Relating Experienced To Recalled breathlessness Observational (RETRO) study: a prospective study using a mobile phone application

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ABSTRACT
Background Breathlessness, the subjective sensation of breathing discomfort, is common and appears in the daily life of people with cardiorespiratory diseases. Physicians often rely on patient’s history based on symptom recall. The relation between recalled and experienced breathlessness is still poorly understood. This paper presents the protocol for a study primarily aimed at evaluating the relationship between experienced breathlessness and (1) recalled breathlessness and (2) predicted future breathlessness.

Methods A mobile phone application will be used to collect data during daily life. Medically stable participants, ≥18 years of age with mean daily breathlessness of Numerical Rating Scale (NRS) 3/10 and able to use a mobile phone with internet will rate their breathlessness intensity on a 0–10 NRS prompted the user several times daily for 1 week. Participants will recall their breathlessness each day and week. Multivariable random effects regression models will be used for statistical analyses.

Results Results of the study will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

Discussion This protocol describes a study aimed at investigating previously unknown areas of the experience and recall of breathlessness using a new method of data collection.

Registration details Prospectively registered with ClinicalTrials.gov (Nr: NCT03468205).

Ethics and dissemination The study has received ethical approval from the Regional Ethical Review Board Lund (Dnr 2017/149). After a general study information including that participation is entirely voluntary, participants will answer the eligibility criteria and be asked to consent to participate before entering the study questions. Written informed consent to participate will be obtained for participants in the clinical sub-cohort. Participation can be discontinued at the discretion of the participant in which case no further data will be collected.

INTRODUCTION
Breathlessness, the subjective sensation of breathing discomfort, is common and appears with varying severity in daily life of people across several diseases such as congestive heart failure, asthma and chronic obstructive pulmonary disease (COPD).1–3 Breathlessness affects nearly a quarter of people aged over 60 years and about half of patients with serious illness.1–3 It is associated with increased anxiety and depression, increased risk of hospitalisation and earlier death.1,3 Several qualitatively distinct sensations of varying intensity constitute breathlessness making it a multidimensional symptom. These dimensions include the experienced intensity and unpleasantness, the associated emotional response and the functional impact on the person’s life.6

Clinical care relies on the patient’s history based on his/her symptom recall. The recalled level of recent breathlessness is used by the health professional to decide on the need for further investigations and treatment. Studies have shown that the recalled intensity of breathlessness during laboratory-provoked symptoms is not the same as the symptom actually experienced in daily life.7 This mismatch has also been shown for other measures for pain or self-perceived happiness.8 Further, previous studies show poor communication about breathlessness between doctors and patients, and ratings performed by healthcare professionals and caregivers of the patient’s symptom...
severity often do not match. This problem increased with higher levels of symptoms. Lack of communication and understanding of the patient’s symptoms lead to poor concordance, inappropriate treatment decisions and influence the patients adherence with treatment. The gold standard for assessing the symptom severity is currently patient recall.

Several factors may influence the recalled symptom intensity including the highest and the final experienced intensity. This association is often referred to as the ‘peak-end rule’ and has been found to be important for the overall recall of pain and happiness. Studies evaluating the ‘peak-end rule’ in breathlessness have previously shown contradictory results between groups. The current intensity of breathlessness is the measure shown to be the most associated with the recalled intensity. Additionally, even a very small decline in cognitive status influenced the differences between recalled and experienced symptoms, giving a bigger difference and increased variance between actual and recalled symptoms.

No previous studies exist on how patients own predictions of future breathlessness influence the actual and recalled breathlessness. The hypothesis that patients own predictions may influence the actual intensity of breathlessness will be tested in this study.

This paper presents the protocol for a study of the relationship between experienced and recalled breathlessness with contemporaneous data collected using a mobile phone application. Through this, new information will be gathered on which factors that influence patients recall of breathlessness which is the foundation of several important clinical decisions regarding treatment and evaluations. Better understanding of these issues may thus have a big impact in the daily interactions between breathless individuals and their doctors. Specific research questions are presented in box 1.

**AIMS**

The primary aim is to evaluate the relationship between experienced breathlessness and (1) recalled breathlessness and (2) predicted future breathlessness. Secondary aims are to identify factors that influence the difference between experienced and recalled or predicted breathlessness, to evaluate how people think when they recall breathlessness over defined time periods and to evaluate a novel method of collecting data in this field. (box 1)

**METHODS AND ANALYSIS**

**Study design and population**

Inclusion criteria are age ≥18 years with a self-reported breathlessness intensity ≥3 on a 0–10 Numerical Rating Scale (NRS) during the prior 2 weeks not caused by an acute infection such as an upper respiratory tract infection or pneumonia. Participants should be clinically stable without expected need for hospital admission within 1 week, be able to walk without a personal aid (rollator allowed), be able to use a device (smartphone/pad) with internet access regularly and be able to read and complete baseline assessments. The default setting is 1 week of participation, but there is a possibility to continue for additional weeks at the discretion of the participant. Participants will be recruited into two different cohorts, one general cohort which include most participants and one smaller clinical subcohort study with fewer participants but with added data.

