Cough monitoring systems in adults with chronic respiratory diseases: a systematic review

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Shareable abstract (@ERSpublications)
Of the different cough monitoring systems for objective symptom evaluation in chronic respiratory diseases, VitaloJAK and the Leicester Cough Monitor have the best evidence for their utility, especially in people with idiopathic chronic cough. https://bit.ly/4gXfmQK

Cite this article as: Witjaksono LE, Schulte M, Holland AE, *et al*. Cough monitoring systems in adults with chronic respiratory diseases: a systematic review. *Eur Respir Rev* 2025; 34: 230212 [DOI: 10.1183/16000617.0212-2023].

Received: 20 Oct 2023
Accepted: 16 Dec 2024

Abstract

Background The role of objective cough monitoring systems for assessments in adults with chronic respiratory diseases (CRDs) is unclear. This systematic review aimed to synthesise current literature on frequency of use and characteristics of these systems.

Methods MEDLINE, Embase and CENTRAL were systematically searched to identify relevant literature evaluating cough in adults with CRDs using objective cough monitoring systems. The primary outcomes were utility and characteristics of the systems, with the secondary outcome being usability.

Results We identified 54 primary studies (4909 patients, with 3364 having idiopathic chronic cough). Included studies were generally of low risk of bias. Objective monitoring systems identified were VitaloJAK (n=19 studies), Leicester Cough Monitor (LCM, n=18), LEOSound (n=2), PulmoTrack (n=2), Hull Automated Cough Counter (HACC, n=1), LifeShirt (n=1), and unnamed devices (n=11). There was limited assessment against manual counting, with low-to-moderate correlation to patient-reported outcome measures for VitaloJAK ($p<0.05$), LCM (r=0.43–0.78) and unnamed devices (r=0.38–0.40). Test–retest consistency was evaluated in two studies, showing favourable results. There was at least moderate effect size of longitudinal measurement changes to various treatments for VitaloJAK (nine out of 16), LCM (two out of eight), HACC (n=1), LCM and HACC (n=1), PulmoTrack (n=1) and unnamed devices (n=3).

Conclusions Few studies evaluated the agreement of objective cough monitoring systems against manual counting. Most studies were conducted in patients with idiopathic chronic cough, with the VitaloJAK and LCM being were the most evaluated objective cough monitoring systems. Further evaluation of objective cough monitoring systems is needed for research and clinic application.

Introduction

Chronic respiratory diseases (CRDs) are a leading cause of morbidity and mortality worldwide, affecting ~7.4% of the global population [1]. Chronic cough is a common symptom of CRDs, which can negatively impact various aspects of patients' lives including physical, social and psychological aspects, as well as health-related quality of life (HRQoL) [2]. Assessment of cough is critical in the evaluation of people with CRD as well as to evaluate the effectiveness of interventions.

Cough can be evaluated both subjectively and objectively, which provide complementary information. While subjective cough assessments using questionnaires are commonly used [3, 4], these measures are subject to bias with individual patient perceptions and experiences. Cough sounds, airflow and muscle

contractions are unique characteristics that allow objective detection of cough. Different cough monitoring systems are now available for objective cough assessment, such as the VitaloJAK [5], Leicester Cough Monitor (LCM) [6] and Hull Automated Cough Counter (HACC) [7]. While satisfactory performance of available cough monitoring systems has been reported in their validation by the developers, which is an essential step of their development, the evaluation often included healthy volunteers, individuals with acute cough, or mixed populations with pulmonary and extrapulmonary causes of chronic cough, some of which have been explored in previous studies [7, 8]. Assessment of their utility and characteristics in the intended populations is important for appropriate clinical and research application. As cough monitors have only been developed in recent years, there is a lack of understanding of their adequacy and usefulness in adults with CRD.

Evaluating the frequency of use and characteristics of cough monitoring systems is essential for better selection of appropriate devices for patient care and research application in clinical trials of cough treatments. This systematic review aimed to synthesise available evidence on the frequency of use, device characteristics, and usability of different cough monitoring systems in adults with CRD.

Methods

The methods for this systematic review were in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols 2015 statement and guidance of the Cochrane Handbook [9]. The review protocol was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022327739).

Eligibility criteria

Inclusion criteria were randomised controlled trials (RCTs), nonrandomised studies and studies analysing clinimetric properties of objective monitoring systems in adults aged ⩾18 years who had CRD. Six types of CRDs were included, namely asthma, bronchiectasis, COPD, cystic fibrosis (CF), idiopathic chronic cough and interstitial lung disease (ILD). Non-English publications, studies that had subjects aged <18 years or diagnosed with non-CRDs, or animal studies, were excluded.

Search strategy

A search using the MEDLINE, Embase and the Cochrane Central Register for Controlled Trials was performed from inception up to 20 April 2022. The complete search strategy can be found in supplementary table S1. The reference list of included studies was searched manually for additional qualifying studies.

Selection process

Study selection was undertaken by two reviewers (L.E. Witjaksono and M. Schulte) independently. Abstract screening was conducted first, followed by full-text review to identify eligible studies. Any discrepancies were adjudicated by a third reviewer (Y.H. Khor).

Data extraction and risk-of-bias assessment

One reviewer (L.E. Witjaksono) extracted data using a standardised data extraction form and a second reviewer (M. Schulte) independently checked for verification. Extracted data included study design, study population characteristics, type(s) of cough monitoring system used, measures of device characteristics, and usability. Device characteristics evaluated included agreement for objective cough monitoring systems compared to manual cough counting and other assessments (including patient-reported outcome measures (PROMs) and disease parameters [10, 11]), test consistency of objective cough monitoring systems, and longitudinal measurements of cough monitoring systems [10]. Usability evaluation included a summary of patient-reported preference of device and percentage of missing data for the device, recording time and cost.

The risk-of-bias assessment for included studies was performed using appropriate tools depending on the study design by two reviewers (L.E. Witjaksono and M. Schulte) independently. The Cochrane Risk-of-Bias Assessment Tool was used for RCTs, assessing the study selection, reporting, performance, detection, attrition and other bias [12]. Nonrandomised studies were assessed using the Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) assessment tool, evaluating bias in confounding, selection, intervention classification, deviations, missing data, measurement outcomes and reporting [13]. The appropriate category within the COSMIN Risk-of-Bias checklist was used for studies of device characteristics [14]. Studies that had more than one component of study design were assessed using all the relevant risk-of-bias assessment tools.

Data synthesis

The primary analyses were performed by pooling data for all CRDs. The primary outcomes were 1) the frequency of reported use of different types of objective cough monitoring systems in research and clinical settings, and 2) measures of device characteristics for objective cough monitoring systems. Secondary outcomes were usability of the cough monitoring systems. Meta-analysis was not possible for this review as studies were heterogeneous in terms of methodology, disease group, cough monitoring device and duration of evaluation. Therefore, study outcomes were reported using narrative synthesis.

Parameters for primary outcomes

The frequency of use of cough monitoring systems was summarised using counts. Evaluation of device characteristics included the following (with the incorporation of statistical evaluation used).

- Agreement of cough count and frequency between objective monitoring systems and manual counting. Reports of sensitivity and specificity were provided where available, with manual counting being considered the gold standard.
- Agreement between measurements of objective monitoring systems and other comparators (except for manual counting) without pre-specified criteria, as different variables would be chosen depending on the investigators' research question(s), including, but not limited to, cough severity in terms of patients' impact and the underlying disease severity. These were interpreted using Pearson's correlation coefficient (r), with $\geqslant$0.7 as high, 0.5–0.7 as moderate, 0.3–0.5 as low and <0.3 as none [15]; and area under curve (AUC), with $\geqslant$0.90 as very good, 0.80–0.90 as good, 0.70–0.80 as fair, 0.60–0.70 as poor and <0.60 as none [16].
- Longitudinal interventional-related changes in the measurements of cough monitoring systems, which is important to ascertain the magnitude of changes detected in the context of disease management [17]. These were interpreted using effect sizes calculated by Cohen's d, with >0.8 as large, 0.2–0.8 as moderate and <0.2 as small [18].

Other reported statistical parameters for each device characteristic by the investigators were also incorporated.

Parameters for secondary outcomes

Usability of the cough monitoring systems was evaluated based on patient-reported preferences of device and percentage of missing data for the device, recording time and cost.

Subgroup analyses

Subgroup analyses were conducted for evaluation of different cough monitoring systems in each specific type of CRD.

Results

Characteristics of included studies

Figure 1 summarises the flow of study selection. Of the 13 770 potentially relevant studies, 361 underwent full-text review, with 54 original articles and seven secondary reports of the original articles being included (supplementary table S2). Six studies were published as conference abstracts only [19–24].

Of the 54 included studies, there were 17 randomised controlled parallel-group studies [22–38], 10 randomised crossover studies [19–21, 39–45], 14 cross-sectional studies [46–59], eight longitudinal cohort studies [60–67] and five clinimetric studies [68–72] (table 1). Most studies were published from 2010 onwards, with United Kingdom being the most common study country (n=23).

