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Early View

Original research article

The demographics, clinical characteristics and quality of life of chronic cough in patients from the Isala Cough Clinic in the Netherlands

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Title

The demographics, clinical characteristics and quality of life of chronic cough in patients from the Isala Cough Clinic in the Netherlands

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A1. Abstract

Introduction

Chronic cough affects approximately 10% of the population and adversely impacts their quality of life. This retrospective observational cohort study aimed to identify the demographics, clinical characteristics and quality of life of the chronic cough population in a Dutch chronic cough clinic, at baseline and following treatment at 6-months. Patients were categorised based on the underlying phenotype and response to treatment.

Methods

Retrospective data on 2,397 patients who were diagnosed according to standard guidelines of the American College of Chest Physicians were analysed. Quality of life was captured via the Leicester Cough Questionnaire, the Cough Numeric Rating Scale and the Hospital Anxiety and Depression Scale.

Results

The mean patient age was 59 years, 62.5% of the patients were female and 69.1% had at least one underlying phenotype associated with chronic cough. Of the latter, 52.1% had bronchial hyperresponsiveness/airflow limitation, 33.3% had airway reflux and 20.1% had upper airway cough syndrome. 46% of patients with a phenotype, and 51% without, experienced no improvement in their quality of life or still had significant cough remaining after 6 months. Of patients with available quality of life data 37.5% were categorised as having refractory chronic cough, and 9.5% were categorised as unexplained chronic cough.

Discussion

This study highlights the poor quality of life outcomes in patients with chronic cough, despite interventions to treat underlying conditions and indicates a need to manage chronic cough irrespective of phenotype.

Keywords: Chronic cough, refractory chronic cough, unexplained chronic cough, quality of life, Leicester Cough Questionnaire, Cough Numeric Rating Scale

A2. Introduction

Cough is commonly defined as chronic when it persists for 8-weeks or longer, whereas less than 3 weeks is considered acute, and 3 weeks to 8 weeks is considered subacute.[1] The global prevalence of chronic cough is estimated to be 9.6%, which is thought to be higher in Europe at around 12.7%.[2] However, there is some degree of variability in Europe, with some countries reporting a prevalence as low as 4%.[3]

There are many different risk factors for developing chronic cough; smoking, and the existence of an underlying comorbid condition, are the most common.[1] A worldwide survey in 2014 found that chronic cough has a preponderance for females and higher age groups; 2 in 3 patients of chronic cough clinics were found to be female, and the modal age range for presentation was 60-69 years.[4]

A more recent observational study supports these findings.[5] Patients with chronic cough typically present signs of cough reflex hypersensitivity, causing a reaction to low levels of thermal, chemical or mechanical stimulation.[1] To further categorise cough hypersensitivity, different phenotypes are used dependent on the location and type of inflammation. The European Respiratory Society 2020 guidelines outline the main phenotypes of chronic cough as asthmatic cough/eosinophilic bronchitis, reflux cough, and iatrogenic cough.[1]

Historically, patients presenting with suspected chronic cough underwent expensive or invasive procedures[8] Since the introduction of ERS guidelines, a chest X-ray, spirometry, and looking for eosinophilia are now the recommended actions to determine the phenotype. Once a phenotype has been identified, treating the specific phenotype often leads to a resolution of, or improvement of chronic cough.[9, 10] However, in a minority of patients, chronic cough cannot be resolved through treatment of the phenotype; these patients are considered to have refractory chronic cough (RCC).[11] After an extensive investigation, there are some chronic cough patients that still elude diagnosis, such patients are considered to have unexplained chronic cough (UCC).[11]

Many patients with chronic cough report adverse impact on their quality of life (QoL), frequently reporting musculoskeletal chest pains, sleep disturbance, gastroesophageal reflux, heartburn, and regurgitation.[12-14] As well as these symptoms, females with chronic cough commonly report urinary incontinence.[15] Patients with chronic cough report QoL impairments comparable to those with other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD).[13] The QoL impact experienced by those with UCC and RCC has yet to be characterised. This presents a significant data gap as recent studies indicate that between 42% and 66% of chronic cough patients have no underlying phenotype or do not respond to treatment for an identifiable underlying condition, though these estimates vary depending on the study setting.[5, 16-18] Filling this data gap will allow the treatment needs of these patients to be better understood.

This study retrospectively investigated the demographic, clinical characteristics and QoL of the chronic cough patients attending the Isala Cough Clinic in the Netherlands at baseline and after intervention at 6-month follow-up.

