Prevalence and Assessment of Breathlessness in people in the General Population and with life-limiting disease

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2022

Document Version:
Publisher's PDF, also known as Version of record

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Printed by Media-Tryck, Lund 2022 NORDIC SWAN ECOLABEL 3041 0903

This thesis is about chronic breathlessness. Breathlessness is a debilitating symptom highly prevalent in general populations and among those with severe illness. There is currently a scarcity of evidence-based knowledge concerning basic epidemiology, assessment and management. This thesis aims to explore and add new knowledge to this area.

The author, Jacob Sandberg, is a physician and specialist in family medicine working clinically at Jämjö health centre in Jämjö, close to Karlskrona in Sweden.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:118
ISBN 978-91-8021-279-3
ISSN 1652-8220

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LUND UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended in the Segerfalk lecture Hall (Segerfalksalen) at BMC, Sölvegatan 17, Lund, Sweden, on Friday, 9th of September 2022 at 13.15.

Faculty Opponent
Assistant professor Janwillem Kocks
University of Groningen, Groningen, The Netherlands.

Organisation LUND UNIVERSITY	Document name DOCTORAL DISSERTATION
	Date of issue 9 September 2022
Author(s) Jacob Sandberg	Sponsoring organisation None

Title and subtitle Prevalence and Assessment of Breathlessness in people in the General Population and with life-limiting disease.

Abstract

Background

Breathlessness, a subjective experience of breathing discomfort, comprises several different sensations in those affected, including physical, psychological, emotional, social, and behavioural aspects. Breathlessness is associated with decreased quality of life, reduced function, and poorer outcomes. Knowledge is lacking on several aspects of basic epidemiology, underlying conditions, and assessment strategies.

Aims

To evaluate the association of breathlessness with chronic obstructive pulmonary disease (COPD) events, cardiac events, and all-cause mortality from middle age throughout life.

To evaluate prevalent and overlapping underlying conditions among individuals reporting breathlessness in a general middle-aged population.

To compare DES with the mMRC in test-retest reliability, concurrent validity, and responsiveness for measuring chronic breathlessness in people with life-limiting illnesses.

To present a protocol for a study exploring the relationship between momentary and recalled breathlessness among individuals with chronic breathlessness.

To evaluate the relationship between recalled and momentary ratings of breathlessness and determine the aspect of breathlessness that shows the strongest positive association with recalled breathlessness: the mean, peak, or the most recent rating.

Methods

The relationship between breathlessness and health outcomes was analysed using survival analysis with data from a cohort study with 45 years of follow-up (Study I). The prevalence and overlap of underlying conditions and associated factors were analysed using multiple logistic regression in observational data from the general population (Study II). Concurrent validity, responsiveness, and test-retest reliability were established for DES using repeated measurements in individuals with severe chronic breathlessness (Study III). The relationships between experienced and recalled breathlessness were explored using longitudinal data collected using a mobile phone application (Study IV and Study V).

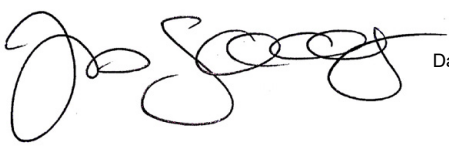
Results and conclusions

Reported exertional breathlessness at age 55 was associated with poorer health outcomes (Study I). Respiratory disease, anxiety or depression and obesity were the most prevalent underlying conditions of exertional breathlessness in the general population, often overlapping (Study II). DES could be used and possibly complement the assessment of breathlessness in people with severe diseases (Study III). The peak intensity of momentary breathlessness ratings for one week impacts the later recalled breathlessness; for one day, it was the mean (Study V).

Keywords Breathlessness, Dyspnea, Assessment, Symptoms, General population, Prevalence, Epidemiology, underlying conditions, momentary assessment, recall

Classification system and/or index terms (if any)

Supplementary bibliographical information		**Language** English
ISSN 1652-8220 Lund University, Faculty of Medicine Doctoral Dissertation Series 2022:118		**ISBN** 978-91-8021-279-3
Recipient's notes	**Number of pages** 76	Price
	Security classification	

Signature  Date 2022-07-18

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Coverphoto by Anatolii Riabokon

Faculty of Medicine
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ISSN 1652-8220
ISBN 978-91-8021-279-3
Lund University, Faculty of Medicine Doctoral Dissertation Series 2022:118

Printed in Sweden by Media-Tryck, Lund University, Lund 2022

"In some cases,
we learn more by looking for the
answer to a question and not finding it
than we do from learning the answer itself."

— Lloyd Alexander, The Book of Three

Table of Contents

Thesis at a glance

Study	Aims	Methods	Results	**Significance**
I	To evaluate the association of exertional breathlessness at 55 years of age with all-cause mortality and COPD or cardiac events.	Cohort study, analysed using survival analysis and competing risk regression.	Breathlessness at 55 years of age was associated with an increased risk of COPD events and increased all-cause mortality throughout life.	Early identification of breathlessness could give prognostic information to clinicians.
II	To evaluate prevalent and overlapping underlying conditions among individuals reporting exertional breathlessness.	Cross-sectional study using random populational sample. Analysis was using multiple logistic regression.	The main underlying contributing were respiratory disease (54%), followed by anxiety or depression (51%), obesity (43%) and heart disease or chest pain (32%); 66% had overlapping conditions.	Respiratory disease is the most common underlying disease, and overlap is highly prevalent among individuals with breathlessness in the general population.
III	To compare and validate DES against the mMRC for measuring breathlessness in individuals with severe breathlessness.	Repeated measurements of DES and mMRC over nine days. Assessment of test-retest, validity and responsiveness.	Compared with mMRC, DES had comparable or better measurement properties in terms of test-retest, reliability and concurrent validity.	DES could be used as a discriminative tool in populations with severe breathlessness.
IV	To present a protocol for a study exploring the relationship between momentary and recalled breathlessness.	Identification of research questions and development of data collection through a mobile phone application	A mobile phone application was developed. Data from 84 individuals were collected; 76 of these concluded the whole study. The compliance rate was 75.8%.	Studying breathlessness through a mobile phone application is feasible. The developed tool could be used in future studies.
V	To evaluate the relationship between recalled and momentary ratings of breathlessness.	Observational study with repeated measurements using mobile ecological momentary assessment technique.	The peak of momentary breathlessness ratings more strongly influenced the recalled severity of breathlessness over the past seven days than the average or most recent (end) values. Over one day, the mean of momentary breathlessness is the most influential.	Peak breathlessness impacts recalled breathlessness for one week more than the mean or end values.

List of publications

The thesis is based on the following publications, referred to in the text by the Roman numerals I-IV.

I. Sandberg J, Engström G, Ekström M
Breathlessness and incidence of COPD, cardiac events, and all-cause mortality: A 44-year follow-up from middle age throughout life. *PLoS ONE*, 2019; 14(3): e0214083.

II. Sandberg J, Ekström M, Börjesson M, Bergström G, Rosengren A, Angerås O, Ekström M.
Underlying contributing conditions to breathlessness among middle-aged individuals in the general population: a cross-sectional study. *BMJ Open Respiratory Research.* 2020;7**:** e000643.

III. Sandberg J, Johnson MJ, Currow DC, Ekström M.
Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness. *J Pain Symptom Management.* 2018 Sep;56(3):430-435.e2.

IV. Sandberg J, Lansing R, Anderberg P, Currow D, Sundh J, Ahmadi Z, Palmqvist S, Ekström M
Relating Experienced To Recalled breathlessness Observational (RETRO) study: a prospective study using a mobile phone application *BMJ Open Resp Res* 2019; 6**:** e000370.