A total of 4909 patients were included (mean age range 19–86 years, with 20–90% females). The included studies mostly involved patients with idiopathic chronic cough (n=27) [19–25, 27–32, 35–37, 39–41, 44, 46, 47, 56–58, 61, 64, 65, 71], with limited studies for asthma (n=6) [42, 48–50, 60, 68], ILD (n=5) [33, 38, 43, 62, 67], COPD (n=4) [34, 46, 52, 63, 69], and bronchiectasis (n=1) [55] and CF (n=1) [51]. 10 studies involved mixed populations of different CRD diagnoses [21, 26, 45, 53, 54, 59, 66, 70, 72]. Most studies evaluated a single type of objective cough monitor, with two evaluating the LCM and HACC simultaneously [32, 64]. Some studies utilised investigational or unnamed cough monitoring instruments (wearable device n=3 [45, 52, 63]; phone application n=2 [54, 68]; phone recorder n=2 [50, 53]; microphone-based recorder n=3 [29, 69, 70]; undescribed n=1 [38]). Full details of study characteristics can be found in supplementary table S3.

Risk-of-bias assessment

Of the 27 randomised studies evaluated using the Cochrane Risk-of-Bias Assessment tool, 17 had low risk of bias [25–32, 34–40, 43, 45] and 10 had unclear risk of bias [19–24, 33, 41, 42, 44], mostly due to

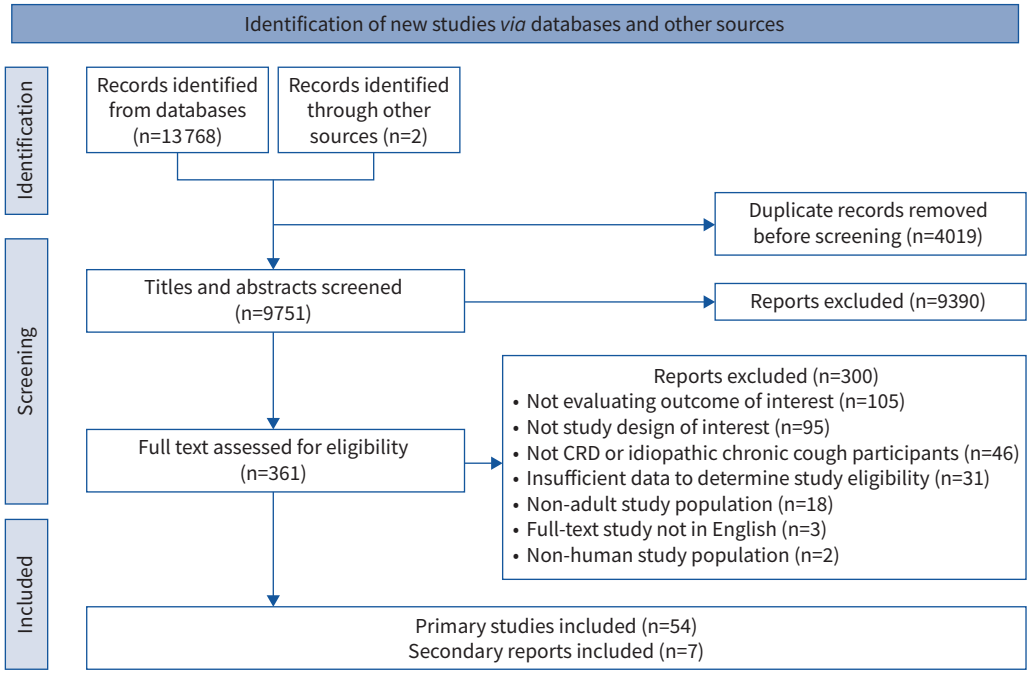

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the systematic review. CRD: chronic respiratory disease.

unclear reporting of participant and personnel blinding. For the 23 nonrandomised studies evaluated using ROBINS-I, most (n=17) were considered at low risk of bias [46, 48, 49, 51, 52, 54–59, 61, 62, 64–66, 71], with the other five at moderate risk of bias [47, 50, 53, 60, 67] due to confounding factors, selection of participants into the study, measurement outcomes and missing data. The COSMIN checklist for validity was used to assess the 19 studies evaluating comparison of objective cough monitoring systems with other parameters, 15 of which were of very good quality, three were of adequate quality and one was of doubtful quality due to inappropriate statistical methods and other potential risks of bias. Two studies of test consistency were assessed using the COSMIN checklist for reliability: one was of very good quality and one was of doubtful quality due to statistical methods and unclear test condition consistency. The COSMIN checklist was also used to assess 31 studies evaluating longitudinal interventional-related changes, 27 of which were of very good quality and four were of adequate quality due to poor description of the intervention. Supplementary table S4 summarises risk-of-bias assessment for each study.

Frequency of use

All studies were conducted in research settings, with the VitaloJAK (n=19) [19–25, 28, 30, 33–35, 39–41, 44, 59, 65, 71] and LCM (n=16) [26, 27, 31, 36, 37, 42, 46, 47, 49, 55–58, 62, 66, 67] being the most evaluated cough monitoring systems. Limited studies evaluated the LEOSound (n=2) [48, 52], PulmoTrack (n=2) [43, 72], HACC (n=1) [60] and LifeShirt (n=1) [51], with two studies evaluating both LCM and HACC (n=2) [32, 64], and 11 studies evaluating investigational or unnamed devices (n=11) [29, 38, 45, 52–54, 63, 68–70] (table 2). Recording of cough was carried out in the patient's home (n=22) [23–27, 29, 35, 37, 39, 40, 42, 48–51, 55, 57, 58, 65, 66, 68, 69], the laboratory (n=8) [28, 31, 43, 45, 53, 54, 70, 72], a mix of both (n=2) [21, 52] and at unknown settings (n=22) [19, 20, 22, 30, 32–34, 36, 38, 41, 44, 46, 47, 56, 59–64, 67, 71]. Outcomes from cough monitoring systems included cough counts (number of coughs detected in a defined period), cough frequency (cough per hour, cough per minute and epochs per hour), cough event distribution and cough intensity.

Comparison against manual cough counting

Comparison between cough monitoring systems and manual counting were assessed in six studies (mixed CRDs: PulmoTrack n=1 [72], VitaloJAK n=1 [59], an unnamed device n=2 [53, 54]; asthma n=1 [68] and COPD n=1 [69] using unnamed devices) (table 3). Cough frequency from the PulmoTrack had low correlation with manual cough counts in a study of 10 patients (median difference 25 cough·h^{-1}) [72]. The VitaloJAK had a sensitivity of 97.8–100% in identifying cough frequency, with the filtering algorithm

TABLE 1 Summary of included studies

	Studies	Participants
Study type		
Cross-sectional study	14	821
Longitudinal cohort study		
Prospective	7	293
Retrospective	1	174
Randomised controlled trial	17	2990
Randomised crossover study	10	246
Clinimetric study	5	385
Publication year		
Before 1999	1	15
2000–2009	0	0
2010–2019	28	1504
Since 2020	25	3390
Study location		
United Kingdom	20	675
Australia	4	443
United States of America	2	89
Germany	2	103
Other[#]	26	3599
Study design		
Single centre	24	1186
National multicentre	11	433
International multicentre	4	275
Unreported	15	3015
CRD type		
Idiopathic chronic cough	27	3373
Asthma	6	290
Interstitial lung disease	5	197
COPD	4	256
Bronchiectasis	1	54
Cystic fibrosis	1	19
Mixed	10	720
Participant characteristics ranges		
Female gender %	20–90	
Mean age years	19–86	
Mean duration of cough years	3–44	

Data are presented as n, unless otherwise stated. CRD: chronic respiratory disease. [#]: other study locations: Japan (n=2), Switzerland (n=2), Germany and United Kingdom (n=1), the Netherlands, Italy, France and United Kingdom (n=1), Australia, Belgium, Czech Republic, Germany, Italy, the Netherlands, New Zealand, Turkey, United Kingdom and United States of America (n=1), the Netherlands (n=1), Israel (n=1), Italy (n=1), Slovakia (n=1), Russia (n=1), Poland (n=1), unreported (n=13).

