)	0.24 (1.27)	U= 11.00	0.18
		IDW	1.90 (2.04)	3.34 (1.27)	U=14.00	0.02*
					U= 5.00	

		LDW	2.97 (1.77)	2.91 (0.61)	U= 20.00	0.95
		2CD	9.61 (10.25)	12.19 (3.82)	U= 19.00	0.53
		F	132.75 (423.90)	152.56 (65.24)		0.84
	Expiration	**No. of children with Cr (n)**	7	9		0.46
		No. of Cr	0.59 (0.70)	0.83 (1.94)	U= 26.00	0.61
		No. of coarse Cr	0.38 (0.68)	0.75 (1.64)	U= 26.50	0.61
		No. of fine Cr	0.10 (0.13)	0.18 (0.34)	U= 20.00	0.25
		IDW	3.65 (1.43)	3.52 (1.84)	U=28.00	0.76
		LDW	2.63 (1.04)	2.95 (0.37)	U= 28.00	0.76
		2CD	12.27 (3.57)	13.48 (4.44)	U= 23.00	0.41
		F	140.00 (237.41)	142.18 (28.67)	U= 22.00	0.35
Lateral Right	**Inspiration**	**No. of children with Cr (n)**	8	8		1.00
		No. of Cr	0.56 (0.42)	0.29 (0.31)	U= 12.00	0.05
		No. of coarse Cr	0.50 (0.52)	0.17 (0.30)	U= 21.00	0.28
		No. of fine Cr	0.15 (0.31)	0.12 (0.13)	U= 25.00	0.51
		IDW	3.17 (1.43)	3.40 (2.88)	U=26.00	0.57
		LDW	2.40 (2.10)	2.89 (2.53)	U= 28.00	0.72
		2CD	11.01 (7.63)	10.98 (11.24)	U= 29.00	0.80
		F	199.15 (774.66)	185.17 (782.30)	U= 32.00	1.00
	Expiration	**No. of children with Cr (n)**	8	8		1.00
		No. of Cr	2.49 (2.53)	0.94 (1.45)	U= 20.00	0.23
		No. of coarse Cr	1.80 (2.07)	0.61 (1.29)	U= 24.50	0.44
		No. of fine Cr	0.33 (0.88)	0.21 (0.54)	U= 21.50	0.28
		IDW	3.65(1.15)	3.51 (1.26)	U=31.00	0.96
		LDW	3.05 (1.11)	3.14 (0.38)	U= 27.00	0.65
		2CD	14.30 (4.22)	13.86 (2.66)	U= 32.00	1.00
		F	159.06 (252. 10)	134.76 (21.52)	U= 26.00	0.57
Lateral Left	**Inspiration**	**No. of children with Cr (n)**	7	9		0.47
		No. of Cr	0.50 (0.58)	0.83 (2.09)	U= 14.50	0.04*
		No. of coarse Cr	0.40 (0.28)	0.70 (1.81)	U= 18.00	0.17
		No. of fine Cr	0.13 (0.17)	0.20 (0.42)	U= 24.00	0.23
		IDW	3.39 (2.36)	4.39 (1.93)	U=23.00	0.41
		LDW	3.07 (1.00)	2.87 (0.98)	U= 30.00	0.92
		2CD	13.00 (6.38)	14.04 (3.55)	U= 30.00	0.92
		F	139.96 (46.68)	127.400 (110.27)	U= 25.00	0.54
	Expiration	**No. of children with Cr (n)**	8	9		1.00
		No. of Cr	1.13 (2.35)	1.67 (2.20)	U= 26.00	0.37
		No. of coarse Cr	0.71 (2.13)	1.00 (1.92)	U= 24.00	0.28
		No. of fine Cr	0.15 (0.22)	0.25 (0.48)	U= 24.00	0.28
		IDW	4.19 (2.62)	3.60 (1.56)	U=31.00	0.67
		LDW	2.88 (1.36)	3.04 (0.77)	U= 24.00	0.28
		2CD	14.12 (8.26)	13.88 (3.68)	U= 29.00	0.54
		F	128.27 (252.59)	124.37 (113.19)	U= 26.00	0.37
Posterior Right	**Inspiration**	**No. of children with Cr (n)**	4	8		0.13
		No. of Cr	0.61 (0.62)	0.49 (0.82)	U= 14.00	0.81
		No. of coarse Cr	0.48(0.64)	0.37 (0.42)	U= 14.00	0.81
		No. of fine Cr	0.06 (0.28)	0.14 (0.26)	U= 13.00	0.68
		IDW	3.95 (1.21)	3.47 (2.07)	U=12.00	0.57
		LDW	2.78 (0.50)	2.86 (0.77)	U= 13.00	0.68
		2CD	14.20 (3.46)	13.11 (4.95)	U= 12.00	0.57
		F	143.00 (56.46)	146.06 (25.21)	U= 12.00	0.57
	Expiration	**No. of children with Cr (n)**	8	9		1.00

		No. of Cr	1.79 (2.86)	1.78 (1.25)	U= 35.50	0.96
		No. of coarse Cr	1.46 (2.60)	1.44 (1.22)	U= 36.00	1.00
		No. of fine Cr	0.13 (0.32)	0.17 (0.30)	U= 33.00	0.82
		IDW	3.96 (0.62)	3.54 (0.84)	U=26.00	0.37
		LDW	2.95 (0.54)	2.90 (0.62)	U= 33.00	0.82
		2CD	13.94 (1.49)	13.62 (2.68)	U= 29.00	0.54
		F	144.99 (97.68)	142.38 (65.86)	U= 34.00	0.89
Posterior Left	**Inspiration**	**No. of children with Cr (n)**	9	8		1.00
		No. of Cr	0.29 (0.42)	1.21 (1.85)	U= 12.50	0.02*
		No. of coarse Cr	0.29 (0.30)	1.00 (1.45)	U= 21.00	0.17
		No. of fine Cr	0.00 (0.17)	0.26 (0.31)	U= 8.00	0.006*
		IDW	3.58 (2.48)	3.66 (2.31)	U=35.00	0.96
		LDW	3.04 (0.91)	2.71 (2.46)	U= 24.00	0.28
		2CD	12.47 (5.60)	12.47 (5.38)	U= 27.00	0.42
		F	135.30 (46.78)	165.43 (226.30)	U= 26.00	0.37
	Expiration	**No. of children with Cr (n)**	9	8		1.00
		No. of Cr	1.70 (1.53)	2.60 (3.32)	U= 20.00	0.14
		No. of coarse Cr	1.29 (1.89)	2.13 (1.28)	U= 25.00	0.32
		No. of fine Cr	0.29 (0.43)	032 (0.70)	U= 31.50	0.67
		IDW	3.61 (1.42)	3.91 (0.90)	U=27.00	0.42
		LDW	2.95 (0.73)	3.00 (0.46)	U= 33.00	0.82
		2CD	14.43 (4.65)	13.60 (2.60)	U= 36.00	1.00
		F	126.16 (58.36)	149.05 (51.76)	U= 26.00	0.37

Results are median (inter-quartile range), unless otherwise stated.

[1]Mann Whitney U test; LRTI: lower respiratory tract infection; Cr: crackles; IDW: initial deflection width; LDW: largest defection width; 2CD: two cycle duration; *F*; frequency;* ρ<0.05



Legend: 1/3 Insp.: early inspiration; 2/3 Insp.: mid inspiration; 3/3 Insp.: late inspiration; 1/3 Exp.: early expiration; 2/3 Exp.: mid of expiration; 3/3 Exp.: late expiration; LRTI: lower respiratory tract infection.

Figure 5 - Crackles' mean number per breathing phase in children aged 3 to 5 years old (all chest sites of auscultation).

4. DISCUSSION

Healthy children and children with LRTI of different ages present ARS (i.e., crackles and wheezes). The Wh% and the mean number of crackles were the parameters that most differed between healthy and children with LRTI in both age ranges (0-2 and 3-5 years old) and therefore may be the best discriminative parameters between the groups.

In this study, children with LRTI were mainly male and presented family history of respiratory diseases and exposure to environmental risk factors (e.g., carpets and animals), in accordance with the risk factors for developing LRTI (66-68). However, healthy children were the ones presenting a higher rate of parental smoking, known as a major risk factor for lower lung volume, poor lung function and increased susceptibility for LRTI (65). General society is widely aware of the risks of passive smoking in children. Therefore, two factors can be in the source of this finding: i) having children with LRTI might have influenced parent's smoking habits and ii) the answer to this question may have been influenced by social desirability bias, because the survey was answered in the presence of the researcher.

Children with LRTI achieved higher scores at the modified Wang Score than healthy peers, and most of them presented mild severity LRTI (score≤3 at the modified Wang Score). According to the literature, this is the most frequent presentation of the disease in infants, and the illness is self-limiting (69). This was an expected result, as all of the children with LRTI in this study were outgoing patients, not requiring hospitalisation. An increased heart rate was observed only in those with LRTI aged 0 to 2 years old compared with healthy children and no differences were found for the respiratory rate. Increased respiratory rate has been reported as a signal commonly observed in patients with LRTI and its absence correlates with the lack of pneumonia in children (70). Therefore, this result may be explained by the low severity of the LRTI presented in this sample, resulting in little or absence of changes in heart/respiratory rates (69, 71). Also, children aged 0 to 2 years old presented higher grades of LRTI severity than those aged 3 to 5 years old, justifying the increased heart rate compared with their healthy peers.

Adventitious respiratory sounds were found in healthy children and children with LRTI of both age ranges; however ARS parameters varied between groups. Wheezes were observed in a reduced number of children, both healthy and with LRTI. The absence of this ARS may be justified by the pathophysiology of LRTI which consists in distal airway oedema and secretions (5). Wheezes are only produced until the 7th generation of the tracheobronchial tree, due to flow constrictions after this point (19, 72), therefore few wheezes can be expected in LRTI. In those presenting wheezes, low frequency wheezes were the most observed in all groups and children with LRTI showed a higher number of wheezes and higher expiratory Wh% than healthy peers. Low frequency wheezes are often associated with airway obstruction due to the secretions movement, leading to flow limitation and therefore wheezing sound (14, 19, 73). Also, children with LRTI reported high levels of productive cough, which is consistent with an excess of secretion production. Type of wheezing (i.e., monophonic or polyphonic) and Wh% is strongly related with the degree of bronchial obstruction and thus with the severity of the disease (54, 74, 75). In the present study, children with LRTI presented approximately the same Wh% (2.63-13.09%), as previously reported (5.5-11.90%) (34). Moreover, wheezes were mainly expiratory monophonic, which supports the results of mild severity LRTI (score≤3) found with the modified Wang Score (69).

Inspiratory and expiratory crackles were found in all children in at least one chest location, which is in accordance with previous studies conducted in healthy adults and adults with pneumonia (76, 77). However, healthy children presented a lower number of crackles than children with LRTI. The crackles found in healthy children may be explained by the increased chest wall compliance, low

number of elastin fibres and low levels of surfactant presented in children. These factors lead to a higher closing volume, which means that airways may collapse at higher volumes during expiration (before reaching the functional residual capacity) and pose an impediment to air entry at the beginning of inspiration (78). When the inspiratory air faces these closed airways, a change in the elastic stress occurs, causing the sudden open of the closed airways and producing the sound waveform of a crackle (79, 80). Conversely, expiratory crackles may have been caused by sudden airway closure events that are similar in mechanism but opposite in sign and less energetic than the explosive opening events that generate inspiratory crackles (79, 80). Children with LRTI presented higher number of inspiratory and expiratory crackles, probably due to the lung inflammation resulting from the disease itself (58). The mean number of crackles found in the present study for children with LRTI was between 1.5 and 2.5 per respiratory cycle, which is in line with the results of the only available study assessing crackles parameters in 27 children with bronchiolitis (1.14-2.48) (34).