V. Sandberg J, Sundh J, Anderberg P, Currow D, Johnson M, Lansing R, Ekström M
Comparing recalled versus experienced symptoms of breathlessness ratings: An ecological assessment study using mobile phone technology. *Respirology.* 2022. https://doi.org/10.1111/resp.14313

Abstract

Background: Breathlessness, a subjective experience of breathing discomfort, comprises different sensations, including physical, psychological, emotional, social, and behavioural aspects. It is associated with decreased quality of life, reduced function, and worse health outcomes. Knowledge is lacking on several aspects of basic epidemiology, underlying conditions, and assessment strategies.

This thesis consists of five studies. Study I explores associations between reported exertional breathlessness and health outcomes throughout life. Study II examines underlying conditions in middle-aged individuals with breathlessness in the general population, while Study III validates the measurement properties of the Dyspnoea Exertion Scale (DES). Finally, Study IV and V explore the relationship between experienced and recalled breathlessness.

Study Design: The relationship between breathlessness and health outcomes was analysed using survival analysis with data from a Swedish cohort study with 45 years of follow-up (Study I). The prevalence of underlying conditions and associated factors were analysed using multiple logistic regression in observational data from the general population in Gothenburg, Sweden (Study II). Concurrent validity, responsiveness, and test-retest reliability were established for DES using repeated measurements in Australian individuals with severe chronic breathlessness (Study III). The relationships between experienced and recalled breathlessness were explored using longitudinal data collected using a mobile phone application (Study IV and Study V).

Results and conclusions: Reported exertional breathlessness at age 55 was associated with worse health outcomes (Study I). Respiratory disease, anxiety or depression, and obesity were the most prevalent underlying conditions of exertional breathlessness in the general population, often overlapping (Study II). DES could be used and possibly complement the assessment of breathlessness in people with severe diseases (Study III). The peak intensity of momentary breathlessness ratings for one week impacts the later recalled breathlessness. Recall for one day was most influenced by the mean of momentary ratings (Study V).

Populärvetenskaplig sammanfattning

Att andas är en förutsättning för att leva. Luft från omgivningen strömmar in genom munnen, åker ner via luftstrupen och fyller lungorna vid varje andetag. Receptorer från muskler, senor, blodkärl och lungvävnad skickar information till hjärnstammen om både det aktuella behovet att andas och hur mycket vi faktiskt andas. Ibland uppträder diskrepans mellan behov och förmåga. Vi blir då medvetna om andningsarbetet och om diskrepansen fortsätter upplever vi andfåddhet. Upplevelsen av andfåddhet innehåller både fysiska, psykologiska, känslomässiga och sociala aspekter som ofta leder till beteendeförändring och har en negativ inverkan på både livskvalitet och funktionsnivå.

Syftet med denna avhandling är: att undersöka sambandet mellan rapporterad ansträngningsutlöst andfåddhet i medelåldern och hälsoutfall genom livet (studie I). Att identifiera de vanligast förekommande underliggande sjukdomarna vid andfåddhet (studie II). Att undersöka om mätskalan Dyspnea Exertion Scale (DES) kan användas för mätning av andfåddhet hos svårt sjuka individer (studie III). Att undersöka sambanden mellan andfåddhetsnivån man upplever i stunden och andfåddheten som man senare återrapporterar, till exempel vid ett läkarbesök (studie IV+V).

Studie I är en kohortstudie där deltagarna rekryterades år 1968 och sedan följdes genom livet. I studie II samlades data in vid ett tillfälle med hjälp av frågeformulär, spirometri och arbetsprov. DES skalan testades gentemot andra, redan validerade, skalor (studie III). I studie IV utvecklades ett studieprotokoll där syftet var att undersöka relationen mellan andfåddhet mätt via mobiltelefon vid olika tidpunkter. Studien genomfördes sedan och resultaten rapporteras i studie V.

Vi kunde genom dessa studier visa att förekomst av andfåddhet i 55 års åldern är associerat med högre nivå av sjukdomsfall och tidigare död (studie I). Lungsjukdom, ångest eller depression, och fetma var de tre vanligast förekommande underliggande tillstånden vid andfåddhet, och ofta överlappande. Mätskalan DES kan användas, och tillföra information, hos individer med svår andfåddhet. Slutligen kom vi fram till att den högsta nivån av andfåddhet under en vecka är starkast sammanlänkat med den återrapporterade andfåddhetsnivån.

Abbreviations

6MWT	6-Minute Walk Test
ACE	Angiotensin-converting enzyme
ALS	Amyotrophic lateral sclerosis
CI	Confidence Interval
CNS	Central nervous system
CO2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COVID 19	Coronavirus disease -19
CPET	Cardiopulmonary Exercise test
CWR	Constant Work Rate
D12	Dyspnea-12
DES	Dyspnoea Exertion Scale
DLCO	Diffusion capacity for carbon monoxide
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FEV1	Forced expiratory volume for 1 second.
FVC	Forced expiratory volume
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICS	Inhaled corticosteroids
MDP	Multidimensional Dyspnea Profile
mEMA	Mobile ecological momentary assessment
mMRC	Modified medical research council
MMSE	Mini-Mental State Examination
MRA	Mineralocorticoid receptor antagonists

NRS	Numerical Rating Scale
O_2	Oxygen
OR	Odds Ratio
RV	Residual volume
SCAPIS	The Swedish Cardiopulmonary BioImage Study
SHR	Subdistribition Hazard Ratio
SSRI	Selective serotonin receptor inhibitors
TLC	Total lung capacity
VIF	Variance Influence Factor
WHO	World Health Organisation

Introduction

This section will introduce the research area – chronic breathlessness [1]. Understanding chronic breathlessness first requires knowledge of anatomy, basic respiratory physiology, and underlying pathophysiological changes before focusing on the qualities, consequences, assessment, and management of breathlessness.

Throughout this thesis, the focus lies mainly on breathlessness of chronic or persistent nature and acute forms of breathlessness caused by, for example, pneumonia or pulmonary embolism will be left out.

Physiology of breathing

Respiratory System

The most basic function of the respiratory system is to enable gas exchange from the ambient air into the blood. Through adequate ventilation, oxygen is supplied to all cells in the body and is used to produce energy. Carbon dioxide is eliminated from the blood, maintaining acid-base homeostasis [2].

The air from the environment is transported with each breath through the nose, throat, larynx, trachea, and bronchi and then into the smallest component of the respiratory system, the alveoli (figure 1) [3]. Each breath is dependent on the elastic properties of the diaphragm and chest wall. The diaphragm's and chest wall's elasticity causes lung volume expands, lowering the air pressure within the alveoli and causing air to move in [4]. The elasticity of the lung then recoils and decreases the lung volume as the muscles relax, increasing the air pressure and causing the air to move out again. Normal quiet breathing only requires activation of the dorsal respiratory group in the medulla, the diaphragm, and the external intercostal muscles, which regulate inspiration [4]. At the same time, expiration is a passive process through the lung's elastic recoil. In case of higher respiratory demand, such as during exercise, the ventral group in the medulla is activated as well as additional muscles [4]. These muscles include abdominal- and accessory muscles, which forcefully increase and decrease pulmonary volume and increase respiratory rate [2, 3].

The airway resistance determines the possible level of airflow through the bronchial tree and is mainly affected by the airway diameter [2]. Almost the whole trachea and bronchi are lined with smooth muscles and layers of mucus, with cilia removing excessive mucus and foreign objects [3]. Under normal conditions, the air flows very smoothly through the pulmonary system. As the need for ventilation increases, the airway diameter may become one of the limiting factors for increasing ventilation [4]. Changes in airway resistance, e.g., airway diameter, will restrict the highest possible amount of air flowing into the lung. Narrowing of the airways may arise through intraluminal, intramural, or extramural pathologies such as secretions, oedema, or loss of interstitial collagen [5].

The higher oxygen concentration in the inhaled air in the alveoli moves over the membrane into the blood and carbon dioxide the other way in the process known as diffusion. Diffusion occurs with each breath in the 300 million alveoli of a healthy pair of lungs and is the final aim of the respiratory system. The total amount of gas exchanged in this process is dependent on the total surface area of the total amount of alveoli, the thickness of the membranes, the pressure differences of the gas, the molecular weight of the gas, and the solubility of the gas in the tissue [2, 4].