TABLE 2 Types of objective cough monitoring systems used for each type of chronic respiratory disease

	COPD	Asthma	CF	ILD	Bronchiectasis	Idiopathic chronic cough	Mixed
HACC		1				2[¶]	
LCM	1	2		2	1	11[¶]	1
LEOSound	1	1					
LifeShirt			1				
PulmoTrack				1			1
VitaloJAK	1			1		16	1
Other devices[#]	2	2		1		1	5

CF: cystic fibrosis; ILD: interstitial lung disease; HACC: Hull Automated Cough Counter; LCM: Leicester Cough Monitor. [#]: other devices included investigational or unnamed devices; [¶]: includes two studies which used both HACC and LCM.

https://doi.org/10.1183/16000617.0212-2023

TABLE 3 Main characteristics of studies comparing against manual counting and patient-reported outcome measures (PROMs) and disease parameters

First author, year [ref.]	Participants	Outcomes	Comparison variable	Assessment protocol	Main results
Comparison against manual counting					
PulmoTrack					
Turner, 2014 [72]	Total 10 COPD 1, IPF 1, idiopathic chronic cough 2, non-CRDs 6[#]	Cough frequency	Manual counting	20-h cough recordings at the hospital by PulmoTrack were compared with assessment by one investigator	Low correlation to manual counting (r= −0.23, p>0.05) A median difference of 100 cough counts to manual counting; 39% inaccuracy due to other sounds (speech, swallowing, microphone interference, breath sounds and background noise) detected as coughs for the PulmoTrack
VitaloJAK					
Smith, 2021 [59]	Total 63 Idiopathic chronic cough 21, IPF 12, COPD 14, asthma 10, bronchiectasis 6	Cough frequency	Manual counting	24-h recordings were analysed by the VitaloJAK algorithm and compared to manual counting	Idiopathic chronic cough: High median sensitivity of 99.9% (IQR 99.2–100%) compared to manual counting High sensitivity with filter efficiency of 7.4% (IQR 5.8–10.0%) in reducing cough recording duration IPF: High median sensitivity of 100% (IQR 99.4–100%) compared to manual counting High sensitivity with filter efficiency of 6.4% (IQR 3.4–10.2%) in reducing cough recording duration COPD: High median sensitivity of 97.8% (IQR 96.1–99.7%) compared to manual counting High sensitivity with filter efficiency of 5.0% (IQR 4.1–8.3%) in reducing cough recording duration Asthma: High median sensitivity of 100% (IQR 100–100%) compared to manual counting High sensitivity with filter efficiency of 7.0% (IQR 4.9–9.5%) in reducing cough recording duration Bronchiectasis: High median sensitivity of 99.3% (IQR 93.6–100%) compared to manual counting High sensitivity with filter efficiency of 3.8% (IQR 2.9–7.8%) in reducing cough recording duration

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TABLE 3 Continued

First author, year [ref.]	Participants	Outcomes	Comparison variable	Assessment protocol	Main results
Investigational or unnamed objective cough monitoring systems					
Barata, 2020 [68]	79 with asthma Age 43±16 years	Cough count Device type: smartphone with a microphone and Clara app	Manual counting	24-h recordings made for 29 days with the Clara app to record cough sounds and compared to manual counting	Good correlation between objective individual cough sounds and manual counting (AUC=0.82) Excellent correlation between objective cough epochs sounds and manual counting (AUC=0.92)
den Brinker, 2021 [69]	25 with COPD Mean age 66 years, standard deviation not reported	Cough frequency Device type: wireless microphone connected to a computer	Manual counting	90-day analysis of cough recorded at the patient's home with a stationary microphone connected to a laptop computer and compared to manual counting	Excellent correlation to manual counting (AUC=0.97)
Monge-Alvarez, 2019 [53]	13 with COPD, asthma or bronchiectasis (10 women)	Cough count Device type: mobile phone recorder	Manual counting	1-h cough recording on the table, in handbag or pocket in the laboratory	Recording on the table: sensitivity 87.37–88.51% specificity 99.70–99.77% Recording in the handbag/pocket: sensitivity 79.04–84.27% specificity 99.69–99.77%
Sharan, 2018 [54]	322 with COPD Age 61.08±6.26 years (116 women)	Cough count Device type: mobile phone app (ResApp Health) and microphone	Manual counting	Cough counts recorded for an unspecified duration at the laboratory	Sensitivity: linear regression 73.33% support vector regression 70.00% Specificity: linear regression 70.00% support vector regression 70.00%
Comparison against PROMs and disease parameters					
Leicester Cough Monitor					
Cho, 2019 [47]	30 with idiopathic chronic cough Age 59.9±9.5 years Median cough duration 7 years	Cough frequency	Capsaicin challenge test: 1 cough (CS1) 2 coughs (CS2) 5 coughs (CS5)	24-h cough recording	Moderate correlation for all evaluations: CS1: r= −0.556 CS2: r= −0.551 CS5: r=0.514

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TABLE 3 Continued

First author, year [ref.]	Participants	Outcomes	Comparison variable	Assessment protocol	Main results
Cho, 2021 [46]	27 with COPD 16 COPD with chronic cough (8 women) 11 COPD without chronic cough (5 women)	Cough frequency	Capsaicin challenge test: 2 coughs without suppression (C2) 5 coughs without suppression (C5) 2 coughs with suppression (CS2) 5 coughs with suppression (CS5)	24-h cough recording	Low correlation for all evaluations: C2: r= −0.411 C5: r= −0.430 CS2: r= −0.413 CS5: r= −0.420
Fukuhara, 2020 [49]	54 with asthma Mean age 54 years (52 women) Median cough duration 6 years	Cough frequency	Cough VAS LCQ D_{min} ACT F_{ENO} FEV_1 (%)	24-h cough recording at home	Good correlation: cough VAS (r=0.78) Moderate correlation: LCQ (r=0.60) Low correlation: D_{min} (r=0.38), ACT (r=0.43) No correlation: F_{ENO} (r=0.06), FEV_1 (r=0.10)
Jackson, 2020 [42]	15 with asthma Mean age 29.3 years (6 women)	Cough frequency	Cough VAS (after exercise) FEV_1 (%)	24-h cough recording at home compared to VAS after exercise	No correlation: VAS and FEV_1, without reporting details of statistical outcomes
Spinou, 2017 [55]	54 with bronchiectasis Age 60.5±15 years (37 women)	Cough frequency	Subjective assessments of cough: LCQ, cough VAS, BHQ, SGRQ Lung function tests: FEV_1 (%), FVC (%), FEV_1/FVC	24-h cough recording at home with automated analysis using customised cough detection software and compared to various subjective assessments	Moderate correlation with LCQ (r= −0.52), VAS (r=0.54) and BHQ (r= −0.62) Low correlation with SGRQ (r=0.32) No correlation with lung function tests (p>0.05)
Vertigan, 2013 [56]	33 with idiopathic chronic cough Age 58.7±14.9 years (27 women)	Cough frequency	None	Cough frequency per hour was recorded for an unspecified duration and at an unspecified location	Significant difference between cough frequency in case group and control group (p=0.002)
Vertigan, 2018 [58]	20 with idiopathic chronic cough Age 57±12 years (16 women)	Cough frequency	None	24-h cough recording at an unspecified location and reported as cough frequency per hour	Significant difference between cough frequency in case group and control group (p<0.001)
Vertigan, 2021 [66]	174 Idiopathic chronic cough 104, asthma 21, non-CRDs 50[#] Age 57±10 years	Cough frequency	LHQ LCQ Unspecified QoL questionnaire	24-h cough recording at home was compared to subjective assessments post-treatment	Low correlation to LHQ (r= −0.430) Low correlation to LCQ (r= −0.430) Low correlation to unspecified QoL questionnaire (r= −0.439)

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TABLE 3 Continued

First author, year [ref.]	Participants	Outcomes	Comparison variable	Assessment protocol	Main results
LifeShirt					
Kerem, 2011 [51]	19 with CF (9 women)	Cough frequency	Unspecified subjective cough score FEV_1 (%)	24-h cough recordings at home were analysed using device-specific software and compared to the spirometry test	No correlation to unspecified subjective cough score (r= −0.057, p=0.816) Low correlation to FEV_1 (r= −0.448, p=0.054)
VitaloJAK					
Nguyen, 2019 [22]	253 with idiopathic chronic cough (192 women)	Cough frequency	None	24-h cough recording at an unspecified location	38% reduction if cough frequency is correlated to PGIC of "somewhat improved", "improved" or "very much improved" 57.5% reduction if cough frequency is correlated to PGIC of "very much improved"
Nguyen, 2021 [71]	253 with idiopathic chronic cough (192 women)	Cough frequency	Cough VAS	24-h sound recordings during times in which the patient was awake Assessed at baseline and weeks 4, 8 and 12 and compared to VAS outcomes	Significant correlation to VAS evaluated by ANOVA (p<0.05) Significant difference between groups stratified into tertiles of cough frequency compared to VAS at baseline (F=8.5, p=0.0003) and 4 weeks (F=27.7, p<0.0001)
Investigational or unnamed objective cough monitoring systems					
Krajnik, 2010 [21]	13 Asthma 12, BHR 4 Age 46.4±11.1 years (11 women)	Cough frequency Device type: microphone	Unspecified daytime and night-time cough scoring NRS	15–24-h cough recording at the home and laboratory setting compared to various subjective assessments	Moderate correlation with daytime cough scoring (r=0.60) and NRS (r=0.52) No correlation with night-time cough scoring (p>0.05)
Ovsyannikov, 2019 [63]	110 patients with COPD Age 61.08±6.28 years (40 women)	Cough frequency Device type: a microphone, an accelerometer, a microcontroller and a breath sensor	Cough VAS	12-h cough recording which is connected to a computer that eliminates silences and automatically counts coughs and compared to VAS	Low correlation to VAS (r=0.42)