Positioning within the respiratory cycle is also a crucial feature to consider in crackles analysis, as it informs about the lung pathological process (52). Difference in the mean number of crackles between healthy and children with LRTI was observed in all respiratory phases in children aged 0 to 2 years old, but specially in mid inspiration in children aged 3 to 5 years old. Previous studies conducted in adults with pneumonia have reported that, in the onset of the disease, crackles are mainly present in mid inspiration. This is in accordance with our results, as the majority of children with pneumonia were those aged 3 to 5 years old (58). Nevertheless, expiratory crackles were the most prevalent type of crackles in both populations, suggesting the sudden opening and closure of the airway in more proximal locations (72, 80, 81).

Similar to the position of crackles in the respiratory cycle, its duration also informs about the place of crackles occurrence (i.e., smaller airways produce crackles of shorter duration) (58). In this study, children aged 0 to 2 years showed shorter inspiratory crackles than healthy peers (i.e., IDW, LDW and 2CD). Therefore, even though both populations had more crackles in proximal locations, children with LRTI seem to have more small airways affected than healthy peers. This is in accordance with the pathophysiology of LRTI, as mentioned earlier in this discussion. Nevertheless, coarse crackles were the most common type of crackle founded in both healthy children and children with LRTI, similar to the results obtained previously by Piirilä (82) in adults with pneumonia. It is known that the genesis of coarse crackles is related with two main phenomena: i) boluses of gas passing through airways as they open and close intermittently (19) and ii) an excessive amount

of secretions in the airways causing airway collapse and reopening (52, 58). The first mechanism is more suitable to explain coarse crackles found in healthy children, as no sputum production was reported or found in their cardio-respiratory assessment. Furthermore, due to the increased functional residual capacity in children, some amount of air trapping during expiration may occur (78), causing these boluses of gas to pass in the next respiratory cycles. In children with LRTI, both mechanisms are likely to be causing crackles as the majority of legal representatives reported the presence of sputum in children's cough.

The analysis of ARS per site of auscultation may provide information about the concrete location of the infection (61, 83). In children with LRTI aged 0 to 2 years old, the wheezes and crackles were dispersed in the chest wall, which may suggest that children differed in the locations of the lungs affected by the infection. However, for those aged 3 to 5 years old, crackles were placed mostly at left chest locations (anterior, lateral and posterior) possibly indicating that left lung infections were predominant in this group. Nevertheless, imaging techniques that could confirm this hypothesis were not possible to obtain, and these results should be further investigated.

4.1. Limitations & Future work

The present study has some limitations that need to be acknowledged. Firstly, the severity of the LRTI was assessed using the modified Wang Score, a scale specifically design to assess bronchiolitis severity. This score is based on five clinical signals (i.e., wheezing, retractions, peripheral oxygen saturation, respiratory rate and heart rate) that also often present in LRTI, and therefore it is believed that, even though the scale was not constructed to assess LRTI in general, an accurate classification was still obtained. LRTI is highly prevalent in children aged less than 5 years old (1, 2), and the correct identification of the severity of the disease is crucial to decide on the most adequate treatment (28). Therefore, it is highly recommended to develop new methods to assess LRTI severity in children that can be reliable and easily implemented in the clinical practice.

Secondly, in this study only one recording per chest location was performed, as small children are extremely restless and agitated. Respiratory sounds reliability have been assessed in adults with bronchiectasis and cystic fibrosis, showing "good" to "excellent" levels of intrasubject reliability (intraclass correlation coefficients between 0.76 and 0.94) (59). It was assumed that respiratory sounds are stable and only one recording per chest location is sufficient, however children's lung anatomy and physiology differ widely from adults, which may affect respiratory sounds stability. Therefore, studies assessing respiratory sounds reliability in healthy children and children with LRTI

are needed to confirm if respiratory sounds are stable between recordings, and can be used as a diagnostic and outcome measure in children with respiratory diseases.

Finally, the sample size used in this study may not be sufficient to detect truly significant changes between healthy children and children with LRTI (type II error). A sample size estimation with 85% power at 5% significance level determined that a significant difference in the mean number of crackles per respiratory phase, would be detected with a minimum of 12 children in each group (76). Nevertheless, this calculation was performed based on a study conducted in adults with pneumonia, which could not reflect the mean number of crackles per breathing phase in children with LRTI. Therefore, this exploratory study is a first step towards the use of CORSA in the objective assessment of children and should be used as a pilot study to compute accurate sample sizes in future studies.

5. Conclusions

Healthy children and children with LRTI of different ages present ARS (i.e., crackles and wheezes). The Wh% and the mean number of crackles were the parameters that most differed between healthy children and those with LRTI in both age ranges (0-2 and 3-5 years old) and therefore may be the best discriminative parameters between groups. Previous studies have reported that the presence of ARS may be indicative of respiratory disease, however this new findings highlight the need to focus essentially in the parameters of ARS than in their presence.

Computerised respiratory sounds are an objective and simple measure to acquire information on the respiratory system status and function of less collaborative population, such as children, where other clinical tests requiring patients collaboration cannot be performed (e.g., spirometry, interviews). Therefore, further research on computerised respiratory sounds is required to move towards a more an easy but objective and precise measure to early diagnose and continuously monitoring respiratory diseases in children.

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Appendix I – Ethics' approval

COMISSÃO DE ÉTICA

da **Unidade Investigação em Ciências da Saúde - Enfermagem** (UICISA: E)

da **Escola Superior de Enfermagem de Coimbra** (ESEnfC)

Parecer Nº P186-10/2013

Título do Projecto: Estabelecimento de valores de referência para sons pulmonares adventícios e o teste de marcha com carga progressiva modificado em crianças saudáveis e com patologia respiratória

Identificação do Proponente

Nome(s): Alda Sofia Pires de Dias Marques; Ana Luísa Araújo Oliveira; Sara Sequeira Silva

Filiação Institucional: Escola Superior de Saúde da Universidade de Aveiro

Investigador Responsável/Orientador: Profª Alda Sofia Pires de Dias Marques

Relator: José Carlos Amado Martins

Parecer

Trata-se de estudo descritivo, correlacional, tendo como objetivo principal: "estabelecer valores de referência para os sons pulmonares adventícios e para o teste de marcha com carga progressiva em crianças com patologia respiratória e saudáveis, contribuindo assim para melhor compreensão das patologias, e consequentemente, melhorar o diagnóstico, monitorização e tratamento de crianças com problemas respiratórios".

Será utilizada amostra de conveniência, com crianças (idade<18 anos), com diagnóstico de patologia respiratória pediátrica e crianças saudáveis. Os critérios de inclusão/exclusão são definidos. Colheita de dados de dezembro de 2013 a dezembro de 2016.

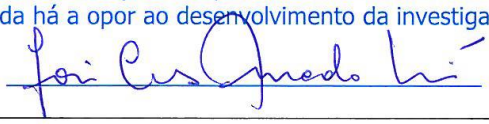
A caracterização decorrerá no Hospital Santa Maria (Porto), Banda Filarmónica Ovarense (Ovar), Clube do Povo de Esgueira (Aveiro) e Clínica Estrela Esteves Unipessoal (Aveiro), instituições com as quais existe protocolo de colaboração com a Universidade de Aveiro e que já aprovaram o estudo, sendo apresentados comprovativos.

São definidas as medidas e testes a utilizar que têm um carácter não invasivo.

É garantida a confidencialidade e o anonimato da informação em todo o processo de recolha e análise. Será solicitado o consentimento do responsável legal de cada criança e à própria criança, em função do seu grau de maturidade. São apresentados os documentos para informação e obtenção do consentimento na forma escrita, que cumprem os requisitos éticos.

Não são previstos desvantagens ou riscos para os participantes.

Tendo em consideração o exposto, é entendimento desta Comissão que, em termos éticos, nada há a opor ao desenvolvimento da investigação.

O relator: 

Data: 20/11/2013 O Presidente da Comissão de Ética: 

Exima Direção Clínica

Da

Cliria, Hospital Privado de Aveiro

A Comissão de Ética reuniu no dia 12 do corrente mês de fevereiro de 2014 com as ausências justificadas do Dr. António Simões, Dra. Filipa Loreto e Dr. Miguel Varela.

Analisou um pedido de colheita de dados para um estudo científico intitulado "sons pulmonares adventícios em crianças saudáveis e com patologia respiratória", formulado pela Dra. Ana Oliveira, aluna a frequentar o Mestrado em Fisioterapia da Escola Superior de Saúde da Universidade de Aveiro, sob a orientação científica da Dra. Alda Sofia Pires de Dias Marques, para ser efetuado nas consultas de pediatria da Cliria, Hospital Privado de Aveiro.

O estudo insere-se no mestrado de fisioterapia.

Tem o consentimento informado obtido pelos tutores das crianças.

Tem autorização dos médicos pediátricos colaborantes.

A investigadora, em reunião da comissão, prestou todos os esclarecimentos suscitados de ordem ética sobre os princípios, meios e fins do estudo.

A comissão é de parecer que estão salvaguardados os princípios éticos inerentes a este estudo pelo que entende nada a haver eticamente que impeça a sua realização.

Aveiro, 12 de fevereiro de 2014

Pel' Comissão de Ética

Cliria - Hospital Privado de Aveiro, S.

(Amorim Figueiredo)

Appendix II – Institutions’ approval

Autorização Institucional

Eu, Hélio Armando Vieira Andrade

responsável pela instituição Beneficência Portuguesa

declaro que fui informado dos objetivos do estudo científico intitulado: "Estabelecimento de valores de referência para os sons pulmonares adventícios e o teste de marcha com carga progressiva modificado em crianças saudáveis e com patologia respiratória", e concordo em autorizar a execução da mesma nesta instituição. Caso necessário, a qualquer momento como instituição CO-PARTICIPNATE desta investigação poderemos revogar esta autorização, se comprovada atividades que causem algum prejuízo à esta instituição ou ainda, a qualquer dado que comprometa o sigilo da participação dos integrantes desta instituição. Declaro também, que não recebemos qualquer pagamento por esta autorização bem como os participantes também não receberão qualquer tipo de pagamento.

Hélio Armando Vieira Andrade	09-07-2013	
Representante da Instituição	Data	Assinatura
Sara Silva	09-07-2013	Sara Isabel Silva
Investigadora	Data	Assinatura

Autorização Institucional

Eu, Alfredo Estrela Esteves

responsável pela instituição Clínica Estrela Esteves Unipessoal declaro que fui informado dos objetivos do estudo científico intitulado: "Sons pulmonares adventícios em crianças saudáveis e com patologia respiratória", e concordo em autorizar a execução da mesma nesta instituição. Caso necessário, a qualquer momento como instituição CO-PARTICIPNATE desta investigação poderemos revogar esta autorização, se comprovada atividades que causem algum prejuízo à esta instituição ou ainda, a qualquer dado que comprometa o sigilo da participação dos integrantes desta instituição. Declaro também, que não recebemos qualquer pagamento por esta autorização bem como os participantes também não receberão qualquer tipo de pagamento.

ALFREDO ESTRELA ESTEVES	18/10/2013	
Representante da Instituição	Data	Assinatura
Ana Pereira	18/10/13	Ana Pereira
Investigadora	Data	Assinatura

Autorização Institucional

Eu, Mª de Lurdes Brandão Sena Campos

responsável pela instituição Hospital de Santa Maria - Porto

declaro que fui informado dos objetivos do estudo científico intitulado: "Estabelecimento de valores de referência para os sons pulmonares adventícios e o teste de marcha com carga progressiva modificado em crianças saudáveis e com patologia respiratória", e concordo em autorizar a execução da mesma nesta instituição. Caso necessário, a qualquer momento como instituição CO-PARTICIPNATE desta investigação poderemos revogar esta autorização, se comprovada atividades que causem algum prejuízo à esta instituição ou ainda, a qualquer dado que comprometa o sigilo da participação dos integrantes desta instituição. Declaro também, que não recebemos qualquer pagamento por esta autorização bem como os participantes também não receberão qualquer tipo de pagamento.