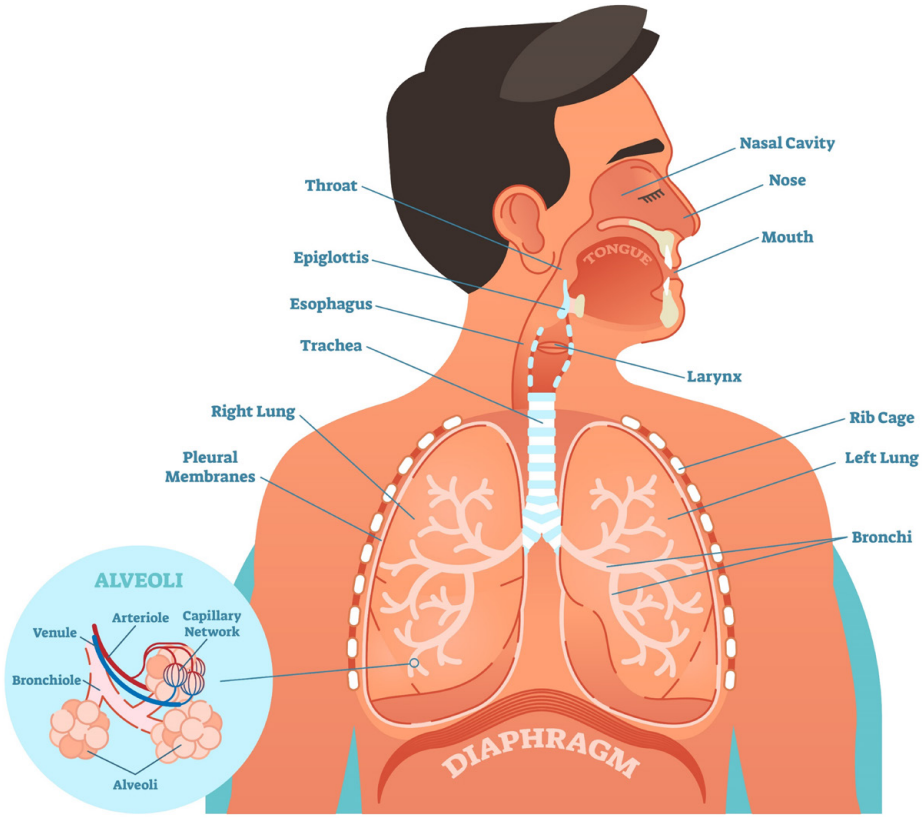

Figure 1 Overview of the respiratory system. Illustration by: Vectormine. Reproduced with permission.

Control of ventilation

Ventilation is monitored by several mechanisms, including several different types of receptors in the thorax, central nervous system, and carotid and aortic vessels. The receptors in the thorax include muscle spindles and tendon organs in the chest wall, diaphragm, and accessory muscles, which respond to changes in lung volume (figure 2) [4]. Stretch, irritant, and c-fibre receptors in the lung parenchyma and upper airways react to changes in volume, histamines, prostaglandins, and other chemicals (figure 3) [6]. When these receptors are stimulated, signals are sent to the central nervous system inducing increased respiratory rate, the volume of each breath (tidal volume), and cough [2, 7, 8]. The receptors in the central nervous system are mainly chemoreceptors located on the ventral surface of the medulla, responding to changes in blood and

cerebrospinal fluid pH and level of CO^2, thereby maintaining the acid-base homeostasis [4]. The peripheral chemoreceptors in the aortic and carotid bodies are the primary controllers of the partial pressure of oxygen but are also stimulated by high levels of CO^2 and acidosis [4]. Information from these peripheral chemoreceptors is mediated through the Vagus and Glossopharyngeal nerves to the medulla of the brainstem (figure 3) [4, 6, 9].

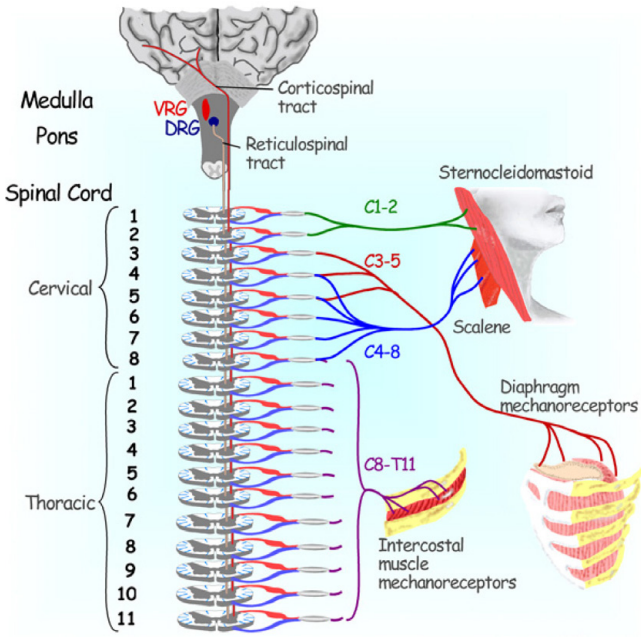

Figure 2: Schematic representation of sensory pathways of respiratory regulation by mechanoreceptors, muscle spindles, and tendon organs in the chest wall, diaphragm, and accessory muscles that respond to lung volume changes. (VRG = ventral respiratory group, DRG = dorsal respiratory group). From Burki et al.010 [6]. Reproduced with permission from © Elsevier. Chest**.** **DOI**:10.1378/chest.10-0534. Published November 2010.

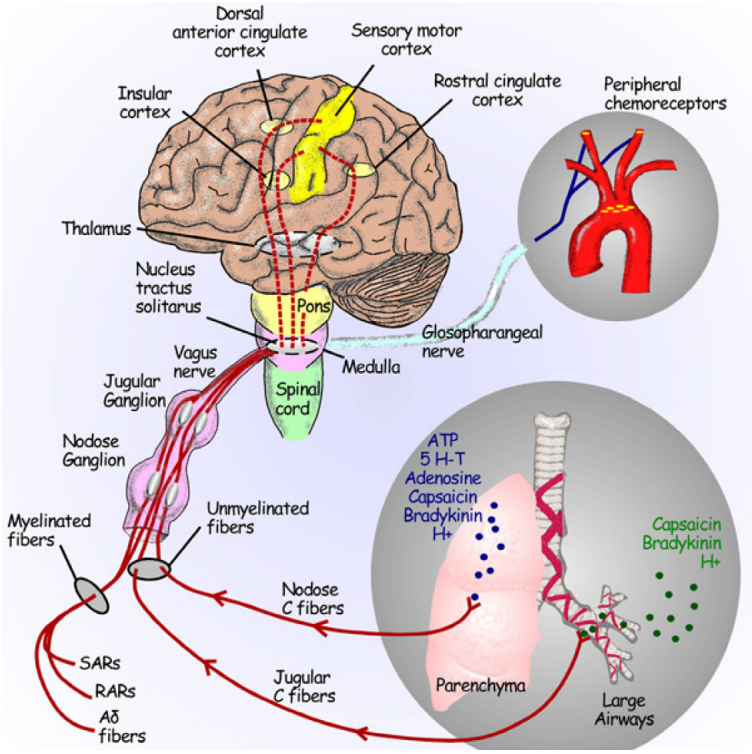

Figure 3: Schematic representation of sensory information arising from the stretch, irritant, and c-fibre receptors in the lung parenchyma and upper airways and then transmitted through the Vagus nerve to the brainstem. Peripheral chemoreceptors in the aortic bodies transmit impulses through the glossopharyngeal nerve to the brainstem. (RAR= rapidly adapting receptors, SAR = slowly adapting receptors). From Burki et.al 2010 [6]. Reproduced with permission from © Elsevier. Chest. DOI:10.1378/chest.10-0534. Published November 2010.

