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Validated Patient Reported Outcome Measures and Objective Monitoring of Cough in Pediatric Patients

Bruna Fernandes da Rocha

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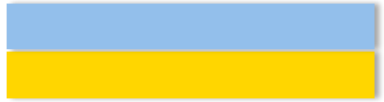

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Resumo

Introdução e objetivos: A tosse é o sintoma respiratório mais prevalente em doenças respiratórias pediátricas, sendo essencial a sua caracterização. O objetivo desta revisão sistemática foi identificar os métodos validados, e respetivas propriedades psicométricas, para avaliação da tosse em idade pediátrica, através de medidas de resultado reportados pelos cuidadores (PROMs) ou instrumentos de monitorização objetiva.

Metodologia: Dois investigadores independentes pesquisaram as bases de dados Pubmed®, Scopus® e Cochrane® Centre Register of Controlled Trials (CENTRAL) e seleccionaram os artigos de validação de métodos de avaliação da tosse em pediatria. Globalmente, a estratégia de pesquisa incluiu vários termos de tosse, crianças, pediatria ou métodos de monitorização. Um terceiro investigador decidiu sobre a inclusão dos artigos em caso de discordância. Posteriormente, após avaliação de qualidade dos artigos (PROMs com COSMIN Risk of Bias Tool; Instrumentos objetivos com QUADAS-2), avaliaram-se as características psicométricas de cada medida/instrumento.

Resultados: Foram incluídos 15 estudos correspondentes a 15 métodos de avaliação de tosse: 7 PROMs e 8 métodos objetivos. Dentro dos PROMs, o CC-QoL e o Burden of Cough apresentavam a melhor consistência interna com um cronbach-α=0,94. O PAC-QoL e o PAC-QoL-6 têm os melhores resultados de fiabilidade teste-reteste com um ICC=0,75 e ICC=0,63, respetivamente. O CC-QoL e o PC-QoL têm moderada fiabilidade teste-reteste. O PC-QoL teve uma correlação baixa, p=0,100, com seu método de referência, o VCD score. Dentro dos métodos objetivos, identificaram-se 6 dispositivos de utilização ambulatória com análise automática e 1 algoritmo de saúde móvel digital (mHealth). O aparelho composto por acelerómetro, video e áudio e o monitor LEOSound tiveram os melhores resultados com uma sensibilidade de 89,0% e 98,8% e especificidade de 99,0% e 97,8%, respetivamente. O único método com uma sensibilidade inferior a 80% foi o algoritmo mHealth para smartphones, com um valor de 47,6%.

Conclusões: Existem diversos instrumentos de avaliação de tosse em pediatria, assim como de avaliação do seu impacto, que são válidos e fiáveis para uso na prática clínica. O método mHealth necessita de maior desenvolvimento para uma potencial utilização disseminada no ambulatório.

Abstract

Introduction and objectives: Cough is the most prevalent respiratory symptom in pediatric respiratory diseases, and its characterization is essential. The objective of this systematic review was to identify validated methods and their psychometric properties for the evaluation of cough in pediatric patients, through patient reported outcome measures (PROMs) or objective monitoring instruments.

Methods: Two independent researchers searched the Pubmed®, Scopus® and Cochrane® Centre Register of Controlled Trials (CENTRAL) databases and selected the validation articles for cough assessment methods in pedriatic patients. Overall, the research strategy included several terms of cough, children, pediatrics or monitoring methods. A third investigator decided on the inclusion of the articles in case of disagreement. Later, after evaluation of the quality of the articles (PROMs with COSMIN Risk of Bias Tool; Objective instruments with QUADAS-2), the psychometric characteristics of each measure/instrument were evaluated.

Results: 15 studies corresponding to 15 cough assessment methods were included: 7 PROMs and 8 objective methods. Within the PROMs, the CC-QoL and the Burden of Cough presented the best internal consistency with a cronbach-α=0.94. PAC-QoL and PAC-QoL-6 have the best test-retest reliability results with an ICC=0.75 and ICC=0.63, respectively. THE CC-QoL and PC-QoL have moderate test-retest reliability. The PC-QoL had a low correlation, p=0.100, with its reference method, the VCD score. Within the objective methods, 6 ambulatory devices with automatic analysis and 1 digital mobile health algorithm (mHealth) were identified. The device composed of accelerometer, video and audio and the LEOSound monitor had the best results with a sensitivity of 89.0% and 98.8% and specificity of 99.0% and 97.8%, respectively. The only method with a sensitivity of less than 80% was the mHealth algorithm for smartphones, with a value of 47.6%.

Conclusion: There are several instruments available to pediatric patients for cough evaluation and for assessing its impact, which are valid and reliable for clinical practice. The mHealth method requires further development for potential widespread use in ambulatory settings.