**Recruitment**

Potential participants will be identified by clinical and research staff at the centres of the participating investigators including primary care, pulmonary clinics and internal medicine/cardiology departments in Blekinge, Örebro and Skane University Hospitals (Lund/Malmö). Participants will also be recruited through advertisements in national and local newspapers and magazines including those of the Swedish Respiratory Society, the Swedish Heart-Lung Foundation and the Heart-Lung Association and on webportals/sites.

**Mobile phone application-based data collection**

The mobile phone application is available on the two major mobile platforms in the market today (iOS and Android) and can be downloaded for free through their respective distribution channels (ie, ‘App Store’ for Apple and ‘Google Play’ for Android) and installed directly on the participants’ personal mobile phones. It was developed by the company ‘Cybercom group’ in close collaboration with the authors of this article and tested repeatedly for functionality in pilot-testing by authors and a small group of healthy volunteers. To access and start the active survey a four-digit code is needed which is distributed to participants.
Figure 1  Overview of the timing of planned assessments, starting with eligibility, consent and baseline assessments then continuing with several daily prompts asking on intensity of breathlessness as well as morning, evening and weekly assessments including daily recall and daily predictions as well as a weekly recall.

Clinical data on sub group
- MoCA-test
- Medical records
- Registry follow-up

Assessments
All planned assessments and scales within the application are presented in table 1. Some modifications and new questionnaires were adapted.

Breathlessness will be assessed using cued questions several times each day asking, ‘How intensive has your breathlessness been in the past 10–15 min?’, rated between
Table 1  Overview of the questionnaires and scales used

| Item                                                                 | Start of study | Start of each day | Up to every 1–2 waking hours | End of day | End of week* | End of study* |
|---------------------------------------------------------------------|----------------|-------------------|-------------------------------|------------|--------------|--------------|
| **Main application-base study**                                     |                |                   |                               |            |              |              |
| Age, sex                                                            |                | X                 |                               |            |              |              |
| Weight and height                                                   |                | X                 |                               |            |              |              |
| Self-reported level of mobility (Grimby-Frändin)24                  |                |                   |                               |            | X            |              |
| Physician-diagnosed diseases (according to participant)             |                |                   |                               | X          |              |              |
| Smoking status (never, past, current smoking)                       |                |                   |                               |            |              |              |
| Modified personality trait of symptom sensitivity (PHQ-15)16       |                |                   |                               |            |              |              |
| Mental state (anxiety/depression) (0–10 NRS)                       |                | X                 | X                             |            |              |              |
| Self-perceived overall well-being (0–10 NRS)                       |                | X                 |                               |            |              |              |
| Self-efficacy regarding breathlessness (online supplementary appendix 1c) |                |                   |                               |            |              |              |
| **Breathlessness (0–10 NRS)**                                       |                |                   |                               |            |              |              |
| Modified Medical Research Council25–28                              |                |                   |                               | X          |              |              |
| Intensity during the previous night (0–10 NRS)                     |                |                   | X                             |            |              |              |
| Intensity ‘last 10–15 min’ (0–10 NRS)                              |                |                   | X                             | X          |              |              |
| Intensity during the time period (0–10 NRS)                        |                |                   |                               | X          | X            |              |
| Unpleasantness of breathlessness and intensity of descriptors of breathlessness (MDP)6 29 |                |                   |                               |            |              |              |
| Emotional responses related to breathlessness during the time period (MDP)6 29 |                |                   |                               |            |              |              |
| Intensity during the past week (0–10 NRS)                          |                |                   |                               |            |              | X            |
| Predicted intensity for the coming week (0–10 NRS)                 |                |                   |                               | X          |              |              |
| Predicted intensity for the coming day (0–10 NRS)                  |                |                   |                               | X          | X            |              |
| Previous technology and Internet experience and usage (online supplementary appendix 1a) |                |                   |                               |            |              | X            |
| User experience of the application used in the trial (online supplementary appendix 1b) |                |                   |                               |            |              | X            |

MDP, multidimensional dyspnoea profile; NRS, Numerical Rating Scale; PHQ, Patient Health Questionnaire.