In the case of low oxygen levels, high CO^2 levels, or changes in pH detected by the central or peripheral chemoreceptors, signals are sent to the nucleus tractus solitarius located in the dorsal group of the medulla [10, 11]. Increased ventilation is then performed through increased tidal volume and respiratory rate signals to ventilatory muscles. Thereby homeostasis of oxygen, carbon dioxide, and acid-base is maintained throughout different situations [2, 4].

Breathing occurs unconsciously and automatically under normal circumstances. This automatic process is generated by central pattern generators located in the medulla [6, 12, 13]. Most of the time, the information is thus "filtered out," preventing the higher brain centres from being flooded by irrelevant information. The conscious breathing sensation is alerted only when needed, such as in increased respiratory demand [14, 15].

Spirometry

Pulmonary ventilatory function and capacity can be assessed using spirometry, a quick, non-invasive, and harmless examination [16, 17]. It is the most available and useful test of pulmonary function. The process of a spirometry test includes a maximal inhalation followed by forceful and complete exhalation. Testing is often performed both with and without bronchodilator medication. Measurements include the total volume of the forced exhalation, forced vital capacity (FVC) and, the volume exhaled during the first second of exhalation, forced expiratory volume during 1 second (FEV1). The ratio between FEV1/FVC is essential for categorising lung function abnormalities [16, 17].

Measurements of lung volumes and diffusing capacity is also often necessary, especially when abnormalities are present during regular spirometry. For measuring lung volumes, body plethysmography is the golden standard [18]. The most common and important additional measurements include total lung capacity (TLC), defined as the volume of air in the lungs at the end of a maximal inspiration, and residual volume (RV), meaning the volume of air left in the lungs after a maximal expiration. Diffusion capacity for carbon monoxide (DLCO) is measured by inhalation of carbon monoxide in a single breath.

Pathophysiological changes associated with breathlessness

The ventilatory muscles, peripheral nerves, airways, pulmonary interstitium, pulmonary vascular system, and cardiovascular system are susceptible to pathological changes affecting the ventilatory capacity. There are no strict lines between the different categories, and pathology in one area usually results in pathology in other [1, 7, 11]. This section will discuss some, but not all, of the most common pathophysiological changes in diseases known to cause chronic breathlessness.

Changes present with acute onset of breathlessness, most caused by infections, thromboembolic events, or other acute situations, are not the primary subject of this thesis and will only be briefly mentioned.

Respiratory system

Pulmonary diseases are usually classified as either obstructive or restrictive. Obstructive disorders involve obstruction of airflow and increased airway resistance caused by, for example, narrowing of airway diameter due to smooth muscle hypertrophy, excessive mucus production, and inflammation in asthma. Asthma is characterised by atopy

(genetic hypersensitivity type 1), acute and chronic inflammation, and reversible bronchoconstriction due to hyperresponsiveness to various stimuli [5, 7]. Spirometry in asthma in typical cases reveals an airway obstruction with an increase in FEV1 or FVC of more than 12 % and greater than 200 ml after bronchodilation (bronchodilator responsiveness) [19].

Obstructed airflow can also be caused by loss of elastic recoil due to the pulmonary wall destruction seen in emphysema (figure 3). There are different types of emphysema, but it most often results in airway obstruction through loss of elastic tissue in the alveoli walls, leading to collapsing bronchioles during expiration. Emphysema can occur in isolation, most commonly in alfa-1-antitrypsin deficiency, but is most often accompanied by chronic bronchitis. Chronic bronchitis includes mucus gland hypertrophy and hypersecretion and begins in the large airways [5]. Airflow obstruction due to chronic obstruction is caused by small airway disease with inflammation, bronchial wall fibrosis, and mucous plugging of the bronchiolar lumen (figure 4) [5]. Chronic bronchitis is defined as a chronic productive cough for three months in two successive years and where other causes of chronic cough have been excluded [20]. Emphysema and chronic bronchitis are highly associated with tobacco use and are often present simultaneously. They are then grouped into COPD [8]. On spirometry, COPD includes a, most commonly, non-reversible airway obstruction with the ratio $FEV_1/FVC < 0.7$. COPD is one of the most common respiratory diseases globally, and breathlessness is often one of the first and most debilitating symptoms [8, 21].

Restrictive pulmonary diseases include pathological processes involving the pulmonary interstitium [5]. These entities cause breathlessness by reducing pulmonary compliance and increasing the force needed to take a breath. The maximum FVC of expiration is reduced, but airflow remains constant in relation to the vital capacity. Interstitial diseases lead to abnormalities in the interstitial areas with subsequent reduction in ventilation and perfusion ratio and hypoxia. Interstitial diseases include, among others, fibrosing diseases (such as idiopathic pulmonary fibrosis), granulomatous diseases (such as sarcoidosis), and pneumoconiosis (inhalation of mineral dust). Breathlessness and dry cough are the most common associated symptoms [5].

Apart from asthma, all chronic respiratory diseases are associated with high mortality risk with small improvements in prognosis in recent years [22].

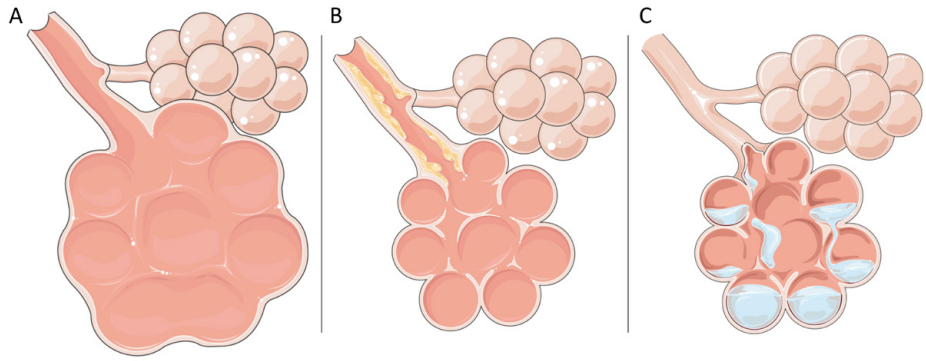

Figure 4: Pathological changes on the alveolar level A) Emfysema B) Chronic bronchitis, C) Pulmonary oedema. Illustration by: Servier Medical Art, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>. Illustrations are arranged in a collage with added annotations.

Cardiovascular system

The cardiovascular system includes the pulmonary, coronary, and systemic circulation [5]. The most common pathologies in the blood or heart that may cause breathlessness are lack of haemoglobin (anaemia), pulmonary ischemia due to occlusion of pulmonary arteries (thromboembolic events), or lack of adequate heart function (heart failure). Heart failure is "a clinical syndrome with symptoms and/or signs caused by structural and/or functional cardiac abnormalities" [23]. It occurs when cardiac output is insufficient for the body's metabolic needs. Heart failure can occur secondary to many different heart diseases, such as ischemic heart disease or hypertension, resulting in impaired contractile function (systolic heart failure) [5]. Diastolic heart failure, on the other hand, is due to an inability to relax and fill the ventricles. It is often caused by ventricular hypertrophy and myocardial fibrosis, among others. Symptoms such as breathlessness on exertion and fatigue often occur due to a reduction in cardiac output [5, 23]. Breathlessness also occurs due to increased pulmonary venous pressure, congestion and oedema in the alveolar spaces (figure 3). Both these mechanisms reduce compliance and stimulate pulmonary receptors, which induce breathlessness. If hypoxia arises secondary to heart failure, breathlessness will also be triggered by central and peripheral chemoreceptors [5, 7, 11, 23].

Central nervous system, muscles, and body composition

The ventilatory muscles and nervous system controlling them must function well to produce the negative pressure in the alveoli needed for air to flow into the lungs in sufficient volume. Dysfunction in muscles or nerves will significantly affect ventilatory capacity. Neuromuscular weakness is present in various diseases affecting the central nervous system, such as myasthenia gravis, Guillain Barré, and ALS. [7, 11].