LURDES SENDA CAMPOS	10/9/2013	FRANCISCANAS MISSIONÁRIAS DE NOSSA SENHORA FUNDAÇÃO SANTA MARIA HOSPITAL SANTA MARIA - PORTO Inst. Part. de Solidariedade Social Reg. nº 11/08 Cont.: 508 079 543 R. CAMÕES, 906 4049-025 PORTO
Representante da Instituição	Data	Assinatura
Ana Oliveira	10/9/2013	Francisca Pereira
Investigadora	Data	Assinatura

Appendix III – Modified Wang Score

Modified Wang Score

Pont.	Frequência respiratória (cpm)	Sibilâncias	Retrações	Saturação periférica de Oxigénio (SpO_2)	Frequencia cardíaca (bpm)
0	<30	Nenhuma	Nenhuma	≥95%	<140
1	31-45	Audíveis no final da expiração e apenas com estetoscópio	Apenas intercostal	92-94%	140-159
2	46-60	Audíveis durante toda a expiração ou sem o estetoscópio durante a expiração	Traqueoesternal	90-91%	160-179
3	>60	Audíveis durante a inspiração e a expiração sem estetoscópio	Severa e com adejo nasal	< 90%	≥ 180

Fonte: Wang EE, Milner RA, Navas L, Maj H (1992). Observer agreement for respiratory signs and oxymetry in infants hospitalized with lower respiratory infections. Am Rev Respir Dis;145(1):106-109

Annex I – Information sheets (Health Institutions)

Folha de informação ao representante legal

A aluna Ana Luísa Araújo Oliveira a frequentar o Mestrado em Fisioterapia da Escola Superior de Saúde da Universidade de Aveiro, sob a orientação científica da Professora Doutora Alda Sofia Pires de Dias Marques, vem por este meio solicitar-lhe a autorização para a participação do seu representando legal no estudo clínico intitulado: "Sons pulmonares adventícios em crianças saudáveis e com patologia respiratória".
Mas, antes de decidir, é importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por favor, leia a informação com atenção e discuta a participação do seu representando, com outros se assim o entender. Se houver algo que não esteja claro para si ou necessitar de informação adicional, por favor não hesite em contactar a aluna ou a sua orientadora (contactos no final deste documento).

Muito obrigado desde já por ler a informação.

Qual é o propósito do estudo?
Este estudo visa contribuir para o estabelecimento de valores de referência para os sons pulmonares adventícios (SPA) em crianças saudáveis e com patologia respiratória infantil. Os SPA são largamente utilizados pelos profissionais de saúde para o diagnóstico e monitorização de diversas patologias respiratórias em crianças. Contudo, não são ainda conhecidos valores de referência de SPA em crianças com patologias respiratórias nem em crianças saudáveis, o que pode afetar a precisão do diagnóstico clínico e a prescrição e monitorização do tratamento. Para que seja possível determinar estes valores de referência, venho então solicitar-lhe autorização para que o seu representando legal participe neste estudo que será realizado no Hospital de Santa Maria (Porto), Clinica Estrela Esteves Unipessoal, Lda (Aveiro), Cliria - Hospital Privado de Aveiro, SA e Banda Filarmónica de Ovar.

Porque foi o meu representando escolhido?
O seu representando foi escolhido porque deu entrada no Hospital de Santa Maria (Porto), Clinica Estrela Esteves Unipessoal, Lda ou Cliria - Hospital Privado de Aveiro, SA e tem idade inferior a 18 anos.

Tenho de aceitar a participação do meu representando?
A decisão de autorizar a participação do seu representando ou não é completamente sua. No entanto, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de saúde prestados a si ou ao seu representando agora ou no futuro.

O que acontecerá se autorizar a participação do meu representando?
Se decidir participar vai-lhe ser pedido que assine dois formulários de consentimento informado, um para si e outro para a aluna de mestrado. Após receber o consentimento informado devidamente assinado, será feita uma avaliação do estado de saúde geral do seu representando. Ser-lhe-á medido o peso e a altura, e realizar-se-á um teste muito simples para avaliar a sua capacidade respiratória, designado de espirometria (apenas se a criança tiver idade ≥5 anos). Este teste consiste em soprar para um tubo, com a maior força e durante o máximo de tempo possível. Ser-lhe-á também pedido que responda a um questionário de para avaliar as atividades físicas que o seu representando realiza.

De seguida, um oxímetro de pulso, equipamento semelhante a um relógio, ser-lhe-á colocado no pulso para medir a quantidade de oxigénio que o seu sangue está a transportar e a frequência cardíaca. Por último, serão gravados os sons que os seus pulmões estão a fazer naquele momento, durante aproximadamente 20 segundos, com um estetoscópio digital ligado a um computador portátil.
A aplicação do protocolo terá a duração de aproximadamente 30 minutos e nenhum dos testes realizados provoca qualquer desconforto para a criança.

Quais são os efeitos secundários dos procedimentos do estudo?

Não existem efeitos secundários de participar no estudo.

Quais são as possíveis desvantagens e riscos se resolver autorizar a participação do meu representando?
Não existem quaisquer desvantagens ou riscos de participar no estudo.

Quais são os possíveis benefícios se eu resolver autorizar a participação do meu representando?
Não existem benefícios diretos de participar no estudo. No entanto, a informação obtida neste estudo poderá ajudar a desenvolver valores de referência para os SPA, largamente utilizados na prática clínica, permitindo uma melhor avaliação e monitorização de crianças com problemas respiratórios.

A participação será confidencial?
Toda a informação recolhida no decurso do estudo será mantida estritamente confidencial. Os dados recolhidos serão salvaguardados com um código e palavra-passe, para que ninguém os possa identificar. Apenas a aluna responsável pelo projeto e a sua orientadora terão acesso aos dados.

O que acontecerá aos resultados do estudo?
Os resultados do estudo serão analisados e incorporados num dissertação de Mestrado e alguns serão publicados em Jornais e/ou conferências de finalidade científica. No entanto, em nenhum momento o seu representando será identificado/a.

Contacto para mais informações sobre o estudo
Se pretender obter mais informações sobre o estudo, pode telefonar ou escrever para:
Ana Oliveira, Alda Marques
Escola Superior de Saúde da Universidade de Aveiro,
Universidade de Aveiro,
Campus de Santiago,
Edifício III, 3810-193, Aveiro
Telefone: 913937469, 234 247 113 ou 234 372 462
e-*mail: alao@ua.pt; amarques@ua.pt*

Muito obrigado por ter lido esta informação

Se pretender obter uma cópia de qualquer relatório ou publicação, por favor indique o seu contacto de e-mail no espaço seguinte:

_____

Annex III – Information sheets (School of music)

Folha de informação ao encarregado de educação

As alunas Ana Luísa Araújo Oliveira e Sara Sequeira Silva, a frequentar o Mestrado em Fisioterapia da Escola Superior de Saúde da Universidade de Aveiro, sob a orientação científica da Professora Doutora Alda Sofia Pires de Dias Marques, vêm por este meio solicitar-lhe a autorização para a participação do seu educando no estudo clínico intitulado: "Estabelecimento de valores de referência para os sons pulmonares adventícios e o teste de marcha com carga progressiva modificado em crianças saudáveis e com patologia respiratória".
Mas, antes de decidir, é importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por favor, leia a informação com atenção e discuta a participação do seu educando, com outros se assim o entender. Se houver algo que não esteja claro para si ou necessitar de informação adicional, por favor não hesite em contactar as alunas ou a sua orientadora (contactos no final deste documento).

Muito obrigado desde já por ler a informação.

Qual é o propósito do estudo?
Este estudo visa estabelecer valores de referência para os sons pulmonares adventícios e para o teste de marcha com carga progressiva modificado em crianças com patologia respiratória e saudáveis (5-17 anos). Estes testes permitem uma avaliação objetiva e segura da condição cardio-respiratória de crianças sendo por isso largamente utilizado pelos fisioterapeutas para prescrever exercício físico em crianças com várias patologias como por exemplo, com asma e fibrose cística. No entanto, ainda não se encontram estabelecidos valores de referência que permitam diferenciar com segurança a normalidade das condições patológicas. Para que seja possível determinar estes valores de referência, venho então solicitar-lhe autorização para que o seu educando participe neste estudo que será realizado no Hospital de Santa Maria (Porto), Clinica Estrela Esteves Unipessoal, Lda (Aveiro), Cliria - Hospital Privado de Aveiro, SA e Banda Filarmónica de Ovar.

Porque foi o meu educando escolhido?
O seu educando foi escolhido porque se encontra a frequentar Banda Filarmónica de Ovar que deu permissão institucional para a realização do estudo e porque o seu educando não apresenta qualquer tipo de problema respiratório.

Tenho de aceitar a participação do meu educando?
A decisão de autorizar a participação do seu educando ou não é completamente sua. Se decidir autorizar vai-lhe ser pedido que assine dois formulários de consentimento informado, um para si e outro para as alunas de mestrado. No entanto, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de educação prestados ao seu educando agora ou no futuro.

O que acontecerá se autorizar a participação do meu educando?
Se decidir participar vai-lhe ser pedido que preencha o documento anexo a esta folha de informação relativamente aos problemas de saúde e medicação habitualmente utilizada pelo seu educando e que o entregue, bem como ao consentimento informado, ao docente que entrou em contacto consigo.

Após receber o consentimento informado devidamente assinado, as alunas dirigir-se-ão à instituição de educação do seu educando e procederão à aplicação do protocolo. Ser-lhe-á medido o peso e a altura, e realizar-se-á um teste muito simples para avaliar a sua capacidade de trazer o ar para fora dos pulmões, com um aparelho designado de espirómetro. Este teste consiste em soprar para um tubo, com a maior força possível. Ser-lhe-á também pedido que responda a um questionário de atividade física para avaliar as atividades físicas que o seu educando realiza dentro e fora da instituição.
De seguida, ser-lhe-á perguntado o quão difícil é para ele respirar, numa escala com diferentes graus de falta de ar. Depois, um oxímetro de pulso, equipamento semelhante a um relógio, ser-lhe-á colocado no pulso para medir a quantidade de oxigénio que o seu sangue está a transportar e a frequência cardíaca. De seguida, serão gravados os sons que os seus pulmões estão a fazer naquele momento, durante aproximadamente 20 segundos, com um estetoscópio digital ligado a um computador portátil. A força muscular dos membros inferiores também será medida através de um teste muito simples que consiste em realizar a extensão do joelho com a máxima força possível contra resistência de um aparelho chamado dinamómetro.
Depois de retiradas todas estas medidas, será realizado o teste de marcha com carga progressiva (modificado). Durante o teste será pedido ao seu educando que caminhe rapidamente, em velocidades crescentes, num percurso de 10 m delimitados por 2 cones (estando um cone em cada extremidade do percurso), que devem ser contornados pelo individuo. O oxímetro que lhe foi colocado, avaliará a saturação periférica de oxigênio (SpO_2) e a frequência cardíaca em intervalos 15 segundos para garantir que o teste decorre em total segurança. Após uma hora de repouso, repetir-se-á o teste. A aplicação do protocolo terá a duração de aproximadamente 30 minutos.
Nenhum destes testes provoca qualquer desconforto e serão realizados em horários compatíveis com as atividades educacionais, de forma a não afetar a o programa letivo de atividades.

Quais são os efeitos secundários dos procedimentos do estudo?

Não existem efeitos secundários de participar no estudo.

Quais são as possíveis desvantagens e riscos se resolver autorizar a participação do meu educando?
Não existem quaisquer desvantagens ou riscos de participar no estudo.

Quais são os possíveis benefícios se eu resolver autorizar a participação do meu educando?
Não existem benefícios diretos de participar no estudo. No entanto, a informação obtida neste estudo poderá ajudar a desenvolver valores de referência para um teste largamente utilizado na fisioterapia, permitindo uma melhor avaliação e monitorização de crianças com problemas respiratórios.

A participação será confidencial?
Toda a informação recolhida no decurso do estudo será mantida estritamente confidencial. Os dados recolhidos serão salvaguardados com um código e palavra-passe, para que ninguém os possa identificar. Apenas as alunas responsáveiss pelo projeto e a sua orientadora terão acesso aos dados.