A3. Methods

This retrospective observational cohort study was performed at the Isala Cough Clinic, an outpatient clinic in the department of pulmonology of Isala Hospital in Zwolle, the Netherlands. This study analysed data that were collected from patients who were first referred to the clinic between January 6th, 2010 and April 26th, 2019. Subjects had to be at least 18 years of age upon first encounter at the Isala Cough Clinic and present with chronic cough, defined as cough persisting for at least 8 weeks. Patients that presented abnormalities in chest x-rays were excluded from the study, with no further exclusion criteria applied. Patients were followed up at 6 months following initial presentation to the clinic, to capture a real-world clinical practice treatment duration of approximately four months. Data included results of diagnostic tests performed to standard hospital procedure, patient reported QoL and demographic characteristics of the patients. All data were anonymised, patients provided signed informed consent on entering the hospital and were free to opt out at any time however, no patients were excluded due to this reason. The Isala Hospital Daily Board of the Medical Ethics Committee had no objections to the research proposal and no additional consent was required (METC number 190107). The patient inclusion flow chart is outlined in Supplementary Figure 1.

B1. Objectives

This study aimed to characterise the demographic and clinical characteristics, and QoL of patients with chronic cough, RCC and UCC at first presentation to the clinic, then again after 6-months.

B2. Diagnostic Tests

Prior to presentation at the clinic, a battery of diagnostic tests was performed on the chronic cough patients as per the 2006 American College of Chest Physicians' (ACCP's) guidelines.[19] These included: lab – complete blood count, total eosinophils, IgE, Phadiatop allergy screen; lung function – spirometry, bronchoprovocation challenge, fraction exhaled nitric oxide (FeNO); radiology – chest X-ray and sinus imaging. Additionally, the Hull Airway Reflux Questionnaire (HARQ) was administered upon presentation to the clinic. For this study three phenotypic categories were formed based on diagnostic tests undertaken in the time period the patients were seen in the clinic and taking into account the ERS chronic cough phenotypes: (1) bronchial hyperresponsiveness(BHR)/airflow limitation (AL); (2) upper airway cough syndrome (UACS); (3) Airway reflux (including both acid airway reflux and non-acid airway reflux).[1] At time of diagnosis, the ERS guidelines had not been published so direct use of the ERS phenotypes in this study was not possible. Bronchial hyperresponsiveness was diagnosed by a methacholine challenge result of PD20<490µg[19] or when $FEV_1/VC<0.70$ and methacholine challenge was negative.[19] UACS was diagnosed by abnormal sinus X-ray exclusively. Airway reflux was diagnosed based on reflux symptoms and/or HARQ ≥14 if no other diagnosis was made.[19] On analysis of patient data, diagnoses were inferred from the presence of the described diagnostic tests and their results.

B3. Health-Related Quality of Life (HRQoL)

HRQoL assessments used in the Isala Cough Clinic were the Leicester Cough Questionnaire (LCQ) and the Hospital Anxiety and Depression scale (HADS), to capture physiological and psychological domains of patients' well-being. The Cough Numeric Rating Scale (NRS-cough), a global 11-point

rating of change scale, was also used as a measure of cough severity.[20] These tools were selected as the optimal measures that may be used, in lieu of an objective cough count device commonly used in clinical trials but not practical in the real-world setting. These assessments were conducted at first presentation to the clinic and at a 6-month follow-up. In this study, the minimal clinically important difference (MCID) for LCQ and NRS-cough were defined as +1.3 and -2.0, respectively.[19, 21, 22] It should be noted that a NRS-cough scale MCID has not yet been determined, therefore to ensure clinical applicability, the MCID of similar Likert Global Rating of Change scale was applied.[23] The MCID for HADS regarding anxiety was -1.7, and -1.5 regarding depression.[24]

B4. RCC and UCC categorisation

Patients were stratified into RCC and UCC subgroups based on response to HRQoL questionnaires, diagnostic tests, and presence of any underlying treatable conditions. Patients with RCC were defined as those with one or more treatable condition where treatment was ineffective. Patients with UCC were defined as those with no identified treatable underlying conditions and treatment failure. Ineffective treatment and treatment failure were defined as any of the following:

- Failure to reach MCID on the LCQ after 6 months
- Failure to reach MCID on the NRS-cough after 6 months
- Reaching MCID criteria on the LCQ after 6 months but having significant cough remaining measured by a LCQ score <13
- Reaching MCID criteria on the NRS-cough after 6 months but having significant cough remaining measured by a NRS-cough >5

B6. Statistical analysis

Demographic and clinical characteristics, and HRQoL were summarised and presented as measures of central tendency and proportions, respectively. The paired t-test or Wilcoxon signed ranks test was performed for inferential analysis of continuous data, whereas dichotomous variables were assessed using the McNemar test. The size of the population that attends the Isala Cough Clinic was calculated as a percentage of the population of the Isala hospital catchment area.