IPF: idiopathic pulmonary fibrosis; CRD: chronic respiratory disease; IQR: interquartile range; AUC: area under the curve; VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire; D_{min}: minimum dose to improve symptom; ACT: Asthma Control Test; F_{ENO}: fractional expiratory nitric oxide; FEV_1: forced expiratory volume in 1 s; BHQ: Bronchial Hyperresponsiveness Questionnaire; SGRQ: St George's Respiratory Questionnaire; FVC: forced vital capacity; LHQ: Laryngeal Hyperresponsiveness Questionnaire; QoL: quality of life; CF: cystic fibrosis; PGIC: Patient Global Impression of Change; BHR: bronchial hyperreactivity; NRS: numerical rating scale. #: results presented only included for patients with CRD.

reducing 24-h recording duration to the 3.8–7.4% containing cough sounds (representing specificity) [59]. For studies of an investigational phone application and an unnamed microphone recorder, there were overall high correlations for cough counts (AUC=0.97), single cough sounds (AUC=0.82) and cough epochs (AUC=0.92) compared to manual counting (n=2) [68, 69]. The ResApp Health mobile and microphone had 70% sensitivity and 70% specificity in recording cough sounds, compared to manual counting [54]. Another study using a mobile phone recorder reported 83.8% sensitivity and 99.7% specificity for cough frequency, compared to manual counting [53].

Comparison against PROMs and disease parameters

Comparison of cough monitoring systems against PROMs and disease parameters were assessed in 13 studies (idiopathic chronic cough n=5 [22, 47, 56, 58, 71]; asthma n=2 [42, 49]; COPD n=2 [46, 63]; bronchiectasis n=1 [55]; CF n=1 [51]; mixed CRDs n=2 [21, 66]) (table 3). This was most studied for the LCM (n=8), with other studies evaluating the VitaloJAK (n=2), LifeShirt (n=1) and unnamed devices (n=2) [68, 69].

In the eight studies using the LCM, the assessment was evaluated for cough frequency. Cough monitoring by the LCM showed a higher mean cough count in patients with CRD compared to control (mean difference 6.8–8.7 cough·h^{-1}) [55, 56, 58, 66]. Overall, there was a moderate correlation between the LCM and PROMs, suggested by the low (r=0.430) and moderate (r=0.52–0.60) correlation to the Leicester Cough Questionnaire (LCQ) (n=3) [49, 55, 66]; low-to-high correlation to the cough visual analogue scale (VAS) (n=3) [42, 49, 55]; moderate correlation to the Bronchial Hyperresponsiveness Questionnaire (n=1) [55]; and low correlation to the Laryngeal Hypersensitivity Questionnaire, Asthma Control Test, St George's Respiratory Questionnaire and an unspecified HRQoL evaluation (n=3) [49, 55, 66]. Comparisons of the LCM to lung function tests showed no correlation for forced expiratory volume in 1s (FEV_1)/forced vital capacity (FVC), FEV_1, FVC and fractional expired nitric oxide (n=2) [49, 55]. Low-to-moderate correlations were found in comparison to capsaicin challenge tests (r= –0.411–0.556) [46, 47].

For the VitaloJAK, cough frequency had significant correlation ($p<0.05$; correlation coefficient not provided) compared to the cough VAS where a lower cough frequency was correlated to a lower severity on cough VAS [71]. Another study using the VitaloJAK found that a higher percentage of reduction in cough counts was correlated to symptom improvement measured by the Patient Global Impression of Change scale (p-value and correlation coefficient not reported) [22].

Cough frequency from the LifeShirt cough monitor correlated weakly with FEV_1 and did not correlate to an unspecified subjective cough score (n=1) [51]. An overall low correlation of cough frequency measured using a wearable device to PROMs can be inferred from the low correlation in comparison with the cough VAS (r=0.38–0.40; n=1) [63] and low-to-moderate correlation in comparison to the daytime numerical rating scale, night-time numerical rating scale and cough scoring (n=1) [21].

Test consistency

Two studies assessed repeated device testing, which were conducted using the PulmoTrack [72] and VitaloJAK [59] for measuring cough frequency in a mixed population of patients with CRD (figure 2). 10 patients underwent recordings with the PulmoTrack, and the authors stated that "automated detected numbers and timings of cough were identical the second time all sequences were analysed" [72]. Repeat cough recording of 11 patients using the VitaloJAK showed similar cough frequency with a median difference in sensitivity of 0.2% (interquartile range (IQR) −4.2% to +2.8%) [59].

Longitudinal interventional-related changes

31 studies reported serial measures of objective cough count at more than one time point, allowing calculation of effect size (d) [19–21, 23, 25–41, 43–45, 49, 60, 62, 63, 65–67], as summarised in table 4 and figure 2. There was one study that evaluated two different devices [32]. Most studies were conducted in patients with idiopathic chronic cough (n=20) [19–23, 25, 27–32, 35, 36, 39–41, 44, 65, 66, 71], with the remainder in patients with ILD (n=5) [33, 38, 43, 62, 67], asthma (n=3) [45, 49, 60], COPD (n=2) [34, 63] and a mix of CRDs (n=1) [26]. The VitaloJAK was most frequently used to detect change over time (n=15), followed by the LCM (n=9), HACC (n=1) [60], HACC and LCM together (n=1) [32], PulmoTrack (n=1) [43] and unnamed devices (n=4).

15 studies used the VitaloJAK in patients with idiopathic chronic cough to assess change in cough counts with treatment against various treatments [19, 20, 23, 25, 28, 30, 33–35, 39–41, 44, 61, 65]. For the 24-h cough count, there was a moderate effect size (d=0.59–0.79) for 16 weeks of gefapixant (n=1) [35]. The response to treatment of 24-h morphine (d=0.72) [20], 4-day 150 mg and 250 mg BAY 1902607 (d=0.28–0.37) [41],

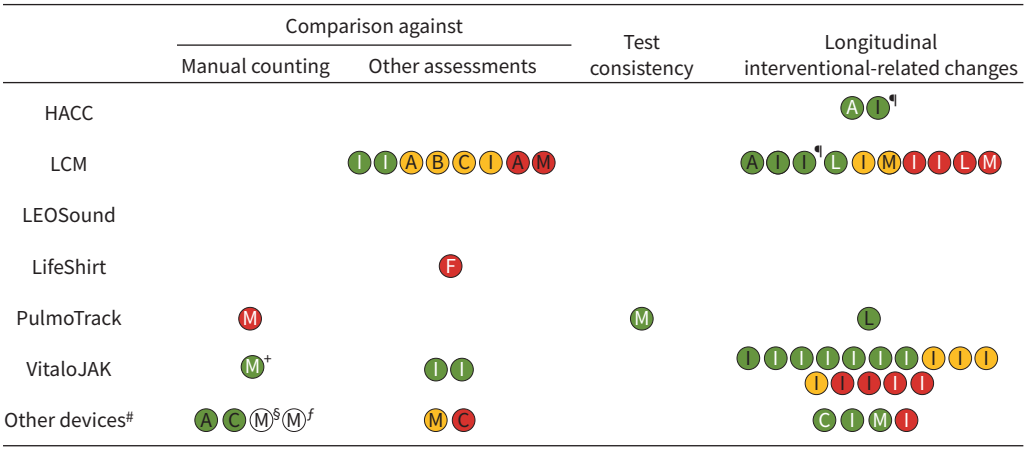

FIGURE 2 Summary of data for device characteristics for the objective cough monitoring systems evaluated. Each circle represents a single study. The letters within the circles indicate disease types: A=asthma, B=bronchiectasis, C=COPD, F=cystic fibrosis, I=idiopathic chronic cough, L=interstitial lung disease, M=mixed diseases. The colour of the symbols indicates the strength of each metric, as follows. Correlation coefficient: green=high, yellow=moderate, red=low or none; area under curve: green=very good and good, yellow=fair, red=poor or none; sensitivity and specificity: white (specific values mentioned in footnotes); intraclass correlation: green=excellent and good, yellow=moderate, red=poor; Cohen's d: green=high, yellow=moderate, red=small; p-values: green=significant, red=insignificant. The text colour represents the statistical analyses: black=studies reporting specific statistical outcomes, white=studies reporting p-value statistics only. Criterion validity: agreement of cough count and frequency between objective monitoring systems and manual counting; convergent validity: agreement of cough count and frequency between objective monitoring systems and all other comparators chosen depending on the investigators' research question(s), including, but not limited to cough severity in terms of patients' impact and the underlying disease severity; reliability: test–retest reliability; responsiveness: longitudinal interventional-related changes. No studies evaluated serial measurements using cough monitoring systems. HACC: Hall Automated Cough Counter; LCM: Leicester Cough Monitor. #: unnamed and investigational devices; ¶: one study used both the HACC and LCM; +: sensitivity 97.8–100%, specificity (recording duration reduction) 3.8–7.4%; §: sensitivity 70%, specificity 70%; f: sensitivity 83.8%, specificity 99.7%.