Key Words

"Cough", "Monitoring", "Assessment", "Patient reported outcome measures", "Questionnaire", "Technological Devices", "Pediatric"

Abbreviations

PROMs: Patient Reported Outcome Measures

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL: Quality of life

PC-QoL-8: Parent Cough Specific QoL's short form

PCQ: Pediatric Cough Questionnaire

PAC-QoL: Parent-proxy Children's Acute Cough-specific QoL

PAC-QoL-6: Parent-proxy Children's Acute Cough-specific QoL's short form

CC-QoL: Chronic Cough-Specific QoL Questionnaire

PC-QoL: Parent-proxy Cough-specific QoL

VCD: Verbal Category Descriptive

ECG: Electrocardiogram

EMG: Electromyography

VAS: Visual Analogue Scale

ICC: Intraclass Correlation Coefficient

CI: Confidence Interval

MIC: Minimal Important Change

SEM: Standard Error of the Mean

PPV: Positive Predictive Value

NPV: Negative Predictice Valu

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Introduction

Cough is one of the main symptoms accounting for pediatric healthcare attention [1]. In school children the most common cause of acute cough is upper respiratory tract infections that can be as frequent as 8 times a year, with up to 140 coughs daily [3]. Cough can be a hallmark of disease and is many times perceived as a negative affliction by caregivers [4]. This is associated with an increased physical, mental and social burden, mainly in acute settings, leading to a high use of over-the-counter cough medication. It is widely accepted that cough supressants are not recommended and should not be given to children [5]. Furthermore, cough's social burden is associated to missed school and work days, making it important for physicians to acknowledge it and further investigate it [4, 6].

Cough's correct evaluation is needed so the most appropriate treatment is chosen, since there are many causes of cough with different approaches. Assessing cough, especially in terms of quantity, quality or frequency can be a hard task for patients or caregivers, especially in the pediatric age group. In the adult population, the cough assessment is simpler because of the patient's ability to cooperate and communicate about the evolution and characteristics of the symptoms. For adults there are already various resources about the different cough assessment methods, but most cannot be applied to the pediatric population, especially small children, since they are unable to properly communicate or pay attention to their symptoms. Most of the times, the complaints come from the caregivers who have a limited perspective and point of view of their children's cough, which is especially difficult during the night time, making the usefulness of non-objective measures dependent on parent recall [10, 11].

Instruments that help patients and physicians to accurately assess cough's characteristics and its impact in quality of life are crucial for cough management [7]. It is important that objective methods of cough assessment are continually developed and validated for use in the future, because they improve the physician's diagnosis and consequently treatment [12]. Currently the different cough evaluation methods can be patient reported outcomes measures (PROMs) or objective cough monitoring by external devices or mHealth apps. Nowadays with the help of technology and automated recordings used along classic patient recorded outcomes measures, this evaluation is getting more and more precise [8]. Still, there is no gold standard method and what many physicians do in a typical consultation is pay attention to the patient's spontaneous or voluntary coughs to assess its characteristics and with their subjective reports on frequency establish a diagnosis [2].

The main objective of this systematic review was to synthesize validated cough assessment methods, namely, PROMs (questionnaires, scores or scales) and objective cough monitoring measures (external devices or mHealth apps). The secondary aims were: i) to compare psychometric characteristics between validated methods; ii) to identify domains of cough measures (intensity, frequency and quality of life [QoL]); iii) to assess age and settings of applicability of the measures.

Methods

Information sources

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13]. We searched the entries in PubMed, SCOPUS and Cochrane Centre Register of Controlled Trials databases. The search queries are listed in supplementary material. Broadly, the queries included several terms for cough, children, pediatrics or outcomes measures. Also, experts in the field were contacted to identify possible ongoing studies.

Elegibility Criteria

All clinical studies published before April 2022 about cough evaluation using validated methods, on patients under 18 years of age and in all languages were included. Reviews or other secondary analysis studies were excluded.

Inclusion Criteria

(1) Validation studies of PROMs and objective measurements of cough severity/intensity, frequency or its impact on quality-of-life
(2) Participants under 18 years of age.

Exclusion Criteria

(1) Studies with methods of evaluating cough validated only in adult population.
(2) Methods of cough assessment that are being developed but not validated yet.
(3) Systematic reviews or other secondary studies.
(4) Studies regarding a method of cough assessment related to a specific cough etiology.

Search Strategy

Firstly, all the title and abstracts were independently read by two different researchers (BR e SM) for selecting studies based on inclusion and exclusion criteria. Any disagreements between individual judgements were solved by a third researcher (MM). Then, the full texts were read to decide which ones were a part of the final review, according to inclusion criteria. The citation pool was further supplemented from manual assessment of the reference lists of the retrieved articles and from other publications identified as being relevant for further review.

Data collection process

Data was extracted and checked by two researchers (BR e SM) and disagreements between individual judgements were resolved by the third investigator (MFM), that made the final decision. After inclusion of all the manuscripts, data synthesis was separated in two groups: i) PROMs, and ii) objective cough monitoring measures, using external devices or mHealth algorithms. In each group, the validation of the tools/methods and the assessment of cough characteristics (severity, intensity, frequency or quality of life) were reported and discussed. For the data extraction, information about the participants' age and condition, study design, settings, the methodology, and results were included.