Obesity is another condition leading to impaired respiratory muscle function, and the condition alters the possibilities for the lung to expand sufficiently. The lower relative lung volumes combined with higher work of breathing due to the increased weight will result in higher susceptibility for breathlessness [24]. Even though obesity is often associated with increased breathlessness, its relationship with other factors, such as deconditioning, is unclear [25-27]. Obesity usually involves muscular and hormonal changes (increased leptin levels), which increase the respiratory drive to maintain normal oxygen and carbon dioxide levels despite the high demand [4, 24].

Physiological role of mental health

Finally, depression and anxiety disorders are common comorbidities to several cardiopulmonary diseases such as COPD or cardiac failure [1, 28]. They also commonly cause breathlessness, most dramatically demonstrated as a panic attack [29]. It has been suggested that the presence of anxiety disorders increases the signals sent to higher brain centres from the medulla, where usually most of the automatic breathing occurs, resulting in an "over perception" of breathlessness or "reduced neural gating" as regarded in some literature [14, 30].

Breathlessness

Breathlessness can arise quickly within seconds or minutes or develop slowly for weeks, months, or years. It is a part of everyday life for healthy individuals usually experienced during exercise. Still, when present in daily life and related to disease, breathlessness is associated with negative emotions and suffering for those affected. This section will cover the basic definition of breathlessness, mechanisms, qualities, assessment methods, and the different treatment options.

Definition

The American Thoracic Society defines breathlessness as "a subjective experience of breathing discomfort comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interaction among multiple physiological, social and environmental factors, and may induce secondary physiological and behavioural responses" [1].

Breathlessness thus contains both a *sensation* and a *perception*. The experience will be highly subjective, and bystanders – such as medical professionals – will often not be able to correctly appreciate the intensity of the breathlessness [31, 32]. Breathlessness is a symptom such as pain and should not be confused with clinical signs such as rapid breathing (tachypnoea), use of accessory muscles, or peripheral oxygen saturation, which could or could not be present concomitantly with breathlessness [1, 33]. Thus, adequate assessment of breathlessness depends entirely on self-report. The subjective report of breathlessness is suggested to have high prognostic importance [34]. Simply asking about breathlessness may give better prognostic information than spirometry testing of FEV_1 in COPD and predicts cardiac death better than angina [35]. Breathlessness is also a strong predictor of all-cause death in general populations [36, 37].

"Chronic breathlessness syndrome" refers to breathlessness that persists despite optimal treatment of underlying pathophysiological abnormalities [38]. The breathlessness should result in a disability and functional decline. Other terms are used interchangeably in the literature, with "persistent breathlessness syndrome" being the most common [39]. This thesis assesses chronic forms of breathlessness in the sense that they are constant. However, it is hard within the presented studies to determine whether the treatment has been optimised for the included individuals. Therefore, the term chronic or persistent breathlessness "syndrome" will not be used unless warranted.

Epidemiology

Chronic breathlessness is reported by 9-11% of the adult population [40, 41]. The prevalence increases with higher age and with increasing disease burden. In older adults (>70), it has been reported that 25-32% suffer from breathlessness in daily life [42, 43] and 45% of men and 43% of women above 80 [43]. In these age groups, as in other, breathlessness was associated with poorer quality of life, lower functional status, and a higher prevalence of anxiety or depression [43].

Women more frequently report breathlessness than men. One proposed explanation is the, on average, smaller lung volumes (FEV_1 or FVC) among women [44, 45]. Breathlessness is also more common in the offspring of individuals suffering from

breathlessness, suggesting a hereditary component. This relationship was not explained by confounding effects such as age, sex, smoking, asthma, and airflow obstruction. There is little knowledge concerning hereditary and genetic factors [46].

Even though the prevalence of breathlessness in palliative care varies between populations, it is clear that breathlessness is widespread in the later stages of life. The overall prevalence of around 50% of all terminally ill patients has been reported, with numbers reaching 78% (lung cancer), 88% (congestive heart failure), and 95% (COPD) in different disease groups [47-52].

Underlying conditions

Respiratory disease, heart disease, and obesity are the most reported underlying conditions among breathless individuals [53-55]. Studies show that COPD and heart failure often coexist and that comorbidity is associated with increased breathlessness [54, 56, 57] and worse clinical outcomes [57, 58]. However, which conditions co-exist and overlap with breathlessness in primary care, or the general population is largely unknown.

Prompt identification of underlying conditions leading to breathlessness is needed to provide optimal management [59]. Individuals with new episodes of acute or chronic breathlessness from the general population often contact primary care for assessment. However, there is a large scarcity of epidemiological data guiding the primary care physician in assessing breathlessness.

Symptoms drive individuals to the primary health care centre, and symptom-guided knowledge for assessment and treatment is needed. The challenges of studying and evaluating breathlessness include complex associations between multiple factors contributing to the sensation, including heart and lung diseases, mental states, hereditary factors, and social and environmental factors [32]. Many of these factors often coexist [60], but detailed information from clinically relevant populations is lacking.

Qualities of breathlessness

Disease-specific mechanisms for breathlessness, as well as pathophysiological changes, have been discussed. However, the perception of breathlessness is complex, and only pathophysiological changes cannot explain the whole experience.

Breathlessness, explained in its most basal form, is a mismatch between the current respiratory demand and the actual work of breathing. Breathlessness arises from complex pathways from the body to the brain stem (figure 5) [8, 11]. Different

receptors from muscle spindles and tendon organs in the chest wall, stretch-irritant and c-fibre receptors in the lung parenchyma and upper airways, and chemoreceptors in the carotids and aorta send signals to the brainstem continuously [11]. In case of a mismatch, the information is forwarded to the brain's sensory cortex, which leads to different motor signals to respiratory muscles, diaphragm, and upper airways to enhance the work of breathing. Thus, these redundant systems constantly control and regulate the current need for ventilation. Signals from different receptors give rise to varying types of qualitatively distinct sensations [61-63]. Several verbal descriptors of these sensations are used by those affected and grouped into the most commonly described sensations; air hunger, work-effort, and tightness.

These qualities seldom occur in isolation in real life, and several sensations are often present simultaneously and all existing qualities will not be described.

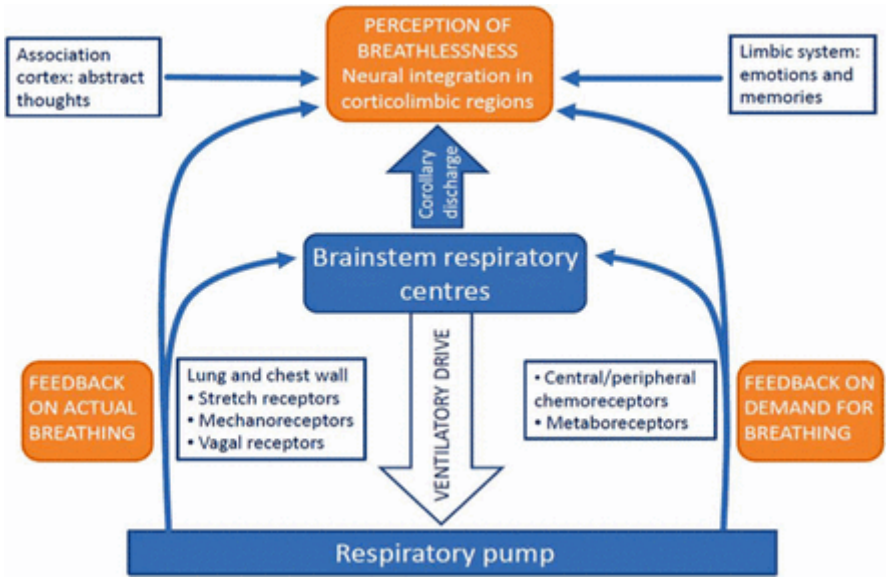

Figure 5: Schematic representation of the pathophysiology of breathlessness. From Chin et al. [49]. Reproduced with permission from © BMJ Publishing Group Ltd. Postgraduate Medical Journal **DOI:**10.1136/postgradmedj-2015-133578. Published 6 April 2016.