A4. Results

B7. Baseline characteristics

Patient characteristics are presented in Table 1. The study population had a mean age of 59 years (SD 13.9), 62.5% (n=1497) of the cohort were female and 6.8% (n=147) of patients included were current smokers. Half of the patients tested positive on the methacholine test for airway reactivity, supporting a diagnosis of bronchial hyperresponsiveness. However, spirometry was normal in the majority of the patients (FEV_1/VC ≥70%, 73.8%, n=1574), as was FeNO (median, 18 [range 12-27] ppb]). The vast majority of patients (91.5%, n=1033) had a HARQ score ≥14, (beyond the upper limit of normal of 13), reflecting a high burden of airway reflux and high probability of cough hypersensitivity in the included patients. In 30.9% of patients no tentative underlying cause was identified (Table 2). A diagnosis of BHR/AL was the modal phenotype, presenting in 60.9% (n=1117/1835) of patients, followed by airway reflux in 33.3% (n=297/891) and UACS in 20.1% (n=459/2282). In 10.5% (n=248/2352) of patients, at least two underlying phenotypes were identified, whereas 58.5% (n=1377/2352) presented with only one. Patients presenting with co-existing phenotypes were treated sequentially, addressing one cause prior to targeting subsequent causes.

Table 1. Study cohort baseline characteristics presented as measures of central tendency or percentages.

	All (n = 2397)	
	n	**Summary statistics**
Demographic		
Age	2397	59.4 (±13.9)
Sex (female)	2397	1497 (62.5%)
Smoking status - Non-smoker - Former - Current	2161	 1169 (54.1%) 845 (39.1%) 147 (6.8%)
Diagnostics		
X-thorax - Abnormal, not contributing to cough	2318	 349 (15.1%)
UACS		
X-sinus - Abnormal	2282	 459 (20.1%)
BHR/AL		
Methacholine test result (PC20/ PD20) - Abnormal	1835	 995 (54.2%)
FEV_1 (L)	2243	2.9 (±0.9)
FEV_1 (%)	2217	96 (±18.4)
VC (L)	2187	3.8 (±1.1)
VC (%)	2179	102.2 (±17.1)
FEV_1 / VC (%)	2134	75.4 (69.5 – 80.4)
FEV_1 / VC (%) < 70% ≥ 70%	2134	 560 (26.2%) 1574 (73.8%)

Methacholine test result normal and FEV1 / VC (%) <70%	2049	122 (6.0%)
FeNO (ppb)	1882	18 (12 – 27)
Airway reflux		
HARQ-total	1129	32.7 (±13.3)
HARQ-total ≥14 - Yes	1129	 1033 (91.5%)
Other		
Inhalation allergy, positive (%)	2292	577 (25.2%)
IgE, Mean (SD)	2234	111.3 (314.6)
IgE >120	2234	422 (18.9%)
Eosinophilic leucocytes Mean (SD)	2330	 0.2 (±0.2)
Eosinophilic leucocytes >0.4	2330	149 (6.4%)

AL, airway limitation; BHR, bronchial hyperresponsiveness; FEV_1, forced expiratory volume in 1 second; VC, vital capacity; FeNO, fractional exhaled nitric oxide; HARQ, Hull airways reflux cough questionnaire**;** IgE, immunoglobulin E; SD, standard deviation; UACS, upper airway cough syndrome;

Table 2. Phenotypic characterisation of patients presenting with chronic cough.

	Available data	
Phenotype group	**n**	**Summary statistics**
BHR/AL	1835	1117 (60.9%)
UACS	2282	459 (20.1%)
Airway reflux	891*	297 (33.3%)
Phenotype number 0 1 ≥2 missing	2352	 727 (30.9%) 1377 (58.5%) 248 (10.5%) 0

AL, airway limitation; BHR, bronchial hyperresponsiveness; COPD, chronic obstructive pulmonary disease; UACS, upper airway cough syndrome. *This sample n=891 concerns those patients with 1) a valid HARQ, 2) a valid methacholine test result, and 3) a valid x-sinus result.