7-day GSK2798745 [44] and 2-week lesogaberan (d=0.23–0.31) [39] demonstrated an overall moderate effect size for change of cough frequency. Three studies found small effect sizes in the reduction of cough count after treatment with 4-day 80 mg BAY 1902607 (d=0.17) [41], 7-day GSK2798745 (d=0.09) [44] and 14-day XEN-D0501 (d=0.11–0.14) [40]. While effect sizes could not be determined, five studies reported statistically significant reductions in cough counts (10-h post-lidocaine throat spray (p=0.017) [25], 5–7-day morphine (p<0.05) [20], 1-week 750 mg eliapixant (p<0.001) [28], 2-week AF-219 (p<0.001) [19], 8-week 30 mg orvepitant p=0.020) [65]) and three reported changes that were not statistically significant (10-h post-nebulised lidocaine (p=0.84) [25], 2-week 150 mg sivopixant (p=0.055) [30], and bradanicline (p>0.05) [61]). Change in mean cough count in the CRD group was compared to that of control in three studies, with significant between-group differences being reported for treatment of 7-day 100 mg VRP700 (4-h cough count) [33], 2-week 62.5 µg umeclidinium and 25 µg vilanterol (24-h cough count, p=0.018) [34], and 16-day 30 mg and 50 mg AF-219 (awake cough count, p<0.05) [23], with a nonsignificant between-group effect for 2-week 600 µg navafenterol (24-h cough count, p=0.11) [34].

Nine studies used the LCM to evaluate changes with treatment. There was a large effect size for reduction of cough frequency with an unspecified medication for patients with asthma (d=0.69–0.97; n=1) [49] and by speech pathology management for patients with idiopathic chronic cough (d=2.0; n=1) [66]. Two studies found a moderate effect size for reduction of cough frequency after 14-day PA101 treatment in patients with ILD and idiopathic chronic cough (d=0.38) [26] and after 4-week pregabalin in patients with idiopathic chronic cough (d=0.40) [36]. In patients with idiopathic pulmonary fibrosis (IPF), a subtype of ILD, there were significant changes in 24-h cough counts with treatment with pirfenidone at −14% at 4 weeks (p=0.002) and −34% at 12 weeks (p=0.002) [67]; however, no significant change was found after treatment with proton pump inhibitor and prokinetic therapy (p=0.59–0.70) [62]. Three studies reported no difference in mean change of cough frequency between intervention and placebo groups after 12-week

https://doi.org/10.1183/16000617.0212-2023

TABLE 4 Main characteristics of studies evaluating longitudinal interventional-related changes

First author, year [ref.]	Participants	Affecter of change Time interval	Assessment protocol	Main results
HACC				
Faruqi, 2020 [60]	11 patients with asthma Age 53.6±11.5 years (5 women)	Cough frequency response to treatment of mepolizumab Baseline to 6 months	Evaluation in a cohort of patients	Significant change in cough frequency after 6 months (p<0.02)
HACC and LCM				
Sadeghi, 2018 [32]	253 patients with idiopathic chronic cough (192 women)	Cough frequency response to treatment of montelukast and/or prednisolone Baseline and week 4	Evaluation for the three patient groups Group 1: montelukast treatment for patients with low F_{ENO} Group 2: montelukast treatment for patients with high F_{ENO} Group 3: montelukast and prednisolone treatment	Large effect size for group 1 (d=0.919) Large effect size for group 2 (d=1.084) Large effect size for group 3 (d=0.834)
LCM				
Birring, 2017 [26]	Total 51 IPF: n=24 (9 women) Cough duration 5.6±4.2 years Idiopathic chronic cough: n=27 (21 women) Cough duration 9.9±9.8 years	Cough frequency response to treatment of PA101 Baseline to day 14	Evaluation for intervention and placebo groups	Medium effect size (d=0.381) and larger in intervention group compared to placebo group (d=0.026) Medium effect size in change of daytime cough for IPF patients (d=0.311) Small effect size in change of daytime cough for idiopathic chronic cough patient (d=0.062)
Fukuhara, 2020 [49]	73 patients with asthma Mean age 54 years (52 women) Median cough duration 6.0 years	Cough frequency response to unspecified treatments for asthma Not reported	Evaluation by comparing changes in cough frequency for 24 h to the changes in daytime and night-time change in cough frequency using correlation coefficient	High correlation to daytime changes in cough frequency (r=0.97, p<0.001) High correlation to night change in cough frequency (r=0.69, p<0.001)
Kilduff, 2014 [62]	18 patients with ILD (5 women)	24-h cough frequency response to proton pump inhibitor therapy Baseline to 8 weeks	Evaluation by comparing the same cohort before and after suppression therapy The main cohort was given omeprazole 40 mg or lansoprazole 30 mg plus ranitidine 300 mg at night A group of three patients was additionally given prokinetic therapy (metoclopramide 10 mg or domperidone 10 mg)	No significant change in 24-h cough count in cohort group before and after treatment (p=0.70) No significant change in 24-h cough counts in patients given prokinetic therapy before and after treatment (p=0.59)

Continued

TABLE 4 Continued

First author, year [ref.]	Participants	Affecter of change Time interval	Assessment protocol	Main results
Chamberlain, 2015 [27]	75 patients with idiopathic chronic cough (26 women)	24-h cough frequency recorded for 2 days response to PSALTI Baseline to 4 weeks and 3 months	Evaluation by comparing mean cough count change for 2 days, 24 h	Significant difference in 24-h cough count after 4 weeks of PSALTI (p=0.002) No significant difference in 24-h cough count after 3 months of PSALTI (p=0.236)
Ryan, 2012 [31]	62 patients with idiopathic chronic cough Age 62.7±14 years (20 women)	1-h cough recording for cough count in response to gabapentin Baseline to 4 weeks and 12 weeks	Evaluation by comparing mean cough count change from baseline to 4 and 12 weeks between the intervention group and placebo group	Significant difference in 1-h cough count between the groups after 4 weeks (change= −27.31, p=0.028) No significant difference in 1-h cough count between the groups after 12 weeks (change= −3.10, p=0.88)
Van Manen, 2017 [67]	43 patients with IPF Age 72±7 years (10 women)	Cough frequency response to pirfenidone treatment Baseline to 4 and 12 weeks	Evaluation by comparing 24-h cough count pre- and post-treatment	Significant difference in cough count after 4 weeks (p=0.002) with 14% reduction Significant difference in cough count after 2 weeks (p=0.002) with 34% reduction
Vertigan, 2016 [36]	40 patients with idiopathic chronic cough Cough duration 123±119 months Group 1: Age 61±13 years (14 women) Group 2: Age 64±12 years (13 women)	Cough frequency response to speech perception test and pregabalin (group 1), and speech perception test and placebo (group 2) Baseline and week 4	Evaluation for cough frequency in two groups of patients	Medium effect size in group 1 (d=0.396) Large effect size in group 2 (d=0.627)
Vertigan, 2021 [66]	Total 174 Idiopathic chronic cough: n=103 Age 60.56±13.95 years (72 women) Cough duration 109±125 months Inducible laryngeal obstruction: n=50 Age 58.3±3.86 years (38 women) Cough duration 83±160 months Severe asthma: n=21 Age 52.25±12.33 years (16 women) Cough duration 94±202 months	Cough frequency response to unspecified treatments Baseline to 3–4 months	Evaluation by comparing geometric cough frequency means pre- and post-treatment	Large effect size between pre- and post-treatment period (d=2.0)