Quality Assessment

For the studies that fit inclusion criteria, their methodological quality was assessed by two researchers (BR e SM) using the COSMIN Risk of Bias tool [14, 15] for PROMs studies and the QUADAS-2 grid [16] for objective measuring studies (Fig. 1).

Results

Study Selection

A total of 537 articles were identified in PubMed (n = 224), Scopus (n = 252) and Cochrane Centre Register of Controlled Trials (n = 61). After exclusion of duplicates, 297 were screened for relevance and 142 assessed for full-text eligibility. Fifteen studies met the inclusion criteria (Fig. 2). Seven of them were validation studies of PROMs [4, 6, 7, 10, 17-19], all of them quality-of-life scores except for one that assessed cough frequency and intensity [6]. The other eight were validation studies of objective cough monitoring measures [11, 12, 20-25], from which seven were external technological devices and one mHealth app [20, 23].

Validation studies of PROMs

The PROMs results were synthetized in table I. Six of the seven PROMs were validated for pediatric patient's and/or family's QoL. These assessed the level of concern and related feelings caused by their children's cough, and included questions about anxiety, sleep disturbance, or changes in family dynamics. All of these use a Likert type scale for the answers. Only the Parent Cough Specific QoL's short form (PC-QoL-8) did not included all World Health Organization domains (physical, social and psychological) [7]. The Pediatric Cough Questionnaire (PCQ) was the only method that was not based on the QoL, and included five questions about cough frequency, intensity, degree of concern caused, and sleep disturbance of the child and caregivers [6].

Four of these measures are designed for patients with chronic cough [7, 10, 17, 19], while only Parent-proxy Children's Acute Cough-specific QoL (PAC-QoL) and its short form, PAC-QoL-6, were for acute cough [4, 18]. In turn, PCQ can be used for both acute and chronic cough [6].

Regarding applicability, four of the PROMs can be used in all ages whereas three excluded smaller children (not validated for children under 5 years old) [7, 10, 17]. These measures can be used in different settings and most of them were caregiver-reported outcomes. Only Chronic Cough-Specific QoL questionnaire (CC-QoL) was designed for children-reported own outcomes, but because of this it could only be applied to school-aged children [17].

The time necessary to fill in these questionnaires varies because of the different number of questions in each score. The PAC-QoL-6, PCQ and PC-QoL-8 had less than ten items [7, 10, 18], the PAC-QoL and CC-QoL had 16 items [4, 17], the Parent proxy cough-specific quality of life (PC-QoL) had 27 items [10] and the Burden of Cough had 50 items [19].

All of the studies used internal consistency as an indicator of reliability and only the Burden of Cough did not measure consistency with the test-retest [19]. The PAC-QoL, PAC-QoL-6, PC-QoL and CC-QoL also measured prospective responsiveness to change, all with an adequate sensitivity to change overtime [4, 10, 17, 18]. The methods with the highest internal consistency were the CC-QoL and the Burden of Cough, both with a cronbach-α=0.94. The PAC-QoL and the PAC-QoL-6 had the highest test-retest with an ICC=0.75 and ICC=0.63, respectively. The CC-QoL and PC-QoL had moderate test-retest reliability. The PC-QoL had a low correlation with one of the standard references, the cough Verbal Category Descriptive (VCD) score.

Validation studies of objective monitoring methods

The objective monitoring methods results were synthetized in table II. Four types of technology had been developed to count coughing events and measure its frequency. The first type of device was based on audio signals plus electrocardiogram (ECG) and electromyography (EMG) [21, 24]; the second type of technology was audio recognition alone [11, 20, 23]; the third type was based on an accelerometer which measured vibrations, alone [25] or with audio and video recording [12]; and the fourth type used audio signals and EMG [22].

Because of the different components in each device, different outcomes were evaluated according to which objective method. All of them measured cough frequency, except for the HMM Classifier [20]. The frequency data was presented in different ways: i) automatically, by the number of cough episodes occurred in the total recording [12, 20, 22, 23, 25], or an average count per hour[11]; ii) manual physician classification of the cough sounds [21, 24]. The HMM Classifier's purpose was to assess the quality of cough sounds and cough etiology (pneumonia or asthma) [20]. Although most devices were capable of assess the intensity of cough, only one did preformed that, and none reported that measure [25]. Also, none of these methods performed an automated analysis these signals. The devices which included an EMG are also able to establish an association between cough events and the patient's state of activity with the comparison with movement and heart rate [22, 24]. Furthermore, the LEOSound monitor besides assessing cough frequency, can also classify audio signals into cough or wheezing sounds [11].

Regarding applicability, three devices could be used in all ages [11, 23, 25], only two could be used in infants [20, 22] and the rest in school aged children or adolescents [12, 21, 24]. Half of the objective cough monitors can be used in any settings [20, 23-25], two can be used either in the hospital or at home [11, 22], one was for ambulatory purposes [21], and only one was just for inpatients [12].