B8. HRQoL

Results of HRQoL and cough severity measures are presented in Table 3. At baseline, more than half of respondents were experiencing significant cough related HRQoL impairments, evidenced by an LCQ <13 (52.8% of respondents) or an NRS-cough >5 (55.2% of respondents) on presentation. For patients that responded to the questionnaire at 6-month follow-up, the mean total LCQ score increased by 2.5 from 12.8 to 15.3 ($p<0.001$), surpassing the MCID, and the mean NRS-cough score decreased by 1.7 from 5.7 to 4.0 ($p<0.001$), which was statistically significant. The MCID on the LCQ was reached in 64.4% (n=519) of respondents and the MCID on the NRS-cough was reached in 50.7% (n=880) (Table 4). The percentage of patients with low LCQ <13 also decreased, from 52.8% at baseline to 21.5% at 6-month follow-up ($p<0.001$), reflecting a notable improvement in the HRQoL for these patients over the 6-month period (Table 3). The median HADS total score decreased by 2.0 from 8.0 to 6.0 ($p<0.001$), surpassing the MCID for HADS.

Upon evaluation, of patients that had responded to both the LCQ and NRS-cough questionnaires, 27.0% failed to reach a MCID on both scores and the cough remained troublesome in 65.6% (n=126/192) of these patients (Table 4).

Table 3. HRQoL and cough severity descriptive statistics at baseline and 6-month follow-up.

	Baseline (initial)		6 months (follow-up)		Difference (change)		
	n	**Summary statistics**	**n**	**Summary statistics**	**n**	**Summary statistics**	**p-value**
Time between LCQ at baseline and follow-up (months) Median		NA		NA	693	6.9 (6.4 – 7.7)	NA
Time between NRS at baseline and follow-up (months) Median		NA		NA	1565	6.6 (6.2 – 7.5)	NA
Discrete/ continuous variables							
LCQ total Mean	1144	12.8 (±3.0)	971	15.3 (±3.3)	806	2.5 (±2.9)	p<0.001

LCQ physical Mean	1194	4.3 (±0.9)	1008	5.0 (±1.0)	870	0.7 (±0.9)	p<0.001
LCQ psychological Mean	1228	4.5 (±1.0)	1034	5.2 (±1.0)	900	0.7 (±1.0)	p<0.001
LCQ social Mean	1250	3.9 (±1.5)	1039	5.1 (±1.5)	929	1.2 (±1.4)	p<0.001
NRS-cough 24h Mean	2235	5.7 (±2.5)	1837	4.0 (±2.7)	1735	-1.7 (±3.0)	p<0.001
HADS total Median	1207	8.0 (4 – 14)	1024	6.0 (2 – 12)	886	-2.0 (-23 – 29)	p<0.001
HADS anxiety Median	1229	5.0 (2 – 8)	1040	4.0 (1 – 6)	917	-1 (-3 – 1)	p<0.001
HADS depression Median	1239	4 (1 – 7)	1043	2 (1 – 6)	922	-2 (-2 – 3)	p<0.001
Binary categorical variables							
LCQ total - ≥13 - <13 (unfavourable)	1144	540 (47.2%) 604 (52.8%)	971	762 (78.5%) 209 (21.5%)	806		p<0.001
NRS-cough 24h - ≤5 - >5 (unfavourable)	2235	1001 (44.8%) 1234 (55.2%)	1837	1253 (68.2%) 584 (31.8%)	1734		p<0.001
Cough severity (LCQ and NRS) - LCQ ≥13 and NRS-cough ≤5 - LCQ ≥13 and NRS-cough >5 - LCQ <13 and NRS-cough ≤5 - LCQ <13 and NRS-cough >5	1071	326 (30.4%) 185 (17.3%) 131 (12.2%) 429 (40.1%)	909	554 (60.9%) 160 (17.6%) 49 (5.4%) 146 (16.1%)	712		p<0.001
HADS total >11	1207	430 (35.6%)	1024	288 (28.1%)	886		<0.001
HADS anxiety >11	1299	99 (8.1%)	1040	68 (6.5%)	917		0.016
HADS depression >11	1239	94 (7.6%)	1043	69 (6.6%)	922		0.801

LCQ, Leicester Cough Questionnaire; NRS-cough, Cough Numeric Rating Scale; HADS, hospital anxiety and depression scale.

Table 4. Patient HRQoL 6-months after presentation to the clinic.