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TABLE 4 Continued

First author, year [ref.]	Participants	Affecter of change Time interval	Assessment protocol	Main results
Yousaf, 2010 [37]	30 patients with idiopathic chronic cough Intervention group: Age 63±9 years (13 women) Placebo group: Age 61±9 years (11 women)	24-h cough frequency recorded for 4 days response to 250 mg erythromycin Baseline to 12 weeks	Evaluation by comparing mean cough change between intervention and placebo group	No significant difference in mean cough count between the groups (change=1.1, p=0.585)
PulmoTrack				
Lavorini, 2016 [43]	8 patients with ILD Age 71±7.07 years (1 woman)	Cough frequency response to treatment of VRP700; 4 h before and after treatment	Evaluation before and after treatment for intervention and placebo groups	Large effect size (d=3.551) and larger than placebo group (d=0.590)
VitaloJAK				
Abdulqawi, 2013 [19]	24 patients with idiopathic chronic cough Age 54.5 years (19 women)	Daytime cough rate response to treatment of AF-219 Baseline to 2 weeks of treatment	Evaluation before and after treatment in reducing daytime cough	Significant change in daytime cough rate −75% (95% CI −50 to −88; p<0.001)
Abdulqawi, 2021 [25]	26 patients with idiopathic chronic cough Age 53.5±12.1 years (21 women) Mean cough duration 10 years, IQR 7–16 years	Cough frequency response to nebulised lidocaine and lidocaine throat spray Baseline to 10 h	Evaluation before and after treatment with two intervention groups for each treatment and placebo	Significant difference between intervention groups for cough frequency 10 h after treatment (p=0.04) Significant difference between intervention groups for 5-h cough frequency (p=0.004) Significant difference between lidocaine throat spray and placebo for 10-h cough frequency (95% CI −52% to 22%; p=0.017) No significant difference between nebulised lidocaine and placebo for 10-h cough frequency (p=0.84)
Al-Sheklly, 2017 [20]	22 patients with idiopathic chronic cough Age 61.7 years (18 women) Mean cough duration 14 years	Daytime, night-time and 24-h cough frequency response to morphine Baseline to end of treatment period (5–7 days)	Evaluation in intervention and placebo groups	Significant change in daytime cough frequency compared to placebo (p<0.05) Significant change in night-time cough frequency compared to placebo (p<0.05) Significant change in 24-h cough frequency compared to placebo (p<0.05) Medium effect size in reduction of 24-h cough frequency (d=0.718)

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TABLE 4 Continued

First author, year [ref.]	Participants	Affecter of change Time interval	Assessment protocol	Main results
Badri, 2022 [39]	21 patients with idiopathic chronic cough Age 63±7 years 73% female Median cough duration 10 years	Daytime, night-time and 24-h cough and bouts of cough response to lesogaberan Baseline to 2 weeks of treatment	Evaluation in intervention and placebo groups	Medium effect size in reduction of 24-h cough compared to placebo (d=0.261) Medium effect size in reduction of daytime cough compared to placebo (d=0.231) Medium effect size in reduction of night-time cough compared to placebo (d=0.281) Medium effect size in reduction of bouts of cough (d=0.310, p=0.04)
Belvisi, 2017 [40]	18 patients with idiopathic chronic cough Mean age 63.1 years (15 women)	Awake, sleep and 24-h cough response to treatment of XEN-D0501 Baseline to 14 days of treatment	Evaluation by comparing between intervention and placebo group for awake and 24 h cough counts	Small effect size for awake cough frequency (d=0.142), but larger than placebo (d=0.007) Small effect size for 24-h cough frequency (d=0.107), but larger than placebo (d=0.019)
Friedrich, 2020 [41]	23 patients with idiopathic chronic cough Mean age 60 years (18 women)	Cough counts per hour response to treatment of oral BAY 1902607 Baseline to 4 days of treatment	Evaluation in three groups given 80 mg, 150 mg and 250 mg of BAY 1902607	Small effect size for group given 80 mg BAY 1902607 (d=0.170, p=0.015) Medium effect size for group given 150 mg BAY 1902607 (d=0.280, p<0.001) Medium effect size for group given 250 mg BAY 1902607 (d=0.370, p<0.001)
Kanemitsu, 2020 [61]	46 patients with idiopathic chronic cough Mean age 63 years (39 women) Mean cough duration 18 years	Cough incident per hour response to treatment of bradanicline	Evaluation and comparison between intervention and placebo groups recorded in one 24-h period	No reduction in cough incidents in both intervention and placebo groups No significant difference between placebo and intervention group (p>0.05)
Ludbrook, 2019 [44]	17 patients with idiopathic chronic cough Mean age 61 years (88% women)	10-h and 24-h cough count response to treatment of GSK2798745 Baseline to 7 days of treatment	Evaluation and comparison between intervention and placebo groups	Medium effect size for average cough count increase in intervention group compared to placebo group (d=0.32) Medium effect size for 10-h cough count increase in intervention group compared to placebo group (d=0.34) Small effect size for 24-h cough count increase in intervention group compared to placebo group (d=0.09)
Morice, 2021 [28]	40 patients with idiopathic chronic cough Age 61.5±10.5 years (31 women)	24-h cough count response to eliapixant Baseline to 1 week	Evaluation and comparison to baseline and between intervention and placebo group	No significant difference in 24-h cough count from baseline to after treatment of 10 mg eliapixant (change=9.4%, p>0.05) Significant difference in 24-h cough count from baseline to after treatment of 50 mg eliapixant (change=29.5%, p=0.001), 200 mg eliapixant (change=36.0%, p<0.001), and 750 mg eliapixant (change=38.1%, p<0.001)

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TABLE 4 Continued

First author, year [ref.]	Participants	Affecter of change Time interval	Assessment protocol	Main results
Niimi, 2022 [30]	31 patients with idiopathic chronic cough Age 50±14.6 years (20 women)	24-h cough frequency response to oral sivopixant Baseline to 2 weeks	Evaluation by comparing change of mean cough counts from baseline to 2 weeks adjusted to placebo	Significant change was found in cough counts after 2 weeks in intervention group adjusted to placebo (change=31.6%, p=0.0546)
Satia, 2015 [33]	20 patients with IPF Age 69.8±6.9 years (12 women)	4-h cough frequency response to VRP700 Baseline to 7 days	Evaluation by comparing mean cough counts of intervention and placebo group	Significantly higher mean cough count change in intervention group compared to control group (p<0.001)
Singh, 2022 [34]	73 patients with COPD Age 66±7.6 years (23 women)	24-h cough frequency response to umeclidinium/vilanterol or navafenterol Baseline to 2 weeks	Evaluation by comparing intervention groups to placebo group	Significant difference was found in change of cough counts between umeclidinium/vilanterol group and placebo group (p=0.018) No significant difference was found in change of cough counts between navafenterol group and placebo group (p=0.108)
Smith, 2016 [23]	30 patients with idiopathic chronic cough Mean age 60 years (24 women)	Awake cough frequency response to AF-219 Baseline to 16 days	Evaluation by comparing mean cough count from baseline to 16 days	No significant change in cough counts in groups given 7.5 mg and 15 mg AF-219 (p>0.05) Significant change in cough counts in groups given 30 mg and 50 mg AF-219 (p<0.05)
Smith, 2020 [35]	59 patients with idiopathic chronic cough Study 1: n=29 Age 63.2±7.35 years (24 women) Median cough duration 15.4 years Study 2: n=30 Age 60.2±11.06 years (24 women) Median cough duration 13.2 years	Cough frequency response to gefapixant (study 1: 50–200 mg, study 2: 7.5–50 mg) Baseline to day 16	Evaluation for awake, night and 24-h cough in intervention and placebo groups in two studies reported within one publication	Study 1: Large effect size for awake cough frequency (d=0.817) and larger than placebo (d=0.071) Medium effect size for night cough frequency (d=0.510) and larger compared to placebo (d=0.186) Large effect size for 24-h cough frequency (d=0.793) and larger than placebo (d=0.110) Study 2: Medium effect size for awake cough frequency (d=0.633) and larger than placebo (0.129) Small effect size for night cough frequency (d=0.245) and smaller than placebo (d=0.346) Medium effect size for 24-h cough frequency (d=0.587) and larger than placebo (d=0.189)
Smith, 2020 [65]	13 patients with idiopathic chronic cough Age 60.1±8.36 years (11 women)	Cough frequency response to 30 mg orvepitant Baseline to 8 weeks	Evaluation for daytime and night-time cough frequency	Significant change in daytime cough frequency from baseline (p=0.020) Significant change in night-time cough frequency from baseline (p=0.017)

Continued

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TABLE 4 Continued

First author, year [ref.]	Participants	Affecter of change Time interval	Assessment protocol	Main results
Unspecified objective cough monitoring systems				
Martinez, 2022 [38]	108 patients with IPF Mean age 71 years (40 women) Mean cough duration 5.2 years	Cough frequency response to RVT-1601 treatment Baseline to 12 weeks	Evaluation by comparing 24-h cough count pre- and post-treatment	No significant difference in cough count after 12 weeks (p>0.05)
Matthys, 1983 [45]	Total 15 Asthma+COPD 7 ILD 1 Age 66±7 years (3 women)	Mean cough frequency response to dextromethorphan and codeine	Evaluation in three groups of patients Group 1: those given dextromethorphan Group 2: those given codeine Group 3: those given placebo	Asthma+COPD: Significant difference between all three groups (p<0.001) Significant difference between group 1 (p=0.0294) and group 2 (p=0.0486) with group 3 No significant difference between group 1 with group 2 (p=0.9519) ILD: Significant difference between all three groups (p=0.001) Significant difference between group 1 with group 3 (p=0.0009) No significant difference between group 2 with group 3 (p=0.3125) and group 1 and group 2 (p=0.1365)
Morice, 2019 [29]	24 patients with idiopathic chronic cough Age 61.1±8.69 years (21 women)	24-h cough frequency response to gefapixant Baseline to 2 weeks	Evaluation by comparing the change in cough counts between intervention and placebo groups	Significant difference in cough frequency between intervention and placebo groups (change=3.6, p=0.008)
Ovsyannikov, 2019 [63]	110 patients with COPD Age 61.08±6.26 years (97 women)	12-h cough frequency response to short acting β_2-agonists, long acting β_2-agonists and antibiotic therapy Baseline to 10 days	Evaluation by comparing the change in cough counts from baseline to 10 days	Significant difference between cough counts at baseline and 10 days (p<0.05)

Data are presented as n or mean±SD unless otherwise stated. HACC: Hull Automated Cough Counter; LCM: Leicester Cough Monitor; F_{ENO}: fractional expiratory nitric oxide; d: effect size; IPF: idiopathic pulmonary fibrosis; r: correlation coefficient; ILD: interstitial lung disease; PSALTI: physiotherapy, speech and language therapy intervention; IQR: interquartile range.