The usage time for these devices varies; three of them could record data up to 24 hours [12, 21, 24], three could only be used for less than two or three hours [20, 23, 25] and two were for overnight recording [11, 12]. All of these had an automated analysis except for two, which require manual review of the recorded data [20, 21].

Five of these studies measured sensitivity and specificity, the highest two being the LEOSound monitor and the device with an accelerometer, video and audio signals with sensitivities of 89% and 98,8% and specificities of 99% e 97,8% respectively [11, 12]. Five of them also measured the correlation between the studied methods and the standard references, all with excellent results [11, 12, 20, 24, 25]. Three studies also evaluated limits of agreement [12, 21, 22]. The LR100 device had a good agreement with the standard reference when patients had infrequent cough but when it was frequent the agreement was low [22]. The smartphone mHealth algorithm had a low sensitivity of 47.6% [23].

Discussion

This systematic review identified several cough QoL questionnaires but only one score that measured cough frequency and intensity. So, apart from assessing impact on the patients'/caregivers' life, there was a lack of options for physicians to assess specific cough characteristics. Also, only one questionnaire was designed for patients with acute cough. In this review there were two validated short forms that were developed a few years after the original PROM. Both had short-to-full length similar psychometric characteristics without losing important information. This made the existence of the full-length PROMs redundant, since the short forms were more practical and faster to fill; there was no apparent justification to use the full-length form [18]. The time consumed by caregivers to answer these questionnaires was an important factor to the adherence to PROMs; if those were too long it was complicated to fit them in most of the doctors' appointments. The Burden of Cough score was fifty questions long, making its frequent application unrealistic.

It is known that patient self-reported outcomes are much more accurate and relevant to clinical use than information that comes from proxy respondents, which has an impact on therapy [17]. However, in this review only one validated score was intended for patient filling in and not the caregivers. This occurred because younger children are unable to properly communicate; but, other than these, it should be available more options for school-aged children and adolescents that no longer need a proxy respondent [17].

All these studies, except for one, used visual analogue scales (VAS) and cough VCD scores as gold standards for validation. These methods were developed using adult participants and might be affected by response bias, making it unlikely to be adequate as gold standards [7]. All PROMs proved to be reliable with excellent internal consistency values and good responsiveness with sensitivity to change overtime proving that they are good diagnostic tools that can also be used to reassess the patient's state after interventions.

In this review were identified several objective cough monitoring methods, six of them based on technological devices and one mHealth algorithm. Most of them only measured cough frequency even though many had components that were able to quantify cough intensity, useful in clinical practice. The devices that had incorporated EMG or video were good for establishing an association between the child's activity and the cough events, allowing interpretations to be made in different daily activities of the child (e.g., sleeping, crying or exercising). Although these informations were useful, the more components a monitor had, the bulkier and more complicated it is to work with. In some studies patients were excluded because electrodes would

dislocate with movement, and because of it could only be used overnight when the child or adolescent was asleep. Simpler and smaller devices had higher chances of being accepted by patients and incorporated into their routine. Seven of these methods could be used in ambulatory settings; one is meant to be applied to inpatient care only.

There were only two devices that were suitable for infants' use, which was a difficult age group to monitor since they are unable to cooperate. In these studies, some concerns were raised regarding safety. In fact, infants needed to wear multiple cords during their sleep and some parents dropped out the study [22]. Another thing that can be a limiting factor when choosing what objective method to use is the requirement of a manual review of the recorded data. This was only necessary in two of the identified devices but these required a trained and skilled professional and many hours counting each cough event, which was not considered to be daily feasible. The rest provided partial or full automated analysis making them more efficient and less time-consuming for physicians. One of the challenges with sound recording is the misinterpretation of other sounds, such as throat clearing, as cough. Furthermore, devices with audio recording can invade privacy by registering conversations, which can impose ethical issues and should be addressed by the developers of this technology [24].

All studies that measured sensitivity and specificity had good results (always above 80%), except the smartphone-based mHealth algorithm that had a sensitivity of 47,6 %, meaning that more than half of coughing events were not detected. Most of the studies had also good agreement with the standard reference. One of them had low level of agreement when evaluating infants with frequent cough, and the team hypothesized that it happened because that method actually performed more accurately than the standard video reference; even though, without a real gold standard it was difficult to prove this hypothesis.

Because of the prevalence of cough there has been a large investment in its treatments, but these efforts have been hampered by the lack of accurate diagnosing tools. More commonly, diary cards and VAS or VCD were the methods used to evaluate cough frequency, intensity or impact but the current validity of these tools is unclear [26]. Previous studies have showed significant differences in the correlation between subjective and objective assessments of cough in several diseases. Published evidence suggested that PROMs were insufficient to evaluate efficacy of treatment in clinical trials, mainly because of the reporting gap when patients were asleep. Objective measures are getting more attention as technology develops because they are great methods, especially at night when underreporting of symptoms is expected [27]. This means that new devices should be designed to be used overnight and for more than just a few

hours. Findings suggested that audio and video recording devices were the best option for cough frequency measurement with high validity and reliability, at least in controlled settings with manual review as the standard reference. In the studies that assessed the correlation between audio recording devices and PROMs, the results were generally poor to moderate, suggesting that higher cough frequency does not directly correlate to worse QoL [26].