Air hunger

Air hunger is the perception of not getting enough air. It is a primal warning signal for the inability to maintain gas exchange. It is demonstrated by holding one's breath for a long time [64]. As with other primal warning signals such as pain, hunger, or thirst, air

hunger is hard to ignore and evokes fear and anxiety [64]. Air hunger is further intensified by hypoxia, hypercapnia, and acidosis, increasing the spontaneous ventilatory drive controlled by the brain stem. It is believed that air hunger arises when information from the spontaneous ventilatory drive in the brain stem is conveyed to the cerebral cortex and is not matched by a sufficient response in ventilation recorded by mechanoreceptors in the lung, airways, and chest wall [11]. Several brain areas are involved (figure 6)[64]. In healthy individuals, the inability to provide adequate ventilation only occurs with a very high level of exercise, severe anxiety, distressful situations, and loss of control [1, 64]. In cardiopulmonary or neurological disease, the sensation arises much more quickly. [62].

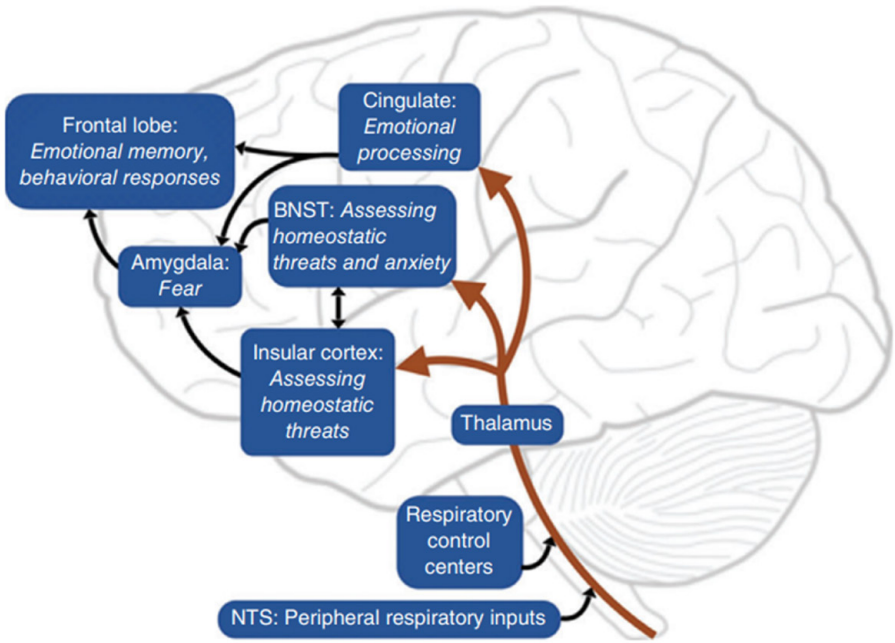

Figure 6: Neural processing of the feeling of air-hunger Proposed central network for air hunger and the emotional and behavioural responses. The brown lines depict the interoceptive pathway, and black arrows represent known available sections. BNST = bed nuclei of the stria terminals; NTS = nucleus tractus solitarius. From Banett et al. [64] Reproduced with permission of the © John Wiley and Sons. Comprehensive physiology 1449-1483 **DOI:**10.1002/cphy.c200001. Published 12 February 2021.

Work and effort

The sensation of increased respiratory work and effort is another distinct sensation within the experience of breathlessness. The work and effort sensation originates from respiratory muscles and cortical motor commands and is conveyed through other neural pathways than air-hunger [63-65]. Increased work and effort are the dominant sensory qualities at the peak of exercise, also experienced by healthy individuals [1, 65, 66]. As the intensity of the exercise increase, the work/ effort needed to match the ventilation with the demand also increase. If the match is maintained, the breathing during the exercise is associated with only low levels of unpleasantness. But once the threshold is reached, the distress rises quickly, often resulting in the termination of the activity [65, 66]. However, if the distress is expected or even sought after, it can often be overruled, and the exercise can continue. In cardiopulmonary disease, unpleasantness from the work and effort is more significant (arises much earlier) and commonly reduces exercise capability. Increased breathing effort is also widely used to describe the breathlessness associated with panic disorder [29].

Tightness

The sensation of chest tightness is associated with bronchoconstriction, commonly present in asthma. As the bronchoconstriction exacerbates, it leads to work/ effort and ultimately air hunger. It is thought that tightness is related mainly to airway receptors as the sensation is believed to respond better to inhalation of beta-stimulating drugs than the feeling of work/effort [1, 11, 62].

The sensation and perception of breathlessness are yet more complex, as the experience does not only rely on the different qualities described above but also on the individuals' perceptions, past experiences, social situations, beliefs, and expectations around breathlessness - all of which influence the interpretation and behavioural changes induced because of breathlessness [67-69].

Breathlessness and the brain

The subjective sensation and perception of breathlessness do not always match objective measures of disease [70]. The mismatch has led to the notion that several brain areas are involved apart from the peripheral neural pathways. Neuroimaging studies have identified these areas as the insula, cingulate, sensory cortex, amygdala, and periaqueductal grey matter [71-73]. Most of these brain areas normally involve emotions such as fear and anxiety [15]. These brain mechanisms, associated with expectations and affective states, seem to have a significant role in the experience of

breathlessness [67, 68, 74]. Expectations of breathlessness, induced by for example approaching a set of stairs or seeing breathlessness in others, seem to induce breathlessness [67, 68, 75]. It is also clear that different affective states significantly impact breathlessness. For example, experimentally induced negative affect has been found to lead to higher levels of unpleasantness from breathlessness [76].

The Bayesian brain hypothesis incorporates some of these thoughts into one proposed model (figure 7) [67]. The hypothesis suggests a balance between brain-generated predictions and afferent sensory input. According to the model, brain-generated predictions are based upon learned behaviours and previous experiences and can be influenced by other factors such as personality traits, negative affect, or anxiety [13, 67, 68].

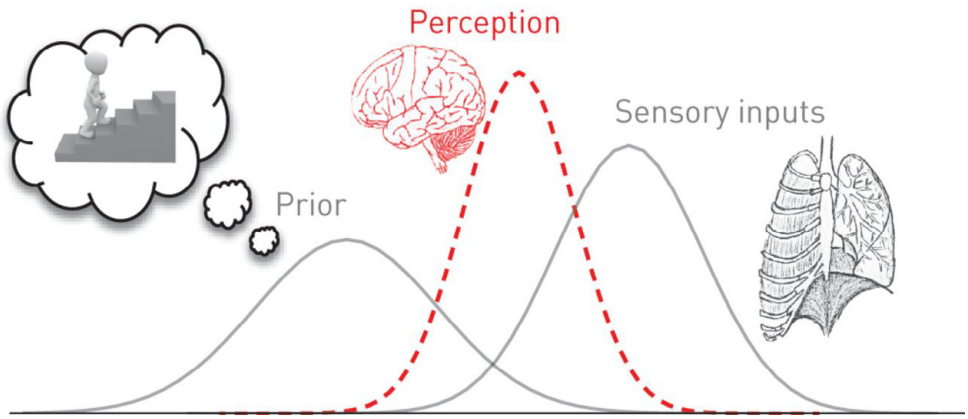

Figure 7: Bayesian brain hypothesis. From Faull et al. [67]. Reproduced with permission of the ©ERS 2022. European Respiratory Journal 51 (1) 1702238; **DOI:** 10.1183/13993003.02238-2017 Published 25 January 2018.