0 (no breathlessness) and 10 (worst imaginable breathlessness). The same type of assessment will be cued each morning (‘How intensive has your breathlessness been during the past night?’) and evening (‘How intensive has your breathlessness been during this day?’), as well as for the whole week (‘How intensive has your breathlessness been during the past week?’). The user will also be asked to predict, using a similar 0–10 NRS scale, how the intensity of breathlessness will be during the coming day, night or week using the question ‘How intensive do you expect your breathlessness to be in the coming day/night/week?’.

The Patient Health Questionnaire (PHQ) is a self-administered version of the Primary Care Evaluation of Mental Disorders diagnostic instrument for common mental disorders which are in the public domain and free to use in research. The PHQ-15 comprises 15 somatic symptoms from the PHQ, each symptom scored from 0 (‘not bothered at all’) to 2 (‘bothered a lot’).16 A minor modification was made in this study by removing one question (pain or problems during sexual intercourse) as the question, during pilot testing, was not deemed to be fully appropriate to ask in this format. The total score of PHQ-15 will be recalculated due to having one question missing in accordance to the instructions from the American Psychiatric Association.17

To assess the self-efficacy of breathlessness, an NRS will be used with the question ‘How confident are you that you can manage breathing difficulty or avoid breathing difficulty during the day’ anchored at 0 (Not at all confident) and 10 (Very confident).

Before and after the main study, the user will be asked some general questions concerning technical knowledge and previous experience on using a smartphone (online supplementary appendix 1a). After the study, some questions will be asked to evaluate the user’s experiences on using the application (online supplementary appendix 1b).

For the participants in the clinical substudy, Montreal Cognitive Assessment Tool (MoCA) will be used to assess for cognitive impairment.18 19 MoCA is a brief and sensitive test for cognitive impairment, assessing visuospatial and executive functions, verbal ability, episodic memory, orientation...
and attention. It has been validated in numerous diseases, including cognitive impairment related to dyspnoea, COPD and heart failure.

Power and sample size
To obtain a power of 80% to detect a clinically and statistically significant difference of 1 point on a 0–10 NRS between the mean experienced and the recalled daily breathlessness score, assuming a pooled SD of 1.81 points, a minimum of 30 participants need to be included into the main study. This is consistent with the sample size of Meek et al. To account for loss of data and ensure adequate power, at least 45 participants with data for at least 2 days will be included prior to analysis of the primary research question. The data collection will continue even after this sample size is reached in order to answer also secondary research questions. Specific statistical analysis plans will be developed for each objective.

Statistical analyses
Baseline descriptive statistics will be tabulated using standard descriptive statistics. Mean, peak and end values of experienced, recalled and predicted breathlessness will be graphed and cross-tabulated. Associations between experienced, recalled and predicted breathlessness will be analysed using a mixed model repeated measures approach. Predictors of the difference score between recalled and experienced breathlessness, and between predicted and subsequently experienced breathlessness, respectively, will be analysed using multilevel mixed effects linear regression. Models will then be adjusted for potential confounders including age, sex, body mass index, level of anxiety, depression and functional status. The choice of an appropriate covariance structure will be evaluated.

The minimal clinically important difference score is defined as a 0.5 (small) and 1.0 (moderate/large) change in NRS score. The percentage of difference scores ≥0.5 and ≥1.0 points will be calculated.

Statistical significance will be defined as a two-sided p value of <0.05.

Confidentiality
In the application, data are de-identified using a study ID number. For patients who do not participate in the clinical substudy, the Swedish social security number is not recorded. For patients in the clinical substudy, clinical data will be cross-linked with data collected through the application using a key between the study ID (used in the application) and the participant’s Swedish social security number stored securely at the clinical centre.

The database used for the unidentified clinical data is located physically at Blekinge Institute of Technology and is used for several other clinical studies including the Swedish National Study of Ageing and Care (http://lithblekinge.se/snac) following all relevant protocols for data security and integrity. The code key containing the identifier are kept in a locked cupboard on a computer/USB memory not connected to the Internet.

Dissemination
Data will be presented on the group level only, ensuring that individual participants cannot be identified. The findings will be published in national and international peer-reviewed scientific journals and presented on relevant scientific conferences. The de-identified data will be posted in an open access data repository in accordance with the requirements of the scientific journal. Planned future papers will be concerning main and secondary endpoints as well as qualitative analyses on breathlessness measurements.

Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines.