250 mg erythromycin (p=0.59) [37], 12-week gabapentin (p=0.88) [31] and 4-week physiotherapy, speech and language therapy intervention (p=0.24) [27].

The HACC was used in one study of patients with asthma, which showed a significant reduction in cough count from baseline after 6-month mepolizumab [60]. A study evaluating cough frequency using both the LCM and HACC found a moderate-to-large effect size after 2-week treatment with both montelukast (d=1.16) and combined treatment with montelukast and prednisolone (d=1.16) [32]. A large effect size (d=3.55) for cough frequency was found for 4-h VRP700 treatment in a study of patients with ILD using the PulmoTrack [43].

A study using an unnamed device evaluated change in cough frequency after treatment with dextromethorphan or codeine in a mixed CRD population [45]. In patients with asthma and/or COPD, a significant difference was found between both interventions compared to placebo, with no significant difference between the two intervention groups [45]. In patients with ILD, a significant difference was reported only for the dextromethorphan group compared to placebo, but not for the codeine group, nor difference between the interventions [45]. Another study on patients with IPF found no difference in cough counts following the treatment of RVT-1601 for 12 weeks, although this study was underpowered with premature termination [38]. An unnamed cough-monitoring device with an accelerometer recorded a significant difference in 10–12-h cough counts in patients with COPD after 10 days of treatment with short-acting β_2-agonists, long-acting β_2-agonists and antibiotic therapy ($p<0.05$) [63]. A significant reduction in mean cough counts was found in a study using an unnamed ambulatory device between patients receiving treatment of 1-day 100 mg gefapixant and placebo (p=0.008) [29].

Usability

No formal evaluation of user preferences for different objective cough monitoring systems was reported in the included studies. However, two studies reported user experiences, with discomfort being described with using the LifeShirt [51] and issues with the recording files for the LCM [66].

19 studies reported missing data (supplementary figure S1), with the most common reason being non-device-related followed by device failure [21, 25, 26, 31, 32, 38, 39, 42, 44, 52, 61, 62, 64–69, 72]. This resulted in missing data of 4–40% of study sample size and was reported in studies using the PulmoTrack, LEOSound, HACC, unnamed devices, LCM and VitaloJAK (22%, 14%, 6.3%, 5.5%, 5%, 0.2%, respectively, for missing subject data from total subjects of studies reporting missing data). Other causes of missing data were uninterpretable recording, occupational issues and patient discomfort.

The recording duration for the cough monitoring systems was reported in 44 studies [20–22, 24–53, 55, 57–60, 62–64, 66–68, 70–72]. An additional three studies reported cough recording while awake (n=1) [71] or at night-time (n=2) [50, 61]. Most studies recorded cough for 24 h (24 h: n=33, <24 h: n=11) using the HACC [53, 60], LCM [26, 27, 32, 36, 37, 42, 46, 47, 49, 55, 57, 58, 62, 66, 67], LifeShirt [51], VitaloJAK [20, 22, 24, 28, 30, 34, 35, 39–41, 44, 59] and unnamed devices [29, 38]. Nine studies recorded for 24 h over multiple days: 2 days (VitaloJAK: n=2 [34, 44], LCM: n=1 [27]), 3 days (VitaloJAK: n=1 [20], LCM: n=1 [26], investigational or unnamed devices: n=1 [29]), 4 days (VitaloJAK: n=1 [40], LCM: n=1 [37]) and 29 days (unnamed device: n=1 [68]).

No studies reported the financial cost of cough monitoring systems. One study reported the time cost of using the LCM, with ∼1.5 h being required for device preparation for each patient, including 5–10 min set-up time (excluding the recording time) [66]. Another study reported that the PulmoTrack set-up took 9 min and its data processing took 7 h for a 24-h recording [72].

Subgroup analysis

28 studies evaluated 3394 patients with idiopathic chronic cough using the VitaloJAK (n=17) [14–20, 23, 25, 30, 33–35, 38, 58, 60, 63], LCM (n=8) [22, 26, 31, 32, 41, 50–52], LCM and HACC (n=2) [27, 57] and an unnamed device (n=1) [24]. The median sensitivity of the VitaloJAK against manual counting was 99.9% (IQR 99.2–100%) and median filter efficiency of reducing cough recording duration was 7.4% (IQR 5.8–10.0%) [59]. The agreement against PROMs for the VitaloJAK in this patient group was high against the cough VAS and Patient Global Impression of Change Scale (correlations not reported) [17, 63]. The reported effect size for evaluation of longitudinal interventional-related changes for the VitaloJAK was moderate-to-large to most interventions (n=6, d= 0.23–0.72) [15, 30, 33, 35, 38, 63], with weak effect sizes for three studies (d=0.09–0.17) [34, 35, 38]. The LCM was also utilised in five studies, revealing a low correlation to PROMs (LCQ, Laryngeal Hypersensitivity Questionnaire and unspecified HRQoL questionnaires, r=0.43) [59]; moderate correlation to capsaicin-induced cough sensitivity (r=0.51–0.55) [41];

and moderate effect size of longitudinal changes to speech pathology treatment with and without pregabalin (d=0.40) [31]. A study that evaluated both LCM and HACC together found large effect sizes of longitudinal changes to montelukast with or without prednisolone in patients with high fractional expiratory nitric oxide (F_{ENO}) and moderate effect size of longitudinal changes to montelukast in patients with low F_{ENO} (d=1.16) [27].

Seven studies focused on asthma, with a total of 300 patients [42, 48–50, 59, 60, 68]. These studies monitored cough using the LCM (n=2) [42, 49], HACC (n=1) [60], LEOSound (n=1) [48], VitaloJAK (n=1) [59] and unnamed devices (n=2) [50, 68]. For evaluation of cough frequency, unnamed devices evaluated 24-h cough count against manual counting, showing good correlation in patients with asthma (r=0.82–0.92) [68]. The median sensitivity of the VitaloJAK against manual counting was 100% (IQR 100–100%) and median filter efficiency of reducing cough recording duration was 7.0% (IQR 4.9–9.5%) [59]. The correlation against PROMs and disease parameters for the LCM was found to have a range of low correlations against the Cough VAS (range r=0.06), although there were large effect sizes of longitudinal changes against treatments (d=0.69–0.97) [42, 49].

For ILD, six studies evaluated cough monitoring in a total of 209 patients using the VitaloJAK [33, 59], LCM [62, 67], PulmoTrack [43] and an unnamed device [38]. The median sensitivity of the VitaloJAK against manual counting was 100% (IQR 99.4–100%) and median filter efficiency of reducing cough recording duration of 6.4% (IQR 3.4–10.2%) [59]. Longitudinal interventional-related changes were evaluated in four studies, with a large effect size for the PulmoTrack after treatment with VRP700 (d=3.55) [43] and the LCM after pirfenidone therapy (d= −14% at 4 weeks; −34% at 12 weeks) [67]; however, no significant changes for cough counts measured by the LCM after acid suppression therapy (p=0.59–0.70) [62] and cough counts measured by an unnamed device after treatment of RVT-1601 [38].

Six studies focused on patients with COPD, with a total of 297 patients [34, 46, 59, 61, 63, 69]. The studies evaluated cough frequency using the VitaloJAK (n=2) [34, 59], LCM (n=1) [46], LEOSound (n=1) [52] and unnamed devices (n=2) [34, 69]. The median sensitivity of the VitaloJAK against manual counting was 97.8% (IQR 97.8–99.7%) and median filter efficiency of reducing cough recording duration of 5.0% (IQR 4.1–8.3%) [59]. One study using unnamed devices showed high correlation against manual counting (r=0.97) [69]. The study using LCM showed low-to-moderate correlations compared to capsaicin challenge tests (r= –0.411–0.556) [46], while the study using unnamed devices revealed low correlation against the Cough VAS (r=0.42) [63].