Consequences of breathlessness

For the individual

Breathlessness is associated with a worse prognosis [77]. It is also strongly associated with impairment of both mental and physical quality of life, with lower functional status and a lower ability for self-care [28, 78-81]. Chronic breathlessness is associated with poorer sleep, impaired sexual health, and social isolation [82, 83]. Activities such as household chores, gardening, and hobbies are often limited and reduced [83][50, 51].

Individuals with chronic breathlessness have decreased workforce participation and subsequent economic consequences on individual and societal levels [84]. The consequences combined often change social roles and relationships with loved ones and ultimately alter self-perception [85].

The presence of breathlessness often induces avoidance of physical activity due to fear of breathlessness; this leads to inactivity and deconditioning, further exacerbating the initial problem with breathlessness. A vicious cycle of inactivity and breathlessness develops [86], which often becomes a barrier to improving and taking part in different types of rehabilitation [87], leading to a continued downward spiral (figure 8).

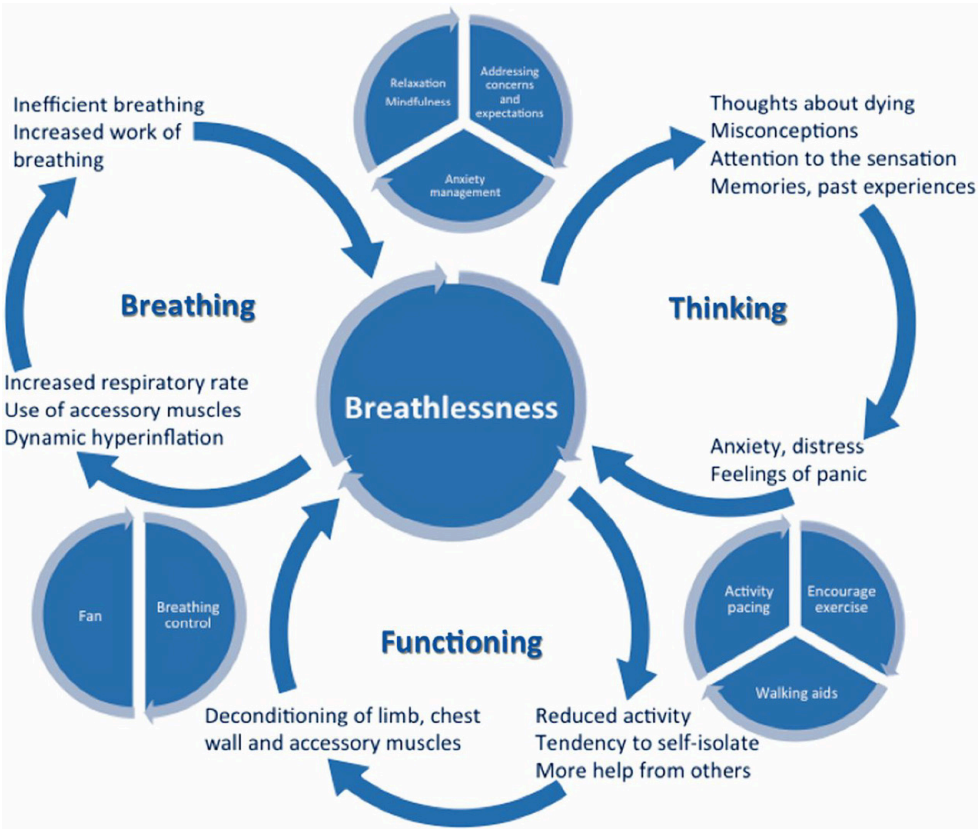

Figure 8: The breathing, thinking, functioning model and non-pharmacological strategies for breathlessness. From Chin et al.[49]. Reproduced with permission from © BMJ Publishing Group Ltd. Postgraduate Medical Journal DOI:10.1136/postgradmedj-2015-133578. Published 6 April 2016.

Increased health care utilisation

Another consequence of breathlessness is increased health care utilisation associated with the symptom [88]. Data suggest that acute exacerbation of pre-existing chronic breathlessness is common among individuals seeking health care. Breathlessness is present among approximately 1- 4% of all primary care visits [89, 90], one in five of all ambulance missions [91], one in twenty of all emergency department visits, one in ten of all admissions to general wards and one in five of all admissions to intensive care units [92, 93]. There is, however, a lack of reliable information on this area with data only from a few different settings (mainly Europe and Australia), especially in the case of primary care and general populations, limiting the possibilities for generalisation of results. There is also significant heterogeneity in studies evaluating primary care data with differences in breathlessness definition, primarily based on non-standardised clinical information. Very few studies concentrate on chronic and acute-on-chronic breathlessness [94]. More details of pre-test probability, the optimal diagnostic procedure, and the optimal testing order from a primary care perspective are needed [94].

Assessment of breathlessness

Identifying breathlessness within health care is essential, given its profound impact on several vital parts of life [34]. Identifying, assessing, and optimally managing this symptom has been suggested to be a human right [95, 96]. Yet, breathlessness remains inadequately assessed on many occasions [97]. Several explanations have been proposed, including that breathlessness is often invisible at rest and at health care visits and misconceptions among healthcare personnel that breathlessness cannot be managed [97, 98]. The golden standard to assess breathlessness is self-report, and several scales and methods are available [99-102]. Careful selection of the proper assessment method for each situation is needed. Both unidimensional and multidimensional tools are available that measure breathlessness directly or indirectly.

Unidimensional tools only assess breathlessness from one dimension or quality, whereas multidimensional tools, such as MDP or Dyspnea-12, aim to assess several dimensions simultaneously [103, 104]. Dimensions include the sensory and affective components of breathlessness. Sensory components include the overall intensity and the distinct qualities (air hunger, work/effort, and tightness). Affective components include feelings of unpleasantness due to breathlessness and triggered emotions such as fear, anxiety, or anger [1, 99, 101]. Some available tools focus on an indirect measure of breathlessness and might include the effects on quality of life and wellbeing [1, 99].

Unidimensional assessment

Commonly used unidimensional assessment methods include the straightforward Numerical rating scale (NRS) and the Borg scale [99]. The NRS is a simple assessment of breathlessness intensity, most commonly involving asking, "how intense are your breathlessness right now" and rating the response between 0-10. The Borg scale is most used to assess breathlessness in relation to exercise testing or provocations; it is rated non-linearly on a 0-10 scale with descriptors ranging from 0 "not at all" to 10 "maximal" [105].

Exertional breathlessness

One of the most used tools in pulmonary research is the modified Medical Research Council (mMRC) scale. It is a unidimensional measure of exertional breathlessness in daily life. The mMRC was developed in the 1950s to categorise disabilities because of breathlessness in research (table 1) [106-108]. MMRC is discriminative and has been proven to be associated with poorer outcomes. It lacks responsiveness, which has been suggested to be due to only having five categories [109]. In addition, mMRC might not be suitable for all patient groups as it has been demonstrated to have a ceiling effect (defined as >15% of a study population selecting the highest score [110]) when assessing more severely ill patients [48, 100].

The dyspnoea exertion scale (DES) is another tool for assessing exertional breathlessness (table 1). It is a further development of the mMRC scale and is intended to be used in populations with more severe illnesses such as cancer patients, severe COPD, or in a palliative care setting. It has better face validity than mMRC for individuals becoming breathless at a minimal activity or rest. DES was never published in a peer-reviewed journal and was never validated or compared against other relevant measures.

Table 1: Dyspnoea Exertion Scale (DES) and Medical Research Council (mMRC) scale

Dyspnoea Exertion Scale (DES)		Medical Research Council (mMRC) scale	
1	I am able to walk at my own pace on the level without getting out of breath.	0	Not troubled by breathlessness, except with strenuous exercise.
2	I become breathless if I walk around the house or on the hospital ward on the level at my own pace.	1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill.
		2	Breathless or has to stop for breathe when walking at own pace on the level.
		3	Stops for breath after walking about 100 yards (90m) or after a few minutes on the level.
3	I become breathless if I move around in bed or get out of bed.	4	Breathless when dressing or undressing.
4	I become breathless on talking.		
5	I am breathless at rest.		