	Total	
	n	**Summary statistics**

MCID's reached		
MCID LCQ +1.3 reached - No - Yes	806	 287 (35.6%) 519 (64.4%)
MCID NRS -2.0 reached - No - Yes	1734	 854 (49.3%) 880 (50.7%)
MCID LCQ and/ or NRS reached - LCQ not & NRS not - LCQ reached & NRS not - LCQ not & NRS reached - LCQ reached & NRS reached	712*	 192 (27.0%) 146 (20.5%) 68 (9.6%) 306 (43.0%)
Any MCID reached - No - Yes	712*	 192 (27.0%) 520 (73.0%)
Residual burden of cough		
LCQ <13 and/ or NRS-cough >5 - No - Yes	909	 554 (60.9%) 355 (39.1%)
Effectiveness of treatment		
Treatment effectiveness - No MCID & R-cough - No MCID & no R-cough - Any MCID & R-cough - Any MCID & no R-cough	712*	 126 (17.7%) 66 (9.3%) 144 (20.2%) 376 (52.8%)
Treatment effectiveness - Not effective - Effective	712*	 336 (47.2%) 376 (52.8%)

* This sample n=712 concerns all patients included in the trial regardless of available diagnosis data.

HRQoL, health-related quality of life; MCID, minimal clinically important difference; LCQ, Leicester Cough Questionnaire; NRS, Cough Numeric Rating Scale; R-cough, remaining cough.

Figure 1 highlights the correlation between patient improvement, severity of initial LCQ and NRS-cough scores. Analysis showed that patients with the lowest scores for LCQ (Figure 1a and Figure 1c) and highest scores on the NRS-cough scale (Figure 1b and Figure 1d) improved the most.

[Insert Figure 1]

B9. RCC and UCC categorisation

Figure 2 shows the categorisation of patients into RCC or UCC according to phenotype and effect of interventions made prior to the six-month follow-up, measured by responses to the LCQ and the NRS-cough questionnaire. If we consider only patients with available MCID data, 37.5% (n=264/704) of the study population were categorised as RCC, and 9.5% (n=67/704) were categorised as UCC. Supplementary table 1 shows the characteristics of the treatment response groups, which were found to be similar regardless of treatment response and underlying phenotype. Considering patients with MCID data (Figure 2), the success rate (defined by patients meeting HRQoL MCID and having no remaining cough) was 54% (n=308/572) in patients with a phenotype and 49% (n=65/132) in patients without a phenotype.

[Insert Figure 2]

A5. Discussion

To the authors' knowledge, this is the first real-world study capturing patient characteristics and HRQoL of patients with RCC and UCC. Our study found that 37.5% of chronic cough patients had RCC and 9.5% UCC after 6-months. Despite systematic investigation, no phenotype could be identified in 30% of patients, meaning they could not receive targeted therapy for any specific chronic cough phenotype. The percentages of the various phenotypes are comparable to another recent epidemiological study whereby the prevalence of chronic cough according to comorbidities was 33% for asthma and 28.6% for COPD,[25] compared to 60.9% for BHR and/or AL in this study. Baseline characteristics, including cough related QoL and cough severity, have also been identified as important predictors of outcomes in patients with chronic cough.[26] The findings of the HARQ taken at baseline, indicate 91.5% of patients were positive, suggesting airway reflux is a major cause of cough hypersensitivity and may speculatively underlie the high incidence of non-asthmatic BHR seen in our study. In-line with existing literature, this study found that baseline LCQ and NRS values were positively correlated with delta-LCQ and NRS. Irrespective of phenotype or reaching an MCID in one or more measures, 39.1% (Figure 2) of respondents still had significant cough remaining after the 6-month follow-up period. The observation that improvement was not seen at 6 months in a significant proportion of patients either with or without a phenotype, could therefore imply that over time cough hypersensitivity may become more dominant in lieu of an underlying phenotype.

Limited attempts have been made to characterise RCC or UCC within a chronic cough population. Estimates vary markedly depending on the study setting and subgroup definition which, in the real-world setting, can vary depending on the diagnosing physician. Two separate UK studies estimate the proportion of patients within the chronic cough population without a phenotype to be 42% and 66%, with the highest prevalence reported in a community setting rather than a specialist cough clinic.[17, 18] The study by Everett et al, conducted in a general UK population, captured only the proportion of chronic persistent cough patients without a co-existing respiratory diagnosis, which may explain the notably higher results at 66%. The Haque et al. study, which took place at the Royal Brompton Hospital Chronic Cough Clinic in London, defined a subgroup with 'chronic idiopathic

cough' where diagnosis could not be made even after thorough systematic investigation and found a prevalence of 42% within their chronic cough population similar to the 30% identified in this study.