O que acontecerá aos resultados do estudo?
Os resultados do estudo serão analisados e incorporados em dissertações de Mestrado e alguns serão publicados em Jornais e/ou conferências de finalidade científica. No entanto, em nenhum momento o seu educando será identificado.

Contacto para mais informações sobre o estudo
Se pretender obter mais informações sobre o estudo, pode telefonar ou escrever para:
Ana Oliveira, Sara Silva e Alda Marques
Escola Superior de Saúde da Universidade de Aveiro,
Universidade de Aveiro,
Campus de Santiago,
Edifício III, 3810-193, Aveiro
Telefone: 913937469, 234 247 113 ou 234 372 462
e-*mail: alao@ua.pt; sarassilva@ua.pt; amarques@ua.pt*

Muito obrigado por ter lido esta informação.

✂_____

Se pretender obter uma cópia de qualquer relatório ou publicação, por favor indique o seu contacto de e-mail no espaço seguinte:

_____

Annex IV – Informed Consent

CONSENTIMENTO INFORMADO

Título do Projeto: Sons pulmonares adventícios em crianças saudáveis e com patologia respiratória

Nome da Orientadora: Prof. Doutora Alda Sofia Pires de Dias Marques
Nome da aluna de Mestrado: Ana Luísa Araújo Oliveira

Por favor leia e marque com uma cruz (X) os quadrados seguintes.

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer. ☐
2. Eu percebo a participação do meu encarregando é voluntária e que ele é livre de desistir, em qualquer altura, sem dar nenhuma explicação, sem que isso afete qualquer serviço de saúde que lhe é prestado. ☐
3. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e que só os investigadores responsáveis pelo projeto têm acesso a eles. E dou portanto, autorização para que os mesmos tenham acesso a esta informação. ☐
4. Eu compreendo que os resultados do estudo serão publicados numa dissertação de mestrado e jornais e/ou conferências de finalidade científica sem que haja qualquer quebra de confidencialidade e anonimato. E dou portanto, autorização para a utilização dos dados para esses fins. ☐
5. Eu confirmo que o meu encarregando foi questionado acerca da sua vontade em participar no estudo e que nenhuma avaliação foi realizada contra a sua vontade, sendo assim respeitada a sua autonomia. ☐
6. Eu concordo então em participar no estudo. ☐

_____	_____	_____	_____
Nome do Participante	Representante Legal	Data	Assinatura

_____	_____	_____
Investigadora	Data	Assinatura

Annex V –Publication I - Respiratory sounds in healthy people: A systematic review

Respiratory Medicine (2014) 108, 550–570

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

Respiratory sounds in healthy people: A systematic review

Ana Oliveira [a], Alda Marques [a,b,*]

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[b] Unidade de Investigação e Formação sobre Adultos e Idosos, Porto, Portugal

Received 29 July 2013; accepted 6 January 2014
Available online 18 January 2014

KEYWORDS
Computerised respiratory sound analysis;
Normal respiratory sound;
Adventitious respiratory sound;
Healthy population

Summary
Background: There is a lack of systematised information on respiratory sounds of healthy people. This impairs health professionals from differentiating respiratory sounds of healthy people from people with respiratory diseases, which may affect patients' diagnosis and treatment. Therefore, this systematic review aimed to characterise respiratory sounds of healthy people.
Methods: The Web of knowledge, MEDLINE, EMBASE and SCOPUS databases were searched and studies using computerised analyses to detect/characterise respiratory sounds in healthy people were included. Data were extracted using a structured table-format.
Results: Sixteen cross-sectional studies assessing respiratory sounds in 964 subjects (aged 1day-70yrs) were included: 13 investigated normal respiratory sounds (frequency, intensity and amplitude) and 3 adventitious respiratory sounds (crackles and wheezes). The highest sound frequencies were observed at the trachea (inspiration: 447–1323 Hz; expiration: 206–540 Hz). Women (444–999 Hz) and infants (250–400 Hz) presented the highest frequencies at maximum power. Inspiratory sounds were more intense at the left posterior lower lobe (5.7–76.6 dB) and expiratory sounds at the trachea (45.4–85.1 dB). Nevertheless, studies establishing direct comparisons between inspiratory and expiratory sounds showed that inspiratory sounds presented the highest intensities ($p < 0.001$). Amplitude was higher at the left upper anterior chest (1.7 ± 0.8 V) and lower at the right posterior lower lobe (1.2 ± 0.7 V). Crackles were the adventitious respiratory sound most frequently reported.
Conclusions: Respiratory sounds show different acoustic properties depending on subjects' characteristics, subjects' position, respiratory flow and place of recording. Further research with robust study designs, different populations and following the guidelines for computerised respiratory sound analysis are urgently needed to build evidence-base.

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Introduction

Respiratory auscultation performed with a conventional stethoscope is an assessment method used by many health professionals to evaluate and monitor patients with respiratory diseases [1,2]. In clinical practice, respiratory diseases may be diagnosed when normal respiratory sounds (NRS) are perceived as having frequencies and intensities that differ from normal [3] or when adventitious respiratory sounds (ARS) are present, namely crackles and wheezes [4,5]. Current research have been reporting on the potential of ARS to provide useful clinical information, as they are directly related to movement of air, changes within lung tissue and morphology and presence of secretions [6]. It is also known that different sections of the airways produce ARS with different characteristics (i.e., their duration and frequency varies; more proximal airways produce coarser crackles and higher frequency wheezes [4,7—9]), which can aid to localise the respiratory problem within the tracheobronchial tree. However, as the detection of ARS is usually performed with conventional stethoscopes, the correct interpretation of these sounds is critically dependent on the experience and hearing ability of the users [10], their knowledge about the range of frequencies and intensities that can be found in NRS and ARS [3] and their capacity to use the same nomenclature and memorise different sound patterns [11]. Furthermore, it can also be influenced by the stethoscope properties [12].

To overcome these limitations, research efforts are being conducted to automatically detect, quantify and characterise respiratory sounds, namely through computerised respiratory sound analysis [13]. Computerised respiratory sound analysis consists on recording subjects' respiratory sounds with an electronic device and then analysing and classifying the acoustic signal based on specific characteristics [14]. This innovative approach is being continuously updated with the use of electronic methods of signal transduction, conditioning, amplification and algorithms for a precise and automatic detection/classification of NRS and ARS [15—17]. However, reports on the classification of computerised respiratory sounds in healthy subjects are dispersed in the literature, unclear and mixed with findings from non-computerised respiratory sound analyses [18,19]. The lack of systematised information impairs health professionals from using this objective technology in their clinical practice and its use could potentially enhance patients' diagnosis treatment and monitoring.

Thus, the purpose of the present systematic review was to characterise respiratory sounds of healthy people through the use of computerised respiratory sound analysis.

Methods

Information sources and search strategy

A systematic electronic literature search was conducted from February to April 2013 on the following electronic databases: Pubmed (1950—2013), Science Direct (1823—2012), Web of Knowledge (1970—2012) and Scopus (1960—2013). A previous search was conducted in the Cochrane database to exclude the existence of reviews with the same purpose as the present one. Search terms were based on a combination of the following keywords: ("healthy people" OR "healthy population" OR "normal people" OR "normal population" OR healthy OR child*) AND ("computerised analyses" OR "digital auscultation" OR "electronic auscultation" OR "automatic auscultation") AND ("breath sounds" OR "lung sounds" OR "respiratory

sounds" OR "added lung sounds" OR "abnormal lung sounds" OR "adventitious lung sounds" OR "adventitious respiratory sounds" OR crackl* OR wheez* OR frequenc* OR duration OR amplitude OR intensity OR "sound spectrum"). 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.

Eligibility criteria and study selection

Articles were included if they: i) used computerised respiratory sound analysis to characterise respiratory sounds in healthy adults or children; ii) were experimental (participants are randomly assigned to experimental or control groups), quasi-experimental (participants are not randomly assigned to experimental or control groups) or observational studies (studies observing human behaviour) [20,21]; iii) were full-text papers published in scientific journals or in conference proceedings; and iv) were written in English, Spanish, French or Portuguese. Articles were excluded if the study i) was conducted in animals; ii) aimed to validate algorithms or instruments for sound acquisition; or iii) aimed to verify the stability of respiratory sounds. 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 study.

This systematic review was reported using the systematic review method proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [22,23].

Data collection process

Two reviewers independently assessed all potential studies identified as a result of the search strategy. A consensus method concerning the selection and inclusion of studies was used to solve any disagreements. The studies were selected based on their titles and abstracts. When the title, abstract and keywords were relevant for the scope of the review, the full-text article was downloaded and read carefully to decide its inclusion in the final report.

Quality assessment

The quality of the included studies was assessed with a checklist adapted by Petticrew and colleagues [24] based on the 'Crombie criteria' for the assessment of cross-sectional studies [25], according to previous systematic reviews [26]. The checklist provides a list of 8 questions to measure the study quality based on research design, recruitment strategy, response rate, sample representativeness, measures and statistics used and power. Quality was assessed independently by two reviewers. 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 categorised as slight (0.0—0.20), fair (0.21—0.40), moderate (0.41—0.60), substantial (0.61—0.80) or almost perfect ($\geq$0.81) agreement [27]. This statistical analysis was performed using PASW Statistics (version 18.0, SPSS Inc., Chicago, IL). Disagreements between raters were further resolved through discussion.

Data extraction and synthesis of results

Data from the included articles were extracted in a structured table-format comprising the following topics: publication details (first author, year of publication); study design; characteristics of the participants (total number, age and gender), data collection protocol (subjects' position and anatomic sites, place and duration of the recordings), target respiratory flows, recording device, sound analysis (sound filters and algorithms applied and sampling rate) outcome measures and findings.

Results

Study selection

The databases search identified 1445 records. After duplicates removal, 1408 records were screened for relevant content. During the title, abstract and keyword screening, 1379 articles were excluded. The full-text of 29 potentially relevant articles was assessed and 27 articles were excluded due to the following reasons: i) did not assess computerised respiratory sounds ($n = 6$); ii) did not included healthy people ($n = 9$); iii) studies were conducted in animals ($n = 1$); iv) were written in German ($n = 1$); v) aimed to validate algorithms ($n = 5$); vi) did not present quantitative data on respiratory sounds ($n = 1$); and vii) analysed artificial respiratory sounds (e.g. sound producer, web source) ($n = 4$). Therefore, 2 original articles were included. The search for relevant articles within the reference list of the included and excluded papers by full-text analysis retrieved 14 additional studies. Therefore, a total of 16 studies were included in this review (Fig. 1).

Quality assessment

The quality of the included studies, using the 'Crombie criteria', is presented in Table 1. All studies had an appropriate research design and used objective measures. Five studies failed to report the recruitment strategy used [3,28—31]. As no study reported dropouts, the response rate indicator was considered in all studies. Studies presented the appropriate statistical analyses, however, they did not use representative samples or justified their sample size. Evidence of bias was not considered to be present, despite the use of convenience samples. The inter-rater agreement was almost perfect ($k = 0.873$; 95% confidence interval = 0.616—1.00; $p = 0.001$).

Study characteristics

Studies included in this review ranged from 1983 to 2008 and used cross-sectional methodologies. A total of 964

healthy subjects (68% male) participated in the studies, 169 were smokers and 258 non-smokers. Most subjects were adults (n = 909; 94%; 18–70 years old) and 6% (n = 54) were children (ages ranged from 1 day to 13 years old).

Three studies provided information on ARS (frequency, number and position in the breathing cycle [31–33]) and thirteen on NRS (frequency [3,18,34–38], intensity [6,18,28–30,34,36,39] and amplitude [40]). Respiratory sounds were recorded mainly from the posterior chest (right and left) [3,18,28–36,38–41], 5 studies recorded from the anterior chest [28,30,32,34,40], 6 from the trachea [29,31,33,35,38,39] and 1 from the nasal cavity [37]. Recordings were performed with the subjects standing [3,28,29,40], lying [18,31,33,36] or sitting [6,30,38,39], with different recording devices such as conventional [3,30,33,37,40], electret [28,31,32] and condenser [35] microphones, piezoelectric contact sensors [6,29,34,35,38], sound transducers [18] and contact accelerometers [39].