Even though objective cough measuring methods have already went though many developments, there is still ways in which they can be improved in the future. Most of these only measure cough frequency, and further additions to the devices are important to expand the evaluation of cough into other domains such as its intensity, its association with a specific etiology, its classification in different types of productive, dry, hoarse or wheezy cough, and others.

Conclusion

This review synthesized all the published subjective and objective methods that were valid and reliable for clinical use. If the purpose is to evaluate QoL then there are different questionnaires and scores, the PC-QoL-8 and the PAC-QoL being the ones with the best psychometric overall results for chronic and acute cough, respectively. If the clinician intends to assess cough frequency or intensity without having to use a technological device there is only one PROM for those outcomes, the PCQ. However, to measure those specific cough's characteristics subjective reporting has been shown to be less accurate and objective measuring should be considered [25]. There is only one device that covers all desired factors including applicability to all ages, ambulatory settings, no need of manual review and recording overnight - LEOSound monitor. Although most objective measures had at least one negative aspect, most of them had good overall results meaning that they are valid, accurate and a very useful resource when assessing cough.

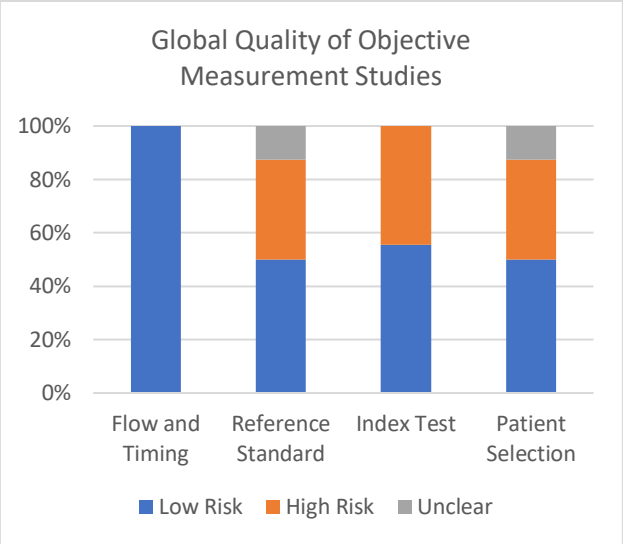

Figure 1. QUADAS-2 Risk of Bias evaluation

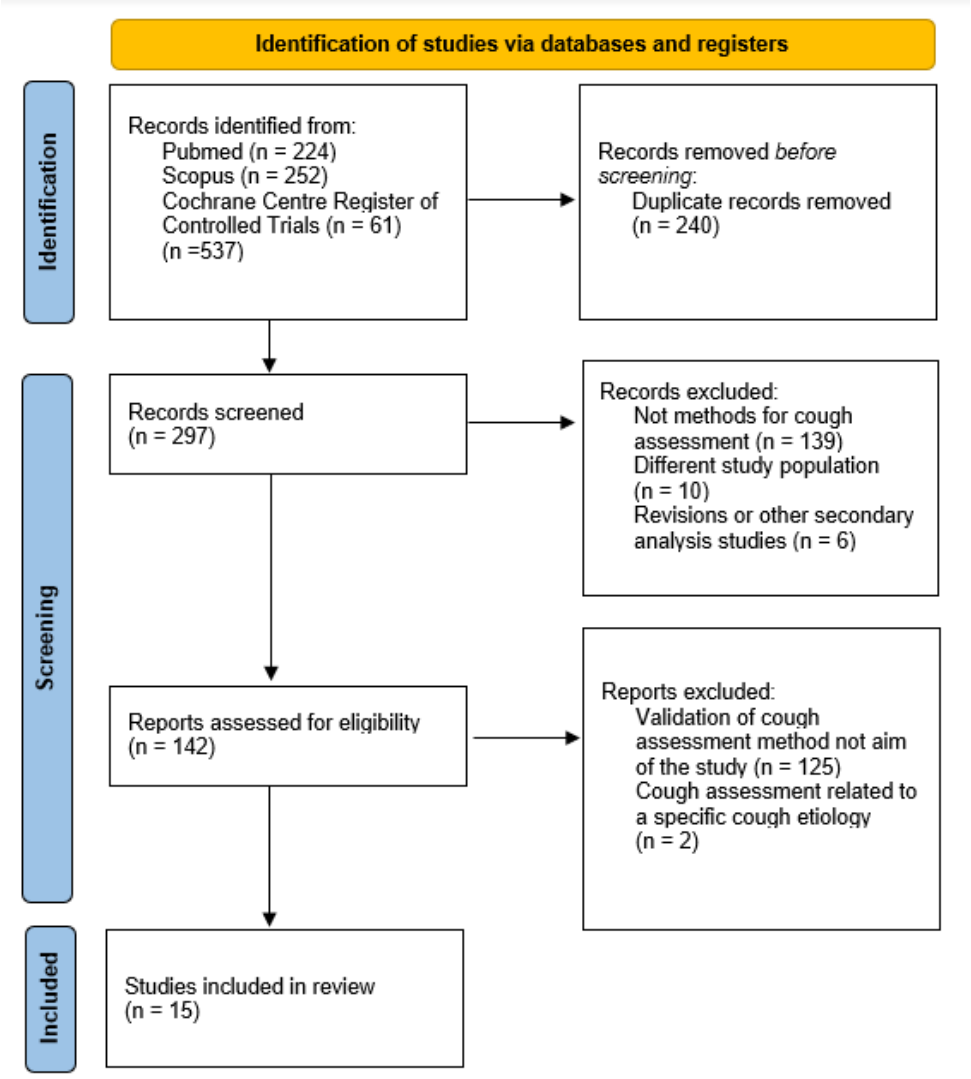

Figure 2. Flow diagram. Results of the literature search and selection

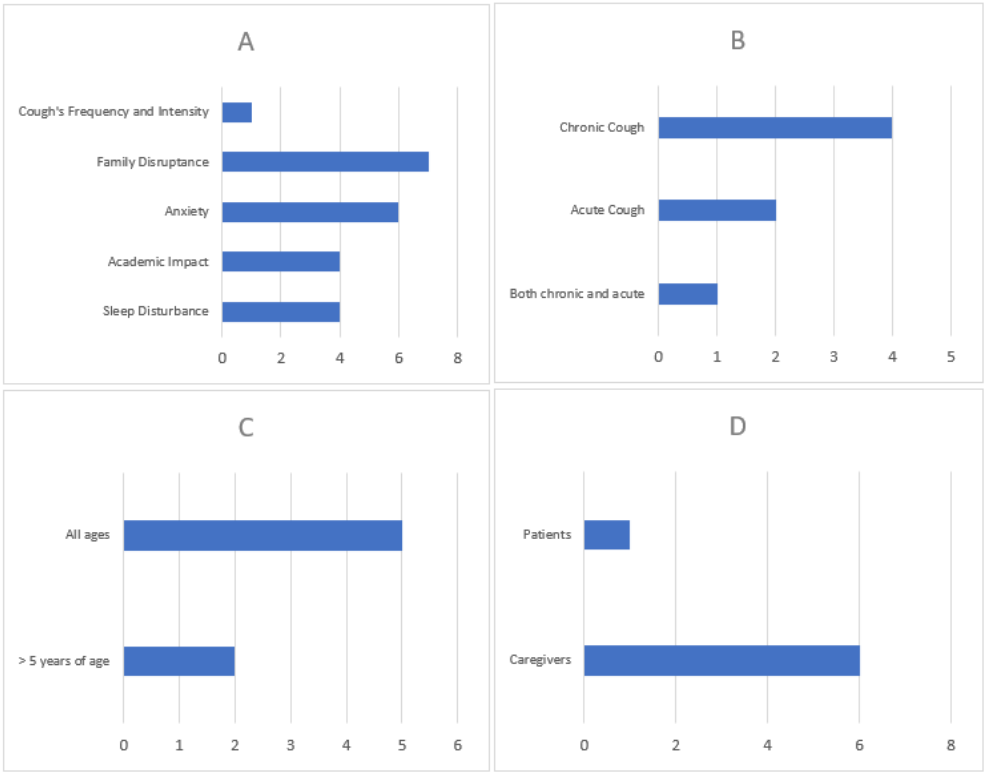

Figure 3. Domains of applicability of PROMs: A- Outcomes assessed in questionnaires; B- Types of cough for which each method is intended; C – Age Applicability; D- Person reporting the questionnaires' answers.