The results show that at baseline more than half of respondents were experiencing significant cough related HRQoL impairments. Given that HRQoL impairment defines categorisation as RCC or UCC in this study, and nearly half of our study population were categorised as such, clearly these patients are in need of effective symptom management. Additionally, more effective diagnosis of RCC and UCC in particular would reduce the economic burden associated with diagnosis. These patients are only diagnosed as endpoints to an arduous and expensive diagnostic process. Furthermore, to the authors' knowledge there have been no attempts to characterise the patient journey of chronic cough patients. A clearer understanding of the patient journey may allow for the streamlining of the current, unstructured approach to diagnosing and managing chronic cough.

There are several limitations of this retrospective study. Despite the large sample size, some analyses were limited due to invalid diagnostic tests and/or due to the retrospective study design. Patient examination was conducted prior to the publication of the ERS chronic cough guidelines. Phenotype grouping was done prospectively so direct use of the ERS phenotypes was not possible. Further, although commonly used in chronic cough studies, reliance on subjective patient reported outcome measures such as the LCQ could potentially lead to underreporting of symptom severity. Additionally, 64.8% (1053/1625) of patients with an underlying phenotype and 81.8% (595/727) of patients without did not respond to the HRQoL questionnaires, so the results may be incomplete. Despite some lack of response, the HRQoL of many patients was able to be evaluated (table 3) however, the authors recognise the smaller numbers of responses in relation to establishing MCID of NRS and LCQ results. A further limitation exists with the lack of standardisation of classification of RCC and UCC populations, which may limit comparability to other studies. The use of disease specific, patient reported QoL measures in the definition of ineffective treatment and treatment failure means that patients can still be considered RCC or UCC even if cough resolves. The study sample is also a bias representation of chronic cough patients as only patients with severe cough are referred to the Isala Cough Clinic and generalisation of these results to a general population should be done with caution.

Our analyses highlighted the difficulty in predicting whether a patient will respond to intervention for specific phenotypes, as treatment response was similar across all subgroups of chronic cough patients, as were distributions of patient characteristics. Our study found that 47% of the chronic cough population may be labelled as RCC or UCC. Of the patients attending the Isala Chronic Cough Clinic, approximately 70% belonged to a phenotype associated with chronic cough and 30% did not. In patients with an underlying diagnosis, 46% of patients showed improvement in HRQoL and had no significant cough remaining after 6 months and 51% of patients did not. The presence or absence of a phenotype had no relationship with HRQoL impact severity, and whether a patient failed to improve in HRQoL or still had significant cough remaining. As such, there is a major unmet clinical need to manage chronic cough irrespective of phenotype. Future studies should aim to characterise the economic and social burden of RCC and UCC so we can better understand their impact and investigate what dictates whether a chronic cough patient will respond to intervention. The similarity in treatment response between patient groups also indicates that development of

additional therapeutic options for symptom management in both RCC and UCC would be clinically and economically valuable.

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A8. Author contributions

All authors attest that they meet the ICMJE criteria for authorship. JVW van den Berg contributed to study design, data acquisition, analysis and interpretation. CA Baxter was involved in study design and data interpretation. MA Edens, A Weijerse and H van der Velden contributed to data analysis and/or interpretation. KW Patberg was involved in data acquisition and S Salomonsson contributed to study design. All authors were involved in the drafting and/or critical revision of the manuscript. The authors have given final approval of the manuscript for publication; and agreement of their full accountability for all aspects of the work.

A9. Data availability

The datasets supporting the conclusions of this article are included within the article or supplementary material. The full datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

A7. References

1. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *European Respiratory Journal* 2020; 55.

2. Song W-J, Chang Y-S, Faruqi S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *European Respiratory Journal* 2015; 45: 1479-1481.

3. Çolak Y, Nordestgaard BG, Laursen LC, et al. Risk factors for chronic cough among 14,669 individuals from the general population. *Chest* 2017; 152: 563-573.

4. Morice AH, Jakes AD, Faruqi S, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *European Respiratory Journal* 2014; 44: 1149-1155.

5. Good Jr JT, Rollins DR, Kolakowski CA, et al. New insights in the diagnosis of chronic refractory cough. *Respiratory medicine* 2018; 141: 103-110.

6. Bhargava A, Fukushima EA, Levine M, et al. Predictors for Severe COVID-19 Infection. *Clinical Infectious Diseases* 2020; 71: 1962-1968. DOI: 10.1093/cid/ciaa674.

7. Fraser E. Long term respiratory complications of covid-19. British Medical Journal Publishing Group, 2020.

8. Ponsioen B, Hop W, Vermue N, et al. Efficacy of fluticasone on cough: a randomised controlled trial. *European Respiratory Journal* 2005; 25: 147-152.

9. Mathur A, Liu-Shiu-Cheong P and Currie G. The management of chronic cough. *QJM: An International Journal of Medicine* 2019; 112: 651-656.