Eleven studies controlled subjects' respiratory flows at different targets from 0.015 to 3 l/s using pneumotachographs [18,28–30,34–36,38–41]. In two other studies subjects were asked to breath normally [3] or deeper than normal [3,33].

To analyse the sound data, studies applied different filters (50–2240 Hz), sample rates (4000–12,000 Hz) and

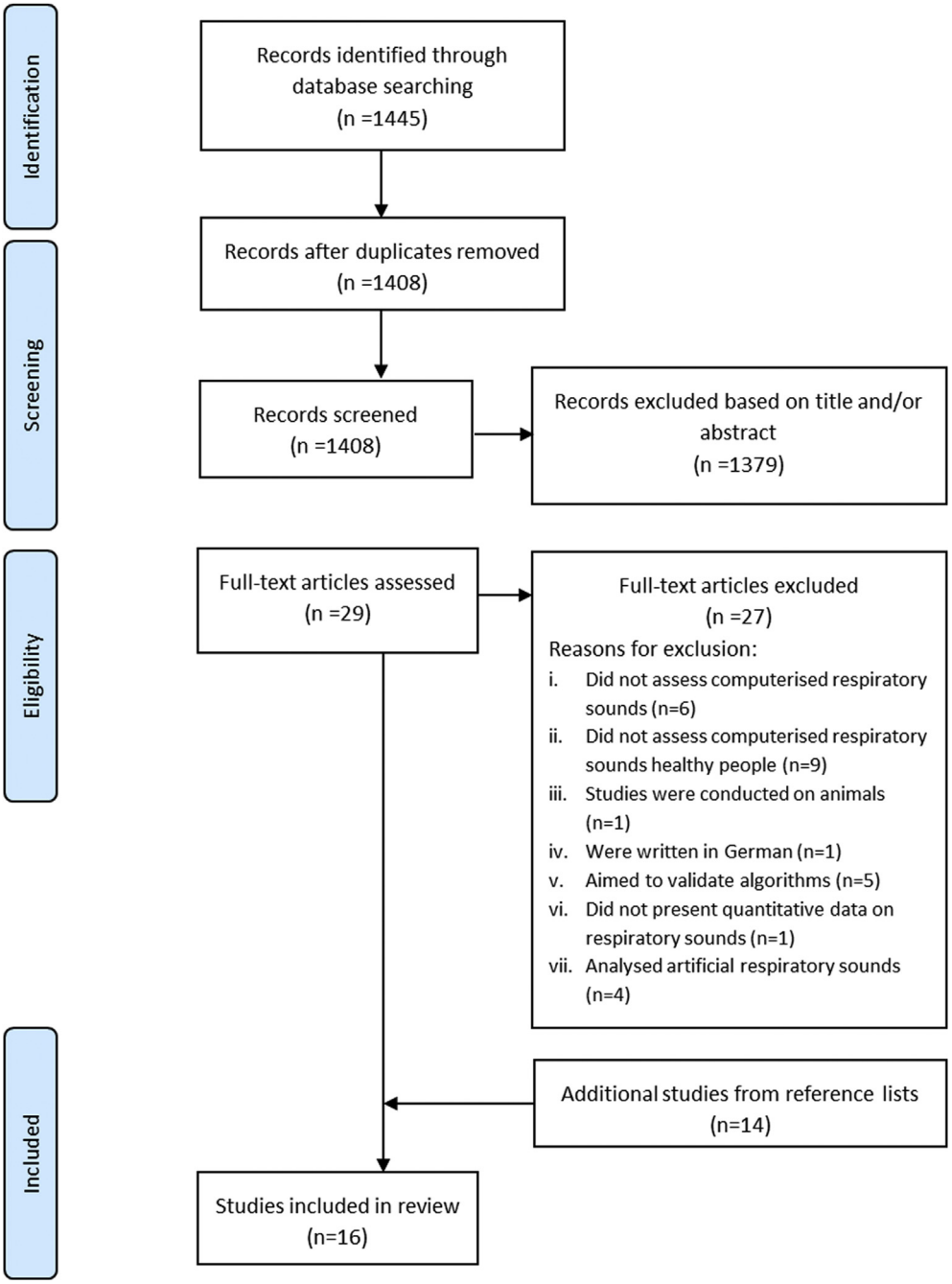

Figure 1 PRISMA flow diagram of the included studies.

Table 1 Quality assessment of cross sectional studies.

Author and year	Appropriate research design?	Appropriate recruitment strategy?	Response rate?	Is sample representative? (all clinic populations)	Objective and reliable measures?	Power calculation/ justification of numbers?	Appropriate statistical analysis?	Evidence of bias?	Quality indicators Met (MS = 8)
Kraman, 1983	√	√			√		√	Convenience sample	4
Kraman, 1984	√				√		√	Convenience sample	3
Hidalgo, 1991	√				√		√	Convenience sample	3
Bettencourt, 1994	√	√			√		√	Convenience sample	4
Malmberg, 1994	√	√			√		√	Convenience sample	4
Malmberg, 1995	√	√			√		√	Convenience sample - suspected to have coronary heart disease	4
Gavriely, 1995	√	√			√		√	Convenience sample	4
Gavriely, 1996	√				√		√	Convenience sample - not stated from where were recruited	3
Pasterkamp, 1996a	√	√			√		√	Convenience sample	4
Pasterkamp, 1996b	√	√			√		√	Convenience sample	4
Kompis, 1997	√				√		√	Convenience sample	3
Jones, 1999	√	√			√		√	Convenience sample	4
Kiyokawa, 2002	√	√			√		√	Convenience sample	4
Murphy, 2004	√	√			√		√	Convenience sample	4
Seren, 2005	√	√			√		√	Convenience sample	4
Murphy, 2008	√				√			Convenience sample	2

MS: maximal score.

Table 2 Characteristic of the respiratory sounds of healthy people.

Study, Year	Type of study	Participants	Data collection protocol	Target flows	Recording device	Sound analyses	Outcomes measures	Findings
Kraman, 1983	Cross-sectional	9 adults (2 smokers). 20-37yrs 5M:4F	-Subjects were in a stand position -Records were made from the back of the thorax (5 cm from the spine and 4 cm above the point of just detectable diaphragmatic dullness, and 1 cm lateral to this point) and from the upper left and right anterior chest (at the midsternum in the 2nd intercostal space, 1 cm lateral to this point and on opposite sides of the sternum, 8 cm apart, in the left and right 2nd intercostal spaces).	Targets flows of at least 2 l/s. Only flow rates above 1.3 l/s were analysed.	Phonopneumography 2 microphones	-Band pass-filtered between 200 and 625 Hz - sampling: 5000 Hz	NRS: - Amplitude	**Inspiratory Sounds** RUAC: 1.3 ± 0.7 V LUAC: 1.7 ± 0.8 V RPLL: 1.2 ± 0.7 V LPLL: 1.4 ± 0.8 V
Kraman, 1984	Cross-sectional	4 adults (1 smoker) 27—38yrs 5M:0F	- Subjects were in a stand position - Records were made from the chest, over the second right intercostal space and mid clavicular line and approximately 6 cm from the spine, immediately below the lower edge of the right scapula. - 20 consecutive breathing cycles were taken	Targets flows between 1.2 and 4 l/s.	2 electret microphone	- High pass filtered at 200 Hz - sampling: 5000 Hz	NRS: - Intensity	**Inspiratory Sounds** RUAC: 68.6 ± 5.7 dB LUAC: 79.1 ± 4.3 dB RPLL: 72.8 ± 3.5 dB LPLL: 76.6 ± 2.1 dB
Hidalgo, 1991	Cross-sectional	G1:35 children 0—13yrs 18M:17F G2: 5 non-smoking adults 34—43yrs 3M:2F	- Subjects were in a stand position - Inside a double-walled acoustic chamber - Records were made from the chest wall over the RPLL at a distance of 0.7 cm.	Children breathed spontaneously Adults breathed at an increased depth and rate	1 air coupled microphone	-Low-pass filter at 2000 Hz - Sampling: 4096 Hz - 12-bit resolution - FFT. - TEWA - Automatic detection	NRS: - Frequency	**Inspiratory sounds** RPLL Children vs Adults F25: 125 ± 6 Hz; 139 ± 15 Hz, $p = 0.02$ F50: 169 ± 14 Hz; 194 ± 26 Hz, $p = 0.03$ F75: 252 ± 19 Hz; 277 ± 34 Hz, $p = 0.11$ F95: 527 ± 52 Hz; 467 ± 45 Hz, $p = 0.02$ F25, F50, F75 differed significantly from children aged 0—3yrs and adults ($p < 0.005$)

(*continued on next page*)

Table 2 (*continued*)

Study, Year	Type of study	Participants	Data collection protocol	Target flows	Recording device	Sound analyses	Outcomes measures	Findings
								F95 differed significantly from children aged >9yrs and adults ($p < 0.05$) F25, F50, F75 decreased significantly with age and height ($p < 0.001$).
Bettencourt, 1994	Cross-sectional	15 adults	- Records were made from eight sites anteriorly, 24 laterally, and 18 posteriorly.	NS	Electret microphone connected to the diaphragm of a Littman stethoscope	- Band pass-filtered between 80 and 2000 Hz TEWA	ARS: - Wheeze - Crackle	All chest locations: Wheeze:0; Crackle:1; Late insp: 1 ± 2; Fine: 1 ± 2 Upper chest: Crackle: 7 ± 26%; Wheeze: 0% Right chest: Crackle: 23 ± 37%; Wheeze: 0%
Malmberg, 1994	Cross-sectional	6 non-smoking adults 22—31yrs 3M:3F	- Subjects were in a sitting position - In a quiet room - Records were made from the chest wall over the RPLL and from the trachea. - 4—6 consecutive breathing cycles were taken	Targets flow of 1.25 l/s;	Phonopneumography 1 air-coupled condenser microfone with a preamplifier 1 piezoelectric contact sensor	- High pass filter at 100 Hz - 13-bit resolution - sampling: 12000 Hz - overlapped segment method	NRS: - Frequency	**Inspiratory sounds** Trachea F_{max}: 93 ± 12 Hz F50: 447 ± 186 Hz RPLL F_{max}: 106 ± 10 Hz F50: 142 ± 8 Hz **Expiratory sounds** Trachea F_{max}: 99 ± 8 Hz F50: 540 ± 174 Hz RPLL F_{max}: 104 ± 6 Hz F50: 131 ± 6 Hz
Malmberg, 1995	Cross-sectional	11 non-smoking adults 44—66yrs 11M:0F	- Records were made from the chest wall over the RPLL, approximately 10 cm below the margin of the scapula and 15 cm to the right of the spine and from the trachea at the right side of the cricothyroid cartilage. - 8—10 consecutive breathing cycles were taken	Targets flow of 1.25 l/s; Only sound samples of inspiratory sounds that occurred at flows from 1.0/s to target flow were used	Phonopneumography 1 coupled condenser microfone 1 piezoelectric contact sensor	- High pass filter at 50 Hz - 13-bit resolution - sampling: 12000 Hz - FFT	NRS: - Frequency	**Inspiratory sounds** Trachea F_{max}: 154 ± 157 Hz F50: 766 ± 178 Hz F75: 1323 ± 192 Hz RPLL F_{max}: 117 ± 18 Hz F50: 206 ± 14 Hz F75: 301 ± 33 Hz