A single study evaluated device characteristics of the VitaloJAK in six patients with bronchiectasis [59]. The median sensitivity of the VitaloJAK against manual counting was found to be 99.3% (IQR 93.6–100%) and median filter efficiency of reducing cough recording duration was 3.8% (IQR 2.9–7.8%) [59].

There was only one study for CF, with 19 patients, which found a low correlation for the LifeShirt compared to FEV_1 (r=0.45) [51]. Bronchiectasis was also only evaluated in one study, with 54 patients, showing moderate correlation of LCM to cough-specific PROMs (range r=0.52–0.62) and low correlation to non-cough-specific PROMs and lung function tests for cough counts (r=0.32–0.4) [55].

Discussion

This is the first systematic review to comprehensively evaluate the utility and characteristics of objective cough monitoring systems across adult patients with different CRDs, which is critical to advance the field of symptom assessment and monitoring for better patient care and drug development. The VitaloJAK and LCM were the most studied objective cough monitoring systems and were used primarily in patients with idiopathic chronic cough. There were limited studies for patients with other CRDs, particularly bronchiectasis and CF. Comparison of cough monitoring systems against manual counting was inadequately studied, with only four studies using the VitaloJAK, PulmoTrak or unnamed devices. However, overall, they had low-to-moderate correlation against PROMs and moderate longitudinal changes for various treatments. Test consistency of different objective cough monitoring systems is yet to be established. There is a lack of evaluation of patient and researcher perspectives on their usability. There was no direct comparison of performance between different objective cough monitoring systems.

Chronic cough is an important symptom found in many patients with various types of CRDs. This symptom may serve as an indicator of disease progression, HRQoL and treatment effectiveness [73–76]. While there is currently a lack of effective treatments for cough in CRDs, there have been an increasing number of clinical trials exploring novel therapeutic agents for cough in recent years [77]. Hence, there is a need to have accurate and consistent assessments of cough to allow evaluation of therapeutic effects and

clinical monitoring of patients. The initial validation studies of cough monitoring systems during the development often involved healthy volunteers, smokers and/or a heterogeneous group of patients of different acute and chronic diseases, such as those with cough secondary to gastro-oesophageal reflux disease and post-infection [5, 7, 78]. Given differences in the cough symptom and disease course of different health conditions, this systematic review focused on the studies that specifically evaluated cough monitoring systems in patients with CRD.

Of the different types of cough monitoring systems evaluated in patients with CRD, the VitaloJAK has the best available evidence for its utility, followed by the LCM. The VitaloJAK had high agreement against manual counting and other disease parameters, with moderate effect size of longitudinal changes against various treatments of cough, while the LCM had moderate agreement to a range of comparators and moderate effect size of longitudinal changes for the treatments for cough. Of note, the presence and magnitude of longitudinal interventional-related changes would be influenced by effects of the investigational interventions and adequacy of the clinical trial design, which are limitations that warrant careful interpretation taking into considerations of other device evaluation including the agreements with manual cough counting and other parameters. Overall, this review shows most favourable evidence for the frequency of use and characteristics of the VitaloJAK in patients with idiopathic chronic cough, and that of the LCM in patients with asthma and idiopathic chronic cough.

While the majority of evaluations in the HACC, PulmoTrack and LifeShirt show favourable results, they were mostly evaluated in single studies that were inadequate to draw a definitive conclusion. It is questionable whether the LifeShirt is still available for commercial use following the liquidation of its company of origin, Vivometrics [79]. The characteristics of LEOSound were not evaluated in any of the included studies. Of note, there are a few investigational or unnamed cough monitoring systems using wearable devices and phone applications with evidence for robust characteristics. These instruments could be less burdensome, particularly with the ubiquitous use of mobile phones, which can aid wider clinical application. In addition, they may also facilitate longer cough recording durations. As demonstrated with cardiac arrhythmia diagnosis and monitoring, the newer loop recorders and mobile cardiac telemetry with prolonged monitoring have superior diagnostic yield and improve therapeutic decisions [80]. While most of the current commercially available cough monitoring systems allow the recommended 24-h cough recording [31], a longer recording duration across multiple days could provide better evaluation given the sporadic nature of cough.

PROMs evaluate the subjective aspect of cough from patients' point of view, which are informative of their perceived impact. In contrast, cough monitoring systems provide objective measurements to quantify cough frequency. It is not surprising to find only low-to-moderate correlations between these two evaluation methods for cough as they assess different aspects of cough. It is likely that the impact of cough on patients is related not only to the frequency of cough, but also to the intensity of the coughs, with more intense coughing likely contributing to distressing symptoms like dyspnoea, urinary incontinence, vomiting and thoracic pain. The cough monitoring systems evaluated in this review primarily provide data on cough frequency. By expanding the measurement capabilities of these devices to evaluation of cough intensity could provide valuable additional information. Although there is still a lack of consensus regarding methods for assessing cough intensity objectively, some potential ways for its evaluation would be to measure cough muscle contractions, airflow, and sound intensity [81, 82]. Ideally, both objective cough monitoring systems and PROMs should be used to provide complementary information on patients' health status.

Given the heterogeneity of included studies, meta-analyses could not be performed. However, this body of work provides an extensive overview of current state of objective cough monitoring systems for use in adults with CRDs in a descriptive synthesis. A focus on the adult population in this study means that our results could not be extended to adolescent and paediatric patients, where the requirements are likely to vary given the need for parental involvement and differences in disease characteristics. In addition, our focus on key types of CRDs prevented us from evaluating cough monitoring systems studied in other diseases such as tuberculosis or the general population [83, 84]. The subgroup analyses allowed evaluation of cough monitoring for different types of CRD; however, there were interstudy variations in the diagnostic criteria and disease manifestations that could influence study findings. There were limited studies comparing cough monitoring systems to the gold standard of manual cough counting. Similarly, data on longitudinal measurements were mostly limited to evaluations based on treatment effect sizes in the setting of clinical trials, which involved highly selected study populations and are affected by the investigational interventions and clinical trial design. Hence, it is important to take these limitations into consideration for interpreting responsiveness findings. Some cough monitoring systems have not been used in clinical trials, and thus their utility for longitudinal measurements is yet to be studied. More work on the evaluation of

device characteristics is required to improve the understanding of performance of objective cough monitoring systems for research and clinical applications. With the rapid technological advancement for wearable devices and patient monitoring systems, validation studies of new objective cough monitoring systems in populations of interest will need to be conducted as they emerge.

Conclusion

This systematic review identified the different cough monitoring systems in use for adult patients with CRDs and summarised current literature on their utility, device characteristics and usability. Overall, there are few studies that have evaluated the agreement of cough monitoring systems against manual counting, which is a key research priority for their primary application in cough assessment. While low-to-moderate correlation with PROMs and disease parameters and moderate effect size in longitudinal interventional-related changes were identified for the VitaloJAK and LCM, there are limited studies for other devices. There is important gap in literature for various aspects of cough monitoring systems regarding their test consistency, longitudinal serial measurements during follow-up, user preference and cost of use, as well as assessments in beyond patients with different CRDs other than idiopathic chronic cough. Further work on the evaluation of objective cough monitoring systems is warranted to establish their roles as clinical trial outcomes and integration into clinical practice, given the burden and significance of chronic cough in adults with CRDs.

Provenance: Submitted article, peer reviewed.

Conflict of interest: A.E. Holland reports non-financial support from BOC Australia and Air Liquide Healthcare; and is the President of the Thoracic Society of Australia and New Zealand (non-paid role). M.S. Wijsenbeek reports grants from The Netherlands Organisation for Health Research and Development, The Dutch Lung Foundation, The Dutch Pulmonary Fibrosis organisation, Sarcoidosis.nl, Boehringer Ingelheim, Hoffman la Roche and AstraZeneca-Daiichi; consulting fees from Bristol Myers Squibb, Boehringer Ingelheim, Galapagos, Galecto, Hoffman la Roche, Horizon Therapeutics, Kinevant Sciences, Molecure, Nerre Therapeutics, Novartis, PureTech Health, Thyron, Trevi and Vicore; lecture honoraria from Boehringer Ingelheim, CSL Behring, Hoffman la Roche and Novartis; travel support from Boehringer Ingelheim, Hoffman la Roche and Galapagos; advisory board participation with Savara and Galapagos; and is the Chair of the Idiopathic Interstitial Pneumonia group of the European Respiratory Society, Member of the board of the Netherlands Respiratory Society, Member of the scientific advisory board of the European Idiopathic Pulmonary Fibrosis and related disorders federation, Chair of the educational committee of the European Reference Network for Rare Lung Diseases, and member of the advisory boards of the Dutch Lungfibrosis and Sarcoidosis patient associations, outside the submitted work. Y.H. Khor reports grants from National Health and Medical Research Council during the conduct of the study; and non-financial support from Air Liquide Healthcare outside the submitted work. All other authors have nothing to disclose.

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