10. Morice A. The diagnosis and management of chronic cough. *European Respiratory Journal* 2004; 24: 481-492.

11. Gibson P, Wang G, McGarvey L, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest* 2016; 149: 27-44.

12. Dicpinigaitis PV, Tso R and Banauch G. Prevalence of depressive symptoms among patients with chronic cough. *Chest* 2006; 130: 1839-1843.

13. French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. *Archives of internal medicine* 1998; 158: 1657-1661.

14. Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. *Chest* 2008; 134: 295-302.

15. Zoglmann R, Nguyen T, Engberts M, et al. Do patients with stress incontinence cough or do cough patients suffer from urinary incontinence? : Eur Respiratory Soc, 2015.

16. Al-Sheklly B, Satia I, Badri H, et al. P5 Prevalence of refractory chronic cough in a tertiary cough clinic. *Thorax* 2018; 73: A98-A98.

17. Everett CF, Kastelik JA, Thompson RH, et al. Chronic persistent cough in the community: a questionnaire survey. *Cough* 2007; 3: 1-7.

18. Haque RA, Usmani OS and Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? *Chest* 2005; 127: 1710-1713.

19. Brown KK. Chronic cough due to nonbronchiectatic suppurative airway disease (bronchiolitis): ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129: 132S-137S.

20. Koo H-K, Jeong I, Kim J-H, et al. Development and validation of the COugh Assessment Test (COAT). *Respirology* 2019; 24: 551-557. DOI: https://doi.org/10.1111/resp.13462.

21. Rebelo P, Oliveira A, Paixão C, et al. Minimal Clinically Important Differences for Patient-Reported Outcome Measures of Cough and Sputum in Patients with COPD. *International journal of chronic obstructive pulmonary disease* 2020; 15: 201.

22. Spinou A and Birring SS. An update on measurement and monitoring of cough: what are the important study endpoints? *Journal of thoracic disease* 2014; 6: S728.

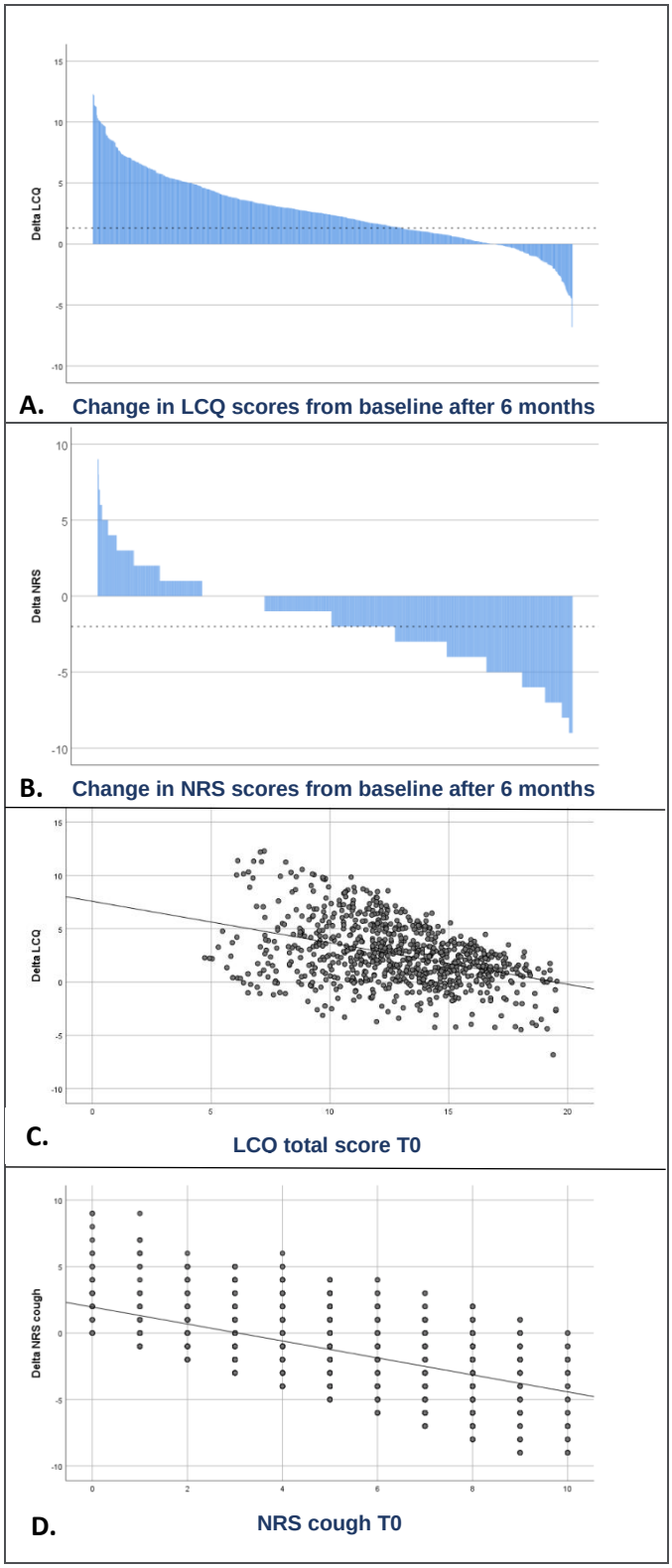
23. Kamper SJ, Maher CG and Mackay G. Global Rating of Change Scales: A Review of Strengths and Weaknesses and Considerations for Design. *Journal of Manual & Manipulative Therapy* 2009; 17: 163-170. DOI: 10.1179/jmt.2009.17.3.163.

24. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica scandinavica* 1983; 67: 361-370.

25. Arinze JT, de Roos EW, Karimi L, et al. Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. *ERJ open research* 2020; 6.

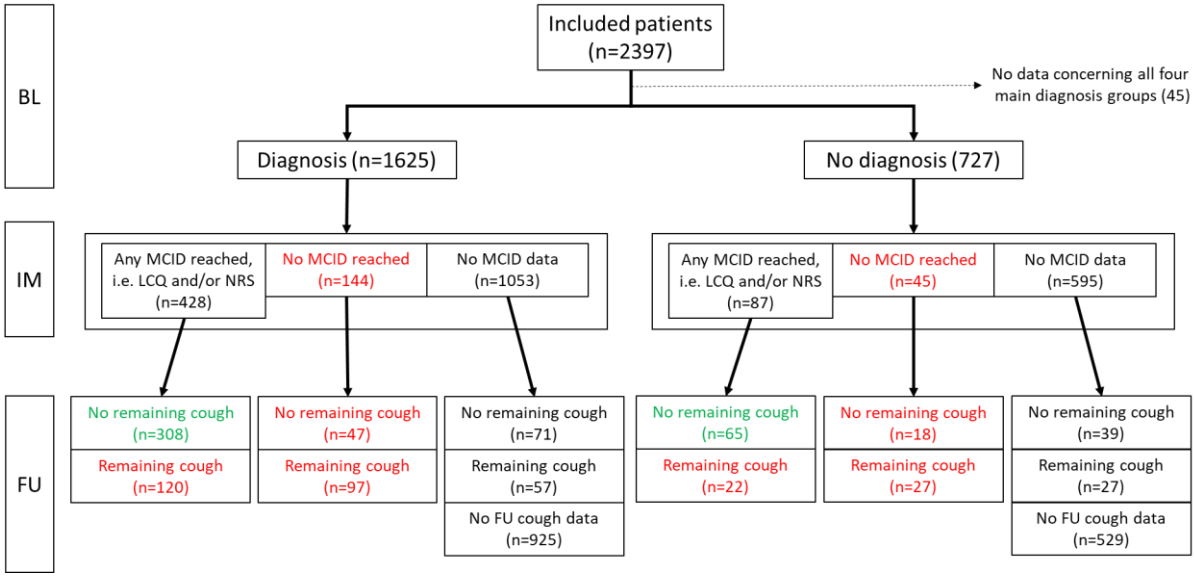
26. Koskela HO, Latti AM and Purokivi MK. Long-term prognosis of chronic cough: a prospective, observational cohort study. *BMC Pulm Med* 2017; 17: 146. 2017/11/23. DOI: 10.1186/s12890-017-0496-1.

Figure 1. Correlation between patient improvement and LCQ and NRS-cough.



(A) Delta-LCQ (n = 806), mean = 2.6 (±2.9), median = 2.4 (0.6 – 0.4). (B) Delta NRS-cough (n = 1734), mean = -1.7 (±2.3), median = -2.0 (-4.0 – 0.0). (C) The correlation of baseline LCQ with delta-LCQ. (D) The correlation of baseline NRS-cough with delta NRS-cough. LCQ, Leicester Cough Questionnaire; NRS-cough, Numeric Cough Rating Scale.

Figure 2. Flow chart showing the categorisation of patients as RCC or UCC.



BL, baseline; IM, intermediate; MCID, minimal clinically important difference; LCQ, Leicester Cough Questionnaire; NRS, Cough Numeric Rating Scale; FU, follow-up.