DISCUSSION
This protocol describes a study aimed at investigating previously unknown areas of the experience and recall of breathlessness. This study also uses and evaluates a novel way of data collection which could prove to have numerous other applications in other research fields as well as in the current one. A potential limitation of this study is that there will be a low level of control over participants included into the general cohort. This will be regulated by giving out the four-digit code, which is needed to start the application, only to a selected population where breathlessness is anticipated to be highly prevalent. The Relating Experienced To Recalled breathlessness Observational study will answer several important questions such as the impacts and covariates of a breathless patients’ symptom recall. This issue has not been addressed previously and knowledge from this study could be used both clinically (to better understand patients) and in research (to better evaluate participants’ breathlessness reports). This study will further use the multidimensional dyspnoea profile in the assessments and analyses of breathlessness recall and experience which have not previously been used.

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**REFERENCES**

1. Gronseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. *Eur Respir J* 2014;43:1610–20.

2. Lopez Varela MV, Montes de Oca M, Halbert RJ, et al. Sex-related differences in COPD in five Latin American cities: the PLATINO study. *Eur Respir J* 2010;36:1034–41.

3. Bowden JA, To THM, Abernethy AP, et al. Predictors of chronic breathlessness: a large population study. *BMC Public Health* 2011;11:33.

4. Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol* 2009;167:53–60.

5. Stevens JP, Dechen T, Schwartzstein R, et al. Prevalence of dyspnea among hospitalized patients at the time of admission. *J Pain Symptom Manage* 2018;56:15–22.

6. Banzett RB, O’Donnell CR, Guilfoyle TE, et al. Multidimensional dyspnea profile: an instrument for clinical and laboratory research. *Eur Respir J* 2015;45:1681–91.

7. Williams M, Garrard A, Cafarella P, et al. Quality of recalled dyspnoea is different from exercise-induced dyspnoea: an experimental study. *Aust J Physiother* 2009;55:177–83.

8. Walentynowicz M, Bogaerts K, Van Diest I, et al. Was it so bad? The role of retrospective memory in symptom reporting. *Health Psychol* 2015;34:1166–74.

9. Miravitlles M, Ferrer J, Baró E, et al. Differences between physician and patient in the perception of symptoms and their severity in COPD. *Respir Med* 2013;107:1977–85.

10. Lari SM, Attaran D, Tohid M. Improving communication between the physician and the COPD patient: an evaluation of the utility of the COPD assessment test in primary care. *Patient Relat Outcome Meas* 2014;5:145–52.

11. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008;63:831–8.

12. Fredrickson BL. Extracting meaning from past affective experiences: the importance of peaks, ends, and specific emotions. *Cogn Emot* 2000;14:577–606.

13. Redelmeier DA, Katz J, Kahneman D. Memories of colonoscopy: a randomized trial. *Pain* 2003;104:187–94.

14. Walentynowicz M, Bogaerts K, Stans L, et al. Retrospective memory for symptoms in patients with medically unexplained symptoms. *J Psychosom Res* 2018;105:37–44.

15. Meek PM, Larena SC, Anderson D. Memory for symptoms in COPD patients: how accurate are their reports? *Eur Respir J* 2001;18:474–81.

16. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med* 2002;64:258–66.

17. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington DC, 2013.

18. Borland E, Nágga K, Nilsson PM, et al. The Montreal Cognitive Assessment: normative data from a large Swedish population-based cohort. *J Alzheimers Dis* 2017;59:893–901.

19. Nasereddine ZS, Phillips NA, Bédriani V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.

20. Crien AF, Oancea C, Timar B, et al. Cognitive impairment in chronic obstructive pulmonary disease. *PLoS One* 2014;9:e102468.

21. Alagiakrishnan K, Mah D, Dyck JR, et al. Comparison of two commonly used clinical cognitive screening tests to diagnose mild cognitive impairment in heart failure with the Golden Standard European Consortium criteria. *Int J Cardiol* 2017;228:558–62.

22. Dag E, Bulcun E, Turkel Y, et al. Factors influencing cognitive function in subjects with COPD. *Respir Care* 2016;61:1044–50.

23. Johnson MJ, Bland JM, Oxberry SG, et al. Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage* 2013;46:957–63.

24. Frändin K, Grimby G. Assessment of physical activity, fitness and performance in 76-year-olds. *Scand J Med Sci Sports* 1994;4:41–6.

25. Harshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012;185:435–52.

26. Fletcher C. Discussion on the diagnosis of pulmonary emphysema. *Proc R Soc Med* 1952;45:576–86.

27. Fletcher CM, Tinker CM. Chronic bronchitis. A further study of simple diagnostic methods in a working population. *Br Med J* 1961;1:1491–8.

28. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;93:580–6.

29. Ekström M, Sundh J. Swedish translation and linguistic validation of the multidimensional dyspnoea profile. *Eur Clin Respir J* 2016;3:32665.