Gavriely, 1995	Cross-sectional	353 subjects (166 smokers) M: 44 ± 11yrs F: 40 ± 11yrs. 272M:81F	- In a quiet room. - Records were made from the right anterior chest at the mid clavicular line in the second intercostal space, and in the RPLL and LPLL at the eighth to tenth intercostal spaces in the mid scapular line	Targets flows of 1 l/s	Phonopneumography 3 piezoelectric contact sensors	- Band pass-filtered between 75 and 2000 Hz - sampling: 4000 Hz - 12-bit resolution - FFT - Regression lines	NRS: - Frequency - Intensity	**Inspiratory sounds** (males) RUAC − A_{high}: −13.6 ± 1.8 dB/oct; A_{low}: −6.3 ± 6.4 dB/oct; F_{int}: 160 ± 45 Hz; P_{int}: 53 ± 28; F_{max}: 822 ± 247 Hz RPLL − A_{high}: −14.1 ± 1.9 dB/oct; A_{low}: −0.0 ± 14.6 dB/oct; F_{int}: 155 ± 39 Hz; P_{int}: 68 ± 61; F_{max}: 760 ± 227 Hz LPLL − A_{high}: −15.2 ± 2.6 dB/oct; A_{low}: −5.0 ± 7.0 dB/oct; F_{int}: 160 ± 17 Hz; P_{int}: 53 ± 41; F_{max}: 736 ± 201 Hz **Inspiratory sounds** (females) RUAC − A_{high}: −12.9 ± 1.7 dB/oct; A_{low}: −5.8 ± 5.6 dB/oct; F_{int}: 182 ± 52 Hz; P_{int}: 48 ± 21; F_{max}: 999 ± 265 Hz RPLL − A_{high}: −13.8 ± 2.0 dB/oct; A_{low}: −5.4 ± 5.2 dB/oct; F_{int}: 157 ± 15 Hz; P_{int}: 71 ± 32; F_{max}: 843 ± 133 Hz LPLL − A_{high}: −14.7 ± 2.6 dB/oct; A_{low}: −6.8 ± 1.4 dB/oct; F_{int}: 157 ± 16 Hz; P_{int}: 74 ± 29; F_{max}: 885 ± 247 Hz **Expiratory sounds** (males) RUAC − A_{high}: −14.9 ± 12.7 dB/oct; (*continued on next page*)

Table 2 (*continued*)

Study, Year	Type of study	Participants	Data collection protocol	Target flows	Recording device	Sound analyses	Outcomes measures	Findings
								A_{low}: -11.4 ± 14.0 dB/oct; F_{int}: 184 ± 81 Hz; P_{int}: 25 ± 22; F_{max}: 604 ± 123 Hz RPLL − A_{high}: -19.7 ± 5.1 dB/oct; A_{low}: -6.5 ± 7.1 dB/oct; F_{int}: 150 ± 16 Hz; P_{int}: 32 ± 45; F_{max}: 419 ± 112 Hz LPLL − A_{high}: -18.8 ± 4.4 dB/oct; A_{low}: -6.7 ± 5.9 dB/oct; F_{int}: 155 ± 30 Hz; P_{int}: 23 ± 17; F_{max}: 426 ± 87 Hz **Expiratory sounds** (females) RUAC − A_{high}: -13.4 ± 1.9 dB/oct; A_{low}: -4.7 ± 7.7 dB/oct; F_{int}: 173 ± 52; P_{int}: 28 ± 14; F_{max}: 794 ± 142 Hz RPLL − A_{high}: -20.3 ± 4.2 dB/oct; A_{low}: -5.3 ± 7.1 dB/oct; F_{int}: 147 ± 21 Hz; P_{int}: 30 ± 14; F_{max}: 420 ± 60 Hz LPLL − A_{high}: -17.7 ± 3.8 dB/oct; A_{low}: -8.0 ± 1.0 dB/oct; F_{int}: 140 ± 18 Hz; P_{int}: 44 ± 9; F_{max}: 444 ± 52 Hz
Gavriely, 1996	Cross-sectional	6 adults 29—70yrs 6M:0F	- Subjects were in a stand position; - In a quiet room	Targets flows of 0.5, 1.0, 1.5, 2.0, 2.5 and	Phonopneumography 3 piezoelectric contact sensors	- Band pass-filtered	NRS: - Intensity	**Inspiratory sounds** TR: 60.8 ± 37.7 dB; RUAC: 4.7 ± 2.2 dB;

			- Records were made from the trachea, right anterior chest at the mid clavicular line in the second intercostal space, and in the RPLL and LPLL at the eighth to tenth intercostal spaces in the mid scapular line - Over 10 consecutive breathing cycles were taken	3.0 l/s		between 75 and 2000 Hz - Sampling: 4800 Hz - 12-bit resolution - FFT		RPLL: 4.3 ± 1.6 dB; LPLL: 5.7 ± 1.7 dB RPLL and LPLL differed significantly ($p < 0.05$) RUAC and LPLL differed dignificantly ($p < 0.05$) **Expiratory sounds** TR: 85.1 ± 54.1 dB; RUAC: 2.3 ± 1.3 dB; RPLL: 1.9 ± 0.8 dB; LPLL: 2.5 ± 0.9 dB RPLL and LPLL differed significantly ($p < 0.05$)
Pasterkamp, 1996a	Cross-sectional	G1: 10 infants 1 ± 0.5days 5M:5F G2: 9 children 7 ± 0.8yrs 4M:5F G3: 10 non-smoking adults 30 ± 3.6yrs 5M:5F	Infants - Subjects were in a prone position; - In a quiet room - Records were made from the chest over the RPLL, below the scapula and approximately 2 cm lateral to the spine. Children and Adults - Subjects were in a prone position; - In the respiration acoustic laboratory - Records were made on the chest, over the RPLL, below the scapula and approximately 3—5 cm lateral to the spine.	Infants breathed spontaneously Children and adults had targets flow of 0.015 and 0.03l/s/kg ± 20% tolerance.	Phonopneumography 1 sound transducer	- Low-pass filtered at 2400 Hz - Sampling: 10.24 Hz - 12-bit resolution - FFT - Logarithmic transformation	NRS: - Frequency - Intensity	**Low flows (15 ml/s/kg):** - Inspiratory Sounds intensity < 100 Hz — Infants: 3.4 ± 2.6 dB; Children: 3.2 ± 2 dB; Adults: 1.5 ± 2.9 dB, $p < 0.05$ - Inspiratory sounds intensity < 300 Hz - Infants: 14.4 ± 3.7 dB Children: 15.1 ± 1.5 dB; Adults: 11.4 ± 3.2 dB, $p = 0.028$ **High flows (30 ml/s/kg ± 20%):** - Inspiratory Sounds intensity < 100 Hz - Children: 8.0 ± 4.1 dB;

(*continued on next page*)

Table 2 (*continued*)

Study, Year	Type of study	Participants	Data collection protocol	Target flows	Recording device	Sound analyses	Outcomes measures	Findings
								Adults: 9.2 ± 2.6 dB, $p < 0.05$ - Inspiratory Sounds intensity > 100 Hz- Children: 8.4 ± 1.7 dB; Adults: 9.7 ± 1.5 dB, $p = 0.107$ - Expiratory sounds 8/10 adults: F: 760 −1.735 Hz; Int: 5.4 −18.5 dB 9/9 children: F: 1040 −1595 Hz; Int: 6.3 −20.4 dB - Both Inspiratory and expiratory sounds F_{hi} was not different between children and adult ($p > 0.05$). Infants had higher F_{max} than either children or adults ($p < 0.01$). F_{hi} was not different among groups ($p = 0.176$) F_{lo}- infants: 126 ± 36 Hz; Children: 57 ± 38 Hz; Adults:79 ± 66 Hz, $p = 0.016$ Adults had lower F_{lo} and higher F_{hi} with increased flows

								($p < 0.05$). Children showed the same changes but also higher F_{max}, ($p < 0.05$).
Pasterkamp, 1996b	Cross-sectional	6 non-smoking adults 29—34yrs 6M.0F	- Subjects were in a sitting position - Records were made from the front the RPLL and at the trachea	Targets flows between 1.3 and 1.7 l/s.	Phonopneumography 2 contact accelerometers	- Band pass-filtered bellow 50 Hz - sampling: 10240 Hz - 12-bit resolution - FFT	NRS: - Intensity	**Inspiratory sounds** (>100 Hz) Trachea: 38.67 ± 1.02 dB RPLL: 17.17 ± 1.47 dB **Expiratory sounds** (>100 Hz) Trachea: 45.33 ± 1.58 dB RPLL: 11.50 ± 0.92 dB
Kompis, 1997	Cross-sectional	4 non-smoking adults 30—39yrs 4M:0F	- Subjects were in a sitting position - In the sound proof chamber - Records were made from the front chest and the back of the thorax	Targets flows of 2 l/s. Only flow rates within ±20% of the target flow were analysed.	Phonopneumography 16 microphones	- Band pass-filtered between 100 and 2000 Hz - sampling: 10240 Hz	NRS: - Intensity	**Average difference between inspiratory/ expiratory sounds** 150—300 Hz: 10.5 dB 300—600 Hz: 12.4 dB 600—1200 Hz: 11.4 dB **Compariso between the left and right hemithorax** Inspiratory Sounds (Front; Back): 150—300 Hz: −4 dB; 3.5 dB 300—600 Hz:−1.3 dB; 4.6 dB 600—1200 Hz: −0.9 dB; 3.4 dB Expiratory Sounds (Front; Back): 150—300 Hz: −4.3 dB; −5.7 dB 300—600 Hz:−2.6 dB; 2.1 dB 600—1200 Hz: −3.0 dB; 1.8 dB
Jones, 1999	Cross-sectional	11 aldults 16—26yrs 6M:5F	- Subjects were side lying and seated; - Records were made from the RPLL and the LPLL at the	Targets flows between 1.5 and 2 l/s.	Phonopneumography 3 microphone attached to 3 stethoscope chest	- sampling: 5000 Hz	NRS: - Intensity - Frequency	**Inspiratory sounds** Sitting (RPLL, LPLL) PI: 20.7 ± 6.3 dB, 25.6 ± 4.3 dB,

(*continued on next page*)

Table 2 (*continued*)

Study, Year	Type of study	Participants	Data collection protocol	Target flows	Recording device	Sound analyses	Outcomes measures	Findings
			eighth intercostal spaces in the mid scapular line - Over 5 consecutive breathing cycles were taken		piece			$p = 0.016$ F_{max}: 244 ± 51.9 Hz, 253 ± 22.9 Hz F_{mean}: 439.5 ± 96.8 Hz; 439.9 ± 107.2 Hz Left side lying (RPLL, LPLLL) PI: 15.7 ± 4.3 dB, 23.5 ± 5.1 dB, $p = 0.000$ F_{max}: 201.6 ± 57.6 Hz, 240.6 ± 31 Hz F_{mean}: 427.5 ± 126.9 Hz; 434.2 ± 109.1 Hz Right side lying (RPLL, LPLL) PI: 22.7 ± 4.2 dB, 19.7 ± 7.2 dB F_{max}: 278.4 ± 42.3 Hz, 236.6 ± 158 Hz F_{mean}: 429.5 ± 80.9 Hz; 445.6 ± 146.3 Hz **Expiratory sounds** Sitting (RPLL, LPLL) PI: 8.3 ± 3.2 dB, 10.2 ± 4.9 dB F_{max}: 192.6 ± 130.9 Hz, 172.6 ± 76.9 Hz F_{mean}: 552.5 ± 164.9 Hz; 516.1 ± 169.2 Hz Left side lying(RPLL, LPLL) PI: 8.7 ± 7.0 dB, 9.3 ± 6.5 dB F_{max}: 155.7 ± 77.5 Hz,

								148.5 ± 37.2 Hz F_{mean}: 532.1 ± 199.9 Hz; 386.7 ± 106.4 Hz Right side lying(RPLL, LPLL) PI: 11.2 ± 4.5 dB, 6.8 ± 4.2 dB F_{max}: 167.5 ± 69.4 Hz, 199.2 ± 146 Hz F_{mean}: 436.3 ± 156.8 Hz; 480.1 ± 144.13 Hz
Kiyokawa et al., 2002	Cross-sectional	5 non-smoking adults 21—50yrs 3M:2F	- Subjects were in a sitting position - In a body plethysmograph - Records were made from the chest over the RUPC, RPLL and LPLL - Over 5 consecutive breathing cycles were taken	Targets flows of 1.2 ± 0.2 l/s.	Phonopneumography 2 contact sensors in each recording site	- 12-bit resolution - Sampling 10240 Hz;	NRS: - Intensity	**Inspiratory sounds** RUAC 75—150 Hz: 10.0 ± 2.9 dB 150—300 Hz: 19.8 ± 5.0 dB 300—600 Hz: 25.2 ± 5.2 dB RPLL 75—150 Hz: 13.7 ± 2.7 dB 150—300 Hz: 20.9 ± 3.0 dB 300—600 Hz: 20.7 ± 3.9 dB LPLL 75—150 Hz: 12.7 ± 3.9 dB 150—300 Hz: 20.1 ± 3.7 dB 300—600 Hz: 23.2 ± 4.3 dB **Expiratory sounds** RUAC 75—150 Hz: 7.9 ± 4.8 dB 150—300 Hz: 16.9 ± 6.5 dB 300—600 Hz: 21.1 ± 8.9 dB RPLL