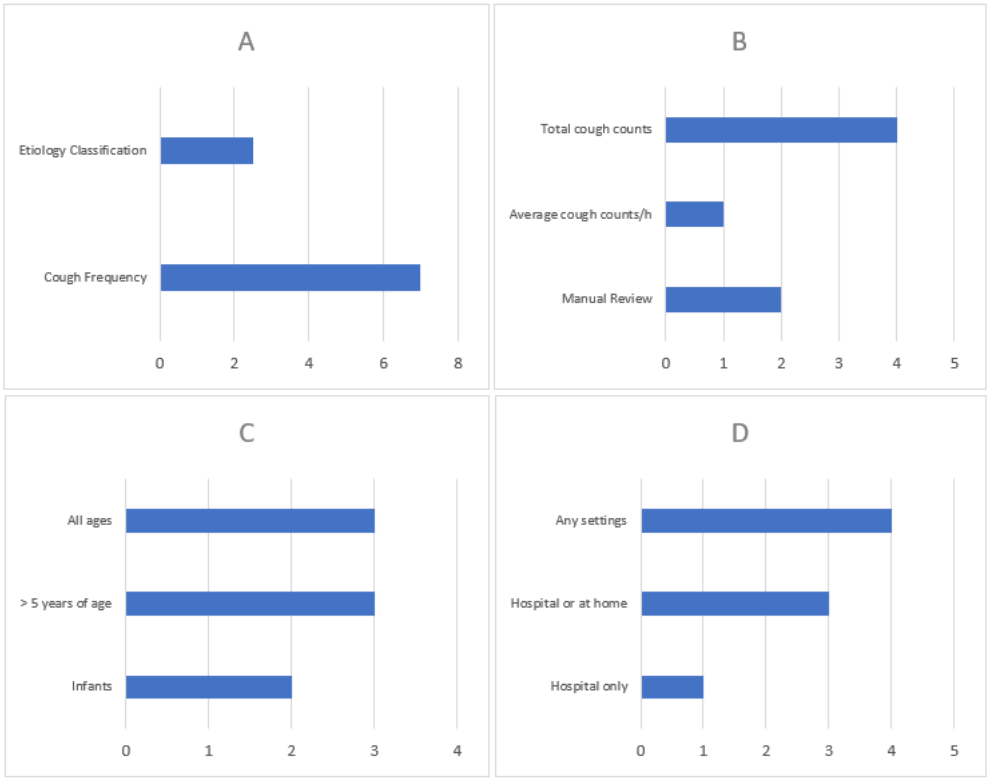

Figure 4. Domains of applicability of Objective Measures: A- Outcomes assessed; B- Presentation of cough frequency measures; C – Age Applicability; D- Settings each method can be used in.

Table I. Results - Validating studies of PROMs

First Author	Patients included	Scale	Standard reference	Creation of scale	Outcomes	Results
Newcombe, 2016 [17]	Children aged 7-17 years with chronic cough (>4 weeks)v n= 130	16-item Chronic cough Quality-of-life questionnaire (CC-QoL)	Cough VAS and VCD score	1. Generation of items 2. Item reduction 3. Allocation into domains	- 16 questions about the impact of cough on the patient's day-to-day life and how they make him feel - Uses a 7-point Likert scale with high results corresponding to better quality of life Ex. If coughing causes you frustration, your sleep is disturbed, etc.	- Excellent internal consistency, cronbach-α=0.94 - Moderate test-retest reliability, ICC=0.40 - Convergent validity with significant correlations, rs≥−0.89, p≤0.001 - Concurrent validity with significant correlations, rs≥0.32, p≤0.003 - Significant sensitivity to change, p<0.001 - SEM < MIC
Newcombe, 2010 [10]	Children with chronic cough n= 43	Parent-proxy quality-of-life questionnaire for paediatric chronic cough (PC-QoL)	Cough VAS and VCD score and a digital voice recorder	1. Generation of items 2. Allocation into domains	- 27 questions that assess the level of frequency with which their children's cough causes them concern and related feelings - Uses a 7-point Likert scale with high results corresponding to better quality of life	- Excelent internal consistency cronbach-α=0.83 - Moderate test-retest reliability ICC= 0.46 - Good ICC for both cough counts/h (rs=0.43, p<0.003) and cough VAS (r=0.36, p=0.013), but not for cough VCD (rs=0.20, p=0.100) - Sensitive to change overtime, p <0.003.
Newcombe, 2013 [7]	Children of a median age of 29 months n= 320	Short form PC-QoL-8	Cough VCD score, VAS and PC-QoL	1. Forward step regression of PC-QoL 2. Item reduction	- 8 questions that assess the level of frequency with which their children's cough causes them concern and related feelings - Uses a 7-point Likert scale with high results corresponding to better quality of life	- Excellent internal consistency, cronbach-α=0.84 - Good test-retest reliability, ICC=0.62 - Strong convergent validity with significant correlations with a cough VCD score and VAS - SEM < MIC
Anderson-James, 2015 [4]	Children of a median age of 2.3 years with a current acute cough (<2 weeks) n=155	Parent-proxy children's acute cough-specific quality-of-life questionnaire (PAC-QoL)	Cough VAS and VCD score	1.Development of items 2. Item reduction 3. Allocation into domains	- 16 questions that assess the level of frequency with which their children's cough causes them concern - Uses a 7-point Likert scale with high results corresponding to better quality of life Ex. If the child was unable to sleep or breathe well due to cough, if it changes the family dynamics, etc.	- Excellent internally consistency, cronbach-α=0.9 - Good test-retest reliability, ICC=0.75 - Criterion Validity with high correlation values with other measures - Significant sensitivity to change, p<0.001
Hartnick, 2009 [6]	Children with a median age of 6.7 years with chronic cough n= 120	Pediatric Cough Questionnaire (PCQ)	None	Not described	- 5 questions about cough frequency, intensity, the degree of concern it causes, sleep disturbance of the child and caregivers - Uses a 6-point Likert scale	- Excellent internal consistency, cronbach-α=0.88 - Good test-retest reliability, *p*<0.001 - Good divergent validity, *p*<0.001
Anderson-James , 2021 [18]	Children with a median age of 2 years with acute cough n= 332	Short form PAC-QoL-6	PAC-QoL, cough VAS and VCD score	1. Revalidation original PAC-Qol 2. Item reduction	- 6 questions that assess the level of frequency with which their children's cough causes them concern - Uses a 7-point Likert scale with high results corresponding to better quality of life	- Good internal consistency, cronbach-α= 0.87 - Good test–retest reliability, ICC= 0.63 - Criterion Validity with good correlation values with other measures - Significant sensitivity to change, p<0.001
Marchant, 2008 [19]	Children referred for chronic Cough n= 170	Burden of cough questionnaire	Cough VCD score	1. Item Generation 2. item reduction	- 50 questions about the impact that children's cough has on their psychological state and family life - Ex. If cough causes stress, if it affects them when they vomit or when they need medication, etc. -Uses a 7-point Likert scale	- Good internal consistency, cronbach-α=0.94