(*continued on next page*)

Table 2 (*continued*)

Study, Year	Type of study	Participants	Data collection protocol	Target flows	Recording device	Sound analyses	Outcomes measures	Findings
								75—150 Hz: 10.5 ± 2.9 dB 150—300 Hz: 15.0 ± 4.1 dB 300—600 Hz: 8.8 ± 6.1 dB LPLL 75—150 Hz: 7.9 ± 4.0 dB 150—300 Hz: 10.2 ± 3.9 dB 300—600 Hz: 9.4 ± 4.6 dB
Murphy, 2004	Cross-sectional	100 adults 69 ± 7yrs 52M:48F	- Subjects were in a supine position; - Records were made from the trachea and from the back of the torax - Two 20″ measurements were taken	Subjects breathed more deeply than normal, with their mouths open	1 regular microphone 14 microphones incorporated into a soft foam pad	- Crackle counter - Wheeze and rhonchus detector	ARS: - Wheeze - Crackle	**Inspiratory Sounds** Wheeze: Patients With Wheeze: 3 Crackle: Patients With Crackle: 28%; mean nBC: 2 ± 4 F: 387 ± 91 Hz **Expiratory sounds** Wheeze; Patients With Wheeze: 1 Crackle: Patients With Crackle: 9%; mean nBC: 4 ± 3; F: 402 ± 104 Hz
Seren, 2005	Cross-sectional	30 non-smoking adults 18—45yrs 13M:17F	- Records we made 0.5 cm inside the nostril of the nasal cavity *via* a 2-cm-long nasal prope.	NS	1 microphone with amplifier	- 16-bit resolution - Sampling: 44.1 Hz - FFT.	NRS: - Frequency	**Expiratory Sounds** Right Nose vs Left Nose HIS: 1254 ± 10.3 Hz vs 1375 ± 18.5 Hz, $p > 0.05$ LIS: 2453 ± 22.2 Hz vs 2234 ± 21.1 Hz, $p < 0.05$.
Murphy, 2008	Cross-sectional	334 participants	- Records were made from the back and lateral bases of the thorax - 6 microphones on the posterior right base, 6 on the	NS	16 microphones incorporated into a soft foam pad	Algorithm analyses acoustic energy versus time and detects wheezes,	ARS: - Wheeze - Crackle	**Inspiratory Sounds** Wheeze: Average wheeze rate (%):0 ± 4; Patients who wheeze

	posterior left base, 1 on the right lateral base, 1 on the left lateral base and 1 over the trachea	rhonchi and crackles	for >4% of the inspiration: 2% Among these patients, average wheeze frequency: 300 ± 136 Hz Crackle: Average crackle/ breath:1 ± 2 Patients with over 2 crackles/breath: 16 Among these patients, average crackle frequency: 371 ± 88 Hz **Expiratory sounds** Wheeze: Average wheeze rate (%):1 ± 5; Patients who wheeze for >4% of the inspiration: 2% Among these patients, average wheeze frequency: 309 ± 122 Hz Crackle: Average crackle/ breath:1 ± 1 Patients with over 2 crackles/breath: 8 Among these patients, average crackle frequency: 337 ± 106 Hz

Data are Mean ± Standard Deviation.

A_{high}: high frequency regression lines; A_{low}: low frequency regression lines; ARS: adventitious respiratory sounds; F: frequency; FFT: fast fourier transformation; F_{hi}: High frequencies; F_{int} = frequency at intersection of low and high frequency regression lines; F_{lo}: Low frequencies; F_{max}: frequency at maximum power; F_{mean}: mean frequency; HIS: higher intensity sound; Int: intensity; LIS: lower intensity sound; LPLL: left posterior lower lobe; RMS: total spectral power; NRS: normal respiratory sounds; NS: not stated; nBC: number per breathing; P_{int} = power at intersection of low and high frequency regression lines; RUAC: right upper anterior chest; LUAC: left upper anterior chest; RUPC: right upper posterior chest; RPLL: right posterior lower lobe; TEWA: time expanded waveform analysis; TR: trachea; Yrs: years.

Table 3 Resume table — Respiratory sounds characteristics of healthy people.

				Variables					
FEMALE	A	Place	BP	F25 (Hz)	F50 (Hz)	F75 (Hz)	F95 (Hz)	F_{max} (Hz)	F_{mean} (Hz)
		RUAC	ins					999 ± 265	
			exp					794 ± 142	
		RPLL	ins					843 ± 133	
			exp					420 ± 60	
		LPLL	ins					885 ± 247	
			exp					444 ± 52	
MALE	A	RUAC	ins					822 ± 247	
			exp					604 ± 123	
		RPLL	ins					760 ± 227	
			exp					419 ± 112	
		LPLL	ins					736 ± 201	
			exp					426 ± 87	
BOTH	I	RPLL	ins						
	C	RPLL	ins	125 ± 6	169 ± 14	252 ± 19	527 ± 52		
			exp					1.040 to 1.595	
	A	TC	ins		447 to 766	1323 ± 192		93 to 154	
			exp		540 ± 174			99 ± 8	
		RUAC	ins						
			exp						
		LUAC	ins						
			exp						
		RPLL	ins	139 ± 15	194 to 206	277 to 301	467 ± 45	106 to 244	439.5 ± 96.8
			exp		131 ± 6			104 to 1.735	552.5 ± 164.9
		LPLL	ins					253 ± 22.9	439.9 ± 107.2
			exp					172.6 ± 76.9	516.1 ± 169.2

A: Adults; A_{high}: high frequency regression lines; A_{low}: low frequency regression lines; Amp: amplitude; BP: breathing phase; C: Children; exp: expiration; F: frequency; F_{max}: frequency at maximum power; F_{mean}: mean frequency; F25: frequency at 25% of inspiratory/expiratory spectral power; F50: frequency at 50% of inspiratory/expiratory spectral power ; F75: frequency at 75% of inspiratory/expiratory spectral power; F95: frequency at 95% of inspiratory/expiratory spectral power; I: Infants; Int: intensity; ins: inspiration; LPLL: left posterior lower lobe; LUAC: left upper anterior chest; RPLL: right posterior lower lobe; RUAC: right upper anterior chest; RUPC: right upper posterior chest; TR: trachea.

resolutions (12—16 bits). Algorithms based on fast Fourier transformation [3,18,29,34,35,37,39], time-expanded wave-form analysis [3,32], overlapped segment method [38] and automatic sound detection [3,31,33] were used to automatically detect and characterise NRS and ARS.

Nine studies did not provide information about gender [31,32], smoking status [29,31,32,33,36], subjects' position [32,34,35,37], target respiratory flows [31,32,37], filters [32,33] or sampling rates [28,30,32,33,36,40] applied for sound analysis.

Synthesis of results

Pooling the results was not possible due to the large heterogeneity in respiratory sounds nomenclature and differences in measurement protocols. Instead a synthesis per NRS (frequency, intensity and amplitude) and ARS characteristics was performed (see Table 2).

Normal respiratory sounds

- Frequency

The frequency of NRS was investigated in seven studies. Hidalgo et al. (1991) reported significant differences in the sound frequency at the right posterior lower lobe (RPLL) between children and adults at 25% (125 ± 6 Hz; 139 ± 15 Hz, $p = 0.02$), 50% (169 ± 14 Hz; 194 ± 26 Hz, $p = 0.03$) and 95% (527 ± 52 Hz; 467 ± 45 Hz, $p = 0.02$) of the inspiratory spectral power (F25, F50 and F95). Furthermore, F25, F50 and F75 decreased significantly with subjects' age and height ($p < 0.001$) [3]. Two other studies analysed inspiratory F50 and F75 in adults at the RPLL and trachea [35,38] and reported that F50 showed lower values (142—766 Hz) than F75 (301—1323 Hz). Expiration was only analysed by one study at F50 [38] and no studies reported on expiratory F75. Therefore, comparisons cannot be established. The highest sound frequencies were observed at the trachea, where the values for inspiration reached 447—766 Hz at F50 [35], [38] and 1323 ± 192 Hz at F75 [35]. Values were slightly lower for expiratory sounds at F50 (540 ± 174 Hz) [38].

Frequency at maximum power (F_{max}) was studied in inspiratory and expiratory sounds at trachea, right upper anterior chest (RUAC), RPLL and left posterior lower lobe (LPLL). Inspiratory F_{max} presented values between 93 and

Int (dB)	A_{high} (dB/oct)	A_{low} (dB/Oct)	Int (<100 Hz) (dB)	Int (>100 Hz) (dB)	Int (<300 Hz) (dB)	Int (75–150 Hz) (dB)	Int (300–600 Hz) (dB)	Amp (V)
	−12.9 ± 1.7	−5.8 ± 5.6						
	−13.4 ± 1.9	−4.7 ± 7.7						
	−13.8 ± 2	−5.4 ± 5.2						
	−20.3 ± 4.2	−5.3 ± 7.1						
	−14.7 ± 2.6	−6.8 ± 1.4						
	−17.7 ± 3.8	−8 ± 1						
	−13.6 ± 1.8	−6.3 ± 6.4						
	−14.9 ± 12.7	−11.4 ± 14						
	−14.1 ± 1.9	−0±14.6						
	−19.7 ± 5.1	−6.5 ± 7.1						
	−15.2 ± 2.6	−5 ± 7						
	−18.8 ± 4.4	−6.7 ± 5.9						
			3.4 to 8.0		14.4 ± 3.7			
			3.2 ± 2	8.4 ± 1.7	15.1 ± 1.5			
6.3 to 20.4								
60.8 ± 37.7				38.67 ± 1.02				
85.1 ± 54.1				45.33 ± 1.58				
4.7 to 68.6					19.8 ± 5.0	10 ± 2.9	25.2 ± 5.2	1.3 ± 0.7
2.3 ± 1.3					16.9 ± 6.5	7.9 ± 4.8	21.1 ± 8.9	
79.1 ± 4.3								1.7 ± 0.8
4.3 to 72.8			1.5 to 9.2	9.7 to 17.17	11.4 to 20.9	13.7 ± 2.7	20.7 ± 3.9	1.2 ± 0.7
1.9 to 18.5				11.50 ± 0.92	15.0 ± 4.1	10.5 ± 2.9	8.8 ± 6.1	
5.7 to 76.6					20.1 ± 3.7	12.7 ± 3.9	23.2 ± 4.3	1.4 ± 0.8
2.5 to 10.2					10.2 ± 3.9	7.9 ± 4	9.4 ± 4.6	

154 Hz at trachea [35,38], 822–999 Hz at RUAC [34], 106–843 Hz at RPLL [3,18,34,35,36,38] and 236.6–885 Hz at LPLL [34,36]. Expiratory F_{max} presented values of 99 ± 8 Hz at trachea [38], between 604 and 794 Hz at RUAC [34], 104–420 Hz at RPLL [18,34,36,38] and 172.6–480.1 Hz at LPLL [34,36]. Frequency at maximum power were significantly higher in women than in man ($p < 0.05$) [34] and infants than in adults ($p < 0.01$) [18].

When assessed in different positions, the inspiratory F_{max} recorded over the right lung reached its highest in the dependent side-lying position (278.4 ± 42.3 Hz), was lower in sitting (244.5 ± 51.9 Hz) and the lowest value was found in the nondependent side-lying position (201.6 ± 57.6 Hz) ($p < 0.001$) [36]. No significant differences were found at the left lung.

One study recorded expiratory nasal sounds and analysed their frequency during the higher and lower intensity of sound. Their findings indicate that, for lower intensity of sound, frequencies of the right nose (2453 ± 22.2 Hz) were significantly higher from those at left nose (2234 ± 21.1 Hz) ($p < 0.05$) [37].

- Intensity

Eight studies investigated the intensity of NRS at trachea, RUAC, RPLL, LPLL and LUAC. Inspiratory intensities presented values between 38.67 and 60.8 dB at trachea [29,39], 4.7–68.6 dB at RUAC [28,29,34], 4.3–72.8 dB at RPLL [18,28,29,34,36,39], 5.7–76.6 dB at LPLL [6,28,29,30,34,36] and of 79.1 ± 4.3 dB at LUAC [28]. Expiratory intensities presented values of 2.3 ± 1.3 dB at RUAC [29,34], between 45.4 and 85.1 dB at trachea [29,39], 1.9–11.2 dB at RPLL [18,29,34,36] and 2.5–10.2 dB at LPLL [29,34,36].

Two studies compared the intensity of respiratory sounds at different frequencies (150–600 Hz) between inspiration and expiration [6,30] and found that inspiratory sounds were louder than expiratory ($p < 0.001$) in all frequency bands. Also, the difference between the two respiratory phases was high in the range of frequencies of 300–600 Hz in both studies [6,30]. The intensity of inspiratory sounds recorded over the posterior left chest wall was found to be higher than the right chest wall (left 25.6 dB vs right 20.7 dB; $p < 0.05$) [30, 36].

When comparing different positions of sound recording, the sound intensity of both lungs was higher in sitting than in nondependent side-lying (inspiration: 20.7–25.6 dB vs 15.7–19.7 dB; expiration 8.8–10.2 dB vs 6.8–8.7 dB; $p < 0.05$). However, no significant differences were found when comparing the sitting with the dependent side-lying position (inspiration: 20.7–25.6 dB vs 22.7–23.5 dB; expiration 8.8–10.2 dB vs 9.3–11.2 dB). In side-lying, the dependent side had higher intensities than the nondependent side (inspiration: 22.7–23.5 dB vs 15.7–19.7 dB; expiration 9.3–11.2 dB vs 6.8–8.7 dB; $p < 0.05$) [36].

The sound intensity increased with higher frequencies and flows and differed significantly among infants, children and adults ($p < 0.05$) [18], i.e., high flows implied lower

sound intensity of infants and children than adults and vice-versa [18]. Respiratory sounds intensity was higher in men and smokers, although these results were not statistically significant [34].

- Amplitude

Respiratory sounds amplitude was analysed in two studies [34,40], however only one presented SI units, allowing interpretation [40]. Kraman (1983) studied the amplitude at different chest locations (RUAC, LUAC, RPLL and LPLL) and presented mean values between 1.2—1.7 V, being higher at LUAC and lower at RPLL [40].

Adventitious respiratory sounds

Three studies focused on the characteristics of ARS in healthy people. The presence of wheezes were reported in two studies [31,33], however only one reported the characteristics of these sounds [31]. The average wheeze occupation rate varied between 0 and 5% both in inspiration and expiration [31] Mean frequencies were higher in expiratory (309 $\pm$ 122 Hz) than in inspiratory wheezes (300 $\pm$ 136 Hz) [31]. The three studies reported the presence of crackles [31,32,33]. The number of crackles varied between 1 and 4 per breathing cycle and these were found mainly in the upper and lateral right chest, especially during inspiration [31,32,33]. However, studies differed on the type of crackle reported: Bettencourt (1999) found fine crackles (shorter than 10 ms) whilst Murphy (2004) found course crackles (longer than 10 ms) [32,33]. Crackles were mainly of low frequency, both in inspiration (371—387 Hz) and expiration (337—404 Hz) [31,33].

Discussion

Four main findings emerged from this systematic review: i) respiratory sound characteristics are affected by several factors (e.g., gender, body size, recording place, subjects' position and respiratory flow), ii) sound frequency is higher at the trachea and during expiration; iii) sound intensity is higher at trachea, during inspiration and when the recording is performed with the subject seated or in dependent side-lying, iv) ARS are present in healthy people however, crackles are the most frequently reported.

Studies analysing different populations reported higher respiratory sound frequencies in children and women [18,34]. The mechanism behind these findings is well understood in children and generally attributed to the acoustic transmission through smaller lungs and thinner chest walls [18]. In women, the mechanism is unclear and different explanations are suggested, such as: differences in sound generation and attenuation in the lung parenchyma, differences in impedance matching between the lung and the chest wall, or altered chest wall mass and physical properties [18,34] due to a smaller rib cage size and shorter diaphragm when compared to men [41]. However, these hypotheses need further investigation.

Sounds appeared to be louder in men and in the left hemithorax. It is known that sound intensity is directly dependent on respiratory flow [5,42] and that males present higher respiratory flows than females [43], hence louder sounds. However, the mechanism explaining the differences between the right and left bases of the lungs is not fully understood. Several authors have tried to justify these differences based on the asymmetry of the airways geometry of both lungs [36,44], i.e., left bronchus is smaller and more horizontal than the right and, the major left segmental bronchi is directed more posteriorly than the right due to the heart position [36,44], increasing flow rate and consequently, the sound intensity at the left bronchi. Therefore, health professionals who assess respiratory sounds should be aware of these differences in lung sound intensity that routinely occur between the left and right bases to prevent potential errors in diagnosis and clinical decisions.

As expected, in most studies both frequency and intensity were higher at the trachea, due to its large diameter and the absence of a structure to filter the sound (contrarily to the chest, due to the presence of lung parenchyma), high and turbulent flows are generated, resulting in high frequencies and intensities [45]. However, when assessed in different positions, frequency and intensity evidenced different behaviours: a clear pattern was not found for frequency, whilst intensity was clearly higher in the sitting and in dependent side lying positions. Although frequency did not differ significantly with positioning, it tended to be higher in the right lung for all the positions assessed [36]. Differences in the anatomy of the airways between the two lungs might contribute to explain this finding however, this phenomenon is not explained by the authors or other literature and therefore, more studies are needed to improve our understanding in this field. The results found for the sitting position may be explained by a better ventilation of the dependent part of the lungs in sitting and dependent side-lying positions, due to the mechanical advantage [36,44]. The sitting position results in a deeper breath for the same amount of muscular effort and consequently a higher inspiratory airflow enhancing the intensity of the respiratory sounds [36,44]. The high intensity sounds found in the dependent lung regions were also expectable, as it is known that lower diaphragm contracts more effectively than the upper diaphragm in the side lying position and, therefore, ventilation distributes preferentially to the dependent lung, despite the diminished lung volume [46,47]. Two studies provided information on the sound amplitude, however, in the study of Gavriely et al. (1995) results could not be interpreted due to the lack of SI units [34]. Kraman et al. (1983) [40] showed that mean amplitude was higher at the LUAC and lower at the RPLL but, as this is the only study in the field, this result should be interpreted with caution. In the literature, the difference between intensity and amplitude is not well described and most authors use both terms indistinguishably using different methodologies, limiting the conclusions that can be drawn.

Adventitious respiratory sounds in healthy people were only investigated in three studies [31,32,33] however, inferential statistics was not reported. A reduced number of ARS were found, however, different types of crackles were reported, i.e., fine [32] vs coarse [33]. Subjects' different mean age may explain this difference (49 $\pm$ 11yrs [32] vs 69 $\pm$ 7yrs [33]). It is known that older people present some degree of physiological degeneration in the respiratory system, diminishing mucociliary function and flow

rates [48,49]. This may lead to retention of secretions, generating coarse crackles on the air passage. Only one study reported wheeze characteristics in healthy subjects, however, it did not analyse the type of wheeze found (monophonic/polyphonic). This information may be of potential interest as it is well known that wheeze type is a good predictor of disease severity (polyphonic wheezes indicate a more serious obstruction than monophonic wheezes) [50]. Due to the reduced number of wheezes and fine crackles found in the studies, it is hypothesised that these results may not be indicative of respiratory disease.

It is clear that the study of NRS and ARS provides valuable information about the tracheobronchial tree. However, much research is needed in this area to improve the knowledge on respiratory sounds of healthy people and people with respiratory diseases. This will contribute for enhancing health professionals' knowledge on the respiratory system, enhancing their skills for diagnosis and monitoring of respiratory diseases.

Limitations

Based on the results of this study, we cannot draw strong conclusions on the characteristics of NRS and ARS in healthy people, due to the lack of: i) well designed studies with large samples; ii) similar methodological approaches (body positions for data collection, breathing flow rates and algorithms for sound analysis) and iii) clear definitions of the variables analysed and SI units used. International Computerised Respiratory Sound Analysis (CORSA) guidelines [10,51,52] are available since the year 2000 to standardise the instruments used and procedures of data acquisition and signal processing techniques. However, none of the studies conducted after this year followed these guidelines. Further research, following the CORSA guidelines, is urgently needed to objectively understand the clinical value of the respiratory sound characteristics to diagnose and monitor respiratory patients.

Implications for practice and research

This systematic review summarises the main characteristics of the respiratory sounds of healthy people, in an attempt to improve the current body of knowledge and provide health professionals with the acoustic characteristics expected to be found in healthy people (see Table 3). This review adds clinical value to the results obtained through computerised respiratory sounds analysis and may potentiate its use as an objective respiratory measure. However, more studies with robust designs (e.g., RCT with sample size calculation) and standardised recording/analysis methodologies are urgently needed to enhance respiratory clinical decision making. It would also be of great value the development of systematic reviews focused in summarising the sound characteristics of different respiratory and cardiac diseases. These reviews could be compared with the findings of the present systematic review to clearly define patterns of healthy and pathological respiratory sounds. Finally, the nomenclature related to the sound analysis should be further clarified to enable the dissemination and comparison of the findings from different studies.

Conclusions

Respiratory sounds show different acoustic properties depending on the subject's characteristics and local of sound acquisition. These characteristics need to be well defined in healthy populations to allow objective interpretations of respiratory sounds alterations in people with respiratory diseases. Further research with robust study designs, exploring different children and adult populations and following CORSA guidelines are urgently needed to build evidence-base in this topic.

Conflict of interest statement

The authors have no conflict of interest.

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Annex VI –Publication II - Physical activity in healthy children and children with Acute Respiratory Infections

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PHYSICAL ACTIVITY IN HEALTHY CHILDREN AND CHILDREN WITH ACUTE RESPIRATORY INFECTIONS

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Introduction: Acute respiratory infections (ARI) are the most common cause of illness worldwide and account for over 1/3 of paediatric consultations in children under the age of five (Thompson et al, 2013). It is known that exercise has anti-inflammatory effects, and adults who exercise regularly experience approximately 21%-41% less risk of developing ARI than sedentary peers (Nieman et al, 2011). However, it is unknown if this association is also observed in children.

Objective: This study aimed to compare physical activity levels of healthy children and children with ARI, under the age of five.

Methods: Children were recruited from the paediatric department of one central hospital. Physical activity was assessed with a 5-question physical activity questionnaire (Telama et al, 1997). This instrument assesses physical activity within a "normal week" (not considering periods of disease) with a score-range of 5-20. Children's physical activity was classified into 4 categories: the sedentary (5); low activity (6–10); moderate activity (11–15) and vigorous activity (16–20). The questionnaire was filled by children's legal representative after written consent was obtained.

Results: Twenty-four children with ARI (3±0.6 years; 14 male) and seventeen healthy children (3.3±0.2 years; 11 male) participated. Children with ARI were significantly less active (median=7.5; Interquartile-range: 6; low activity) than their healthy peers (median=12; Interquartile-range: 4.5; moderate activity).

Conclusions: Similar to adults, children with higher levels of physical activity may be at lower risk of developing an ARI. Further studies are needed to establish the most appropriated types and levels of physical activity for children under the age of five.

Descriptors: Acute Respiratory Infections; Children; Physical Activity.

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