Table II. Results - Validating studies of objective monitoring measures

First Author	Patients included	Method description	Settings of the study	Standard reference	Outcomes	Results
Munyard, 1994 [24]	4 healthy adults, 1 healthy child, 1 child with asthma, and 14 children with cystic fibrosis n= 20	Microphone + ECG + EMG Manual review of graphical Interface	Short duration (1–8 h), Adults at work, children at home or in hospital	Conventional audio recording	-Frequency: Manual counting of cough signals reproduced on the monitor by combining sound reading and electrical activity capture in EMG -Relation of cough with activity and heart rate	- Intraclass correlation coefficient: 0.99 (95% CI 0.96–0.99) - Good reproducibility with p=0.44, (95% CI, -0.01-0.23)
Hirai, 2015 [12]	Hospitalized children with a median age of 9.1 years with cough n= 10	Video camera + sound recorder + accelerometer Automated analysis	8h recording, In hospital	Video-audio recording and manual counting of cough events in the 1st and last hours	- Frequency: System shows the number of coughs that occurred in total recording	- Excellent sensitivity and specificity (98.8% and 97.8%, respectively) - Good agreement between defined cough events/ video-audio counts and this cough monitoring system (r=0.972, p<0.0001) - Excellent correlation between the number of coughs by this cough monitoring system and the other methods
Chang, 1997 [21]	Children with nonspecific recurrent cough n= 18	EMG + microphone + Holter monitor + cough processor Manual review of graphical interface	24 ambulatory recording	Tape recorder with manual counting of cough events	- Frequency: Manual review of recordings to count the number of cough events	- Mean difference (tape recorder was -0.3 coughs·h-1 (95% confidence interval-0.7 to 0.2). -The limits of agreement between the two methods were -2.2 to 1.7 coughs·h-1
Corrigan, 2003 [22]	13 infants with coughing illnesses and 17 healthy infants, all under 1 year of age n= 30	EMG + microphone= LR100 processor Automated analysis software	24h ambulatory recording or in hospital	Audio-video recording with manual counting of cough events	- Frequency: System shows the number of coughs that occurred in the total recording by combining sound reading and capturing vigorous thoracic movement -Cough pattern -Assessment of child's state when coughing	- Good sensitivity=81% with a PPV=0.8 - Good agreement between the two methods for infrequent cough (<5 coughs per hour, 95% CI –0.53 to 0.63 coughs/h). - Low agreement in infants with frequent cough
Urban, 2021 [11]	Children and adolescents with and without respiratory conditions n= 115	Microphone + Automated analysis software and classification	Overnight recording in hospital	Manual counting of cough events by an expert	- Frequency: System shows the average number of coughs/h - Automatic classification of sounds captured in cough or wheeze	- Sensitivity= 89% and a specificity of 99% -Excellent correlation between methods (cough: rS = 0.85, 95% CI: 0.76–0.91)
Amrulloh, 2017 [20]	Pediatric patients with a mean age of 25 months within first 12 of cough + breathlessness/fever n= 20	Microphone + pre-amplifier + converter Automated analysis and classification	In hospital	Leave one out validation tecnique	- Analysis of respiratory sounds and classification in Pneumonia or Asthma	- Sensitivity=100% and Specificity=80% (kappa static=0.8)
Paul, 2006 [25]	Subjects with frequent cough n= 15	Accelerometer + Portable device Automated analysis	Home, outpatient, inpatient for 15–60 min	Video recording	- System shows the number of coughs that occurred while recording -Cough intensity	- Excellent correlation for audio counts, ICC=0.998 (p < 0.001). - Excellent correlation for video counts, ICC=0.997 (p < 0.001).
Kruizinga, 2022 [23]	Children age 0-16 admitted due to pulmonary disease + Audio from publicly available Youtube videos n= 21	Microphones of a Motorola smartphone + Cough detection algorithm Automated analysis	In hospital admission	Classifiers Random Forests + Gradient Boosting Machines	- Frequency: System reveals the number of coughs that occurred while recording	- Accuracyy= 99.7% - Sensitivity= 47.6% - Specificity= 99.96% - NPV= 99.8% - Excellent correlation, ICC= 0.97 (p<.001)

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