A pitfall with measures of exertional breathlessness, such as mMRC and DES, is that individuals with breathlessness often adapt their lives because of breathlessness and profoundly lower their physical activity [86]. The actual functional capacity cannot be accurately assessed using these scales alone, as demonstrated by a large overlap in walking distances between mMRC grades [111]. Using different types of exercise stimuli might be a way around this. Possible methods include self-paced tests such as the 6-minute walking test, where individuals walk for 6 minutes straight while the total walking distance is recorded [112, 113]. Other variants include the incremental shuttle walk test and the endurance walk test. Symptom-limited tests include a regular cardiopulmonary exercise test (CPET) and constant-work rate tests (CWR), where the exercise stimulus is standardised. Tests of the latter type, using standardised exercise stimulus, are considered favourable since they are the most specific for assessing breathlessness [99].

Multidimensional assessment

Instruments intended for simultaneous assessment of several of the multiple dimension present with breathlessness include D12 and MDP. The studies included in this thesis only briefly mention these types of measurements. The multidimensional measures include both the physical (sensory intensity and quality) and affective (unpleasantness) sensations and the emotional responses (anxiety, fright, frustration) to breathlessness

[114]. The D12 instrument comprises individual ratings of 12 different descriptors of breathlessness on a 4-item scale. A total score and sub-scores of the different dimensions can be calculated [115]. MDP includes 11 different numeric ratings of the different dimensions, and an overall level of unpleasantness can be used and the different sub-scores [116]. Both scales have been validated and are increasingly used in various populations [114].

Experienced (momentary) and recalled breathlessness

When assessing and measuring breathlessness, it is essential to acknowledge that there might be a difference between the experienced breathlessness assessed using momentary ratings and the recalled version. Recalling events, or as in this case, symptoms, involve cognition and memory, which might introduce bias, altering the recalled values [117]. There is some knowledge on the relationship between recalled and momentary symptom reporting but mainly from areas such as pain or experienced happiness [118-120]. Patients' recall of such events differs from what they rated when they occurred. The recalled version is often just a part of the experience and is frequently rated higher than the momentary rating [121, 122]. Therefore, the recalled symptom might be different from the experienced symptom intensity, which might be important to acknowledge in the clinical and research setting [118, 119, 123-126].

In clinical care, we often ask our patients to recall their symptom levels; "How have your breathlessness been since you started the new medication?". When reflecting on this question, we soon realise that the task of answering this is more complex than it initially may seem [127]. People often use different heuristic techniques in these types of situations. Heuristic techniques are ways of problem-solving and can be described as "mental shortcuts" helping us to make quick decisions. The resulting decision is not always optimal, but it is good enough for everyday situations. Several heuristic techniques, such as the peak-end rule [120] and availability heuristic [128], are relevant to reporting symptoms in clinical care.

The peak-end rule and other influences on recall

Studies on the symptom of pain have shown that the highest experienced intensity during the recall period and the intensity at the end of the period have the most significant impact on the recall. This phenomenon is called the peak-end rule [120, 129]. Painful examinations ending with less pain were perceived as significantly less unpleasant than shorter examinations with more painful endings [129]. That also

recalled *breathlessness* ratings might differ from momentary ratings for the same period or event seems likely, but knowledge is largely lacking [118, 125, 130]. A lower recalled breathlessness rating was demonstrated after adding a less strenuous ending to a breathing exercise using a rebreathing technique, indicating the presence of the peak-end rule, at least in that short laboratory experiment (figure 9) [131].

Impaired cognitive functions, assessed with a mini-mental state examination (MMSE), were found to negatively influence the recall quality of breathlessness by increasing the difference between recalled and experienced breathlessness [122]. The breathlessness intensity at the time of the recall seems to also affect the recalled rating to a large degree, which could be clinically meaningful, as we know that breathlessness is usually lower in rest at clinical visits than in daily life [122, 126].

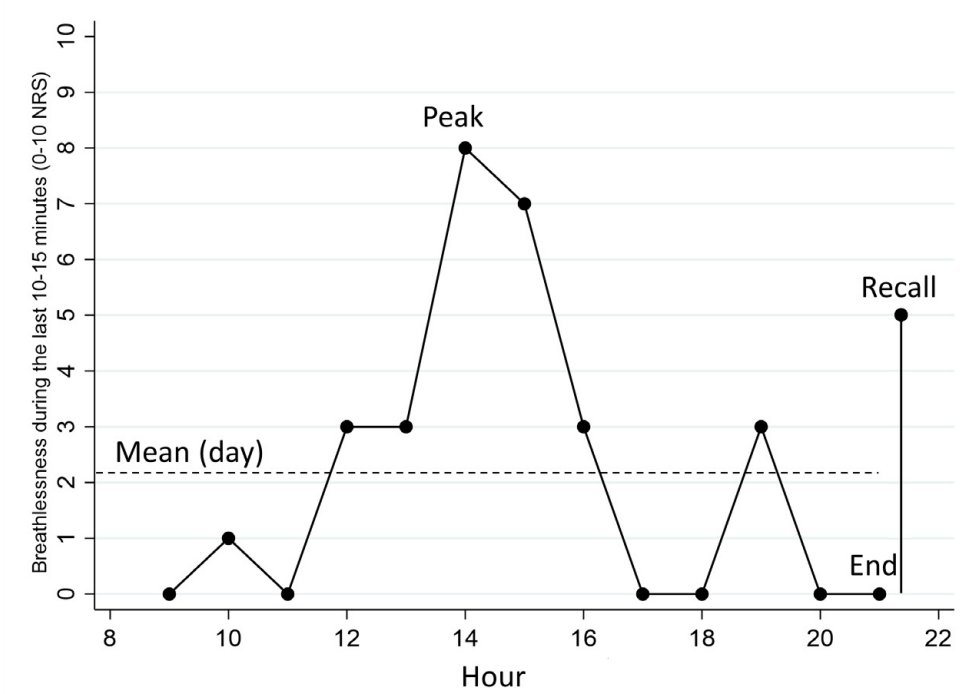

Figure 9: Example of momentary and recalled ratings of breathlessness from one illustrative individual. Showing the peak and the end values. From Study V.

Studies have shown that the more frequent or recent an event is, the higher it may be rated when recalling [127, 128]. This is called the availability heuristic. The same applies if the individual has been recently reminded of the event or if the event was particularly intense or memorable in any other way. Availability heuristics may induce some bias in studies and complicate communication in the clinical setting.

The current mood and social context can also influence the recall of past events. For example, an individual with a current negative mood will more easily recall negative information than positive. Certain moods or social situations might also affect the recall by making the individual weigh specific momentary values as more significant than others when remembering [117, 127]. For instance, there might be different weights in recall of breathlessness attacks in a socially inappropriate environment than at home in solitude. Memories are also affected by prior knowledge and beliefs, and the experienced situation might be reorganised and adjusted to fit the individual's assumptions and views [117, 127]. These types of bias might be tough to detect. How all these areas relate to breathlessness is mainly unknown.

Experienced breathlessness (momentary ratings)

Different factors and biases might affect the perception of momentary breathlessness. Associations between experienced breathlessness and several psychological factors have been suggested. These factors include social rejection [132], increasing the perception of breathlessness, and the presence of other individuals in the same room, lowering reported intensities [75]. Individuals with frequent COPD exacerbations had an enhanced perception of breathlessness compared to a group with few exacerbations [133], suggesting that different perception of breathlessness is involved in the generation of exacerbations. The perception of breathlessness at the moment is likely associated with even more unknown aspects with unknown relevance to clinical care [134].

Management of breathlessness

The clinical assessment and treatment of breathlessness are outside the scope of the current thesis, but an overview will be presented to aid the understanding of the field. Several reviews concerning different populations are available for more in-depth reading [8, 59, 135-137]. There have been reports of under and overdiagnosis of COPD [138, 139] and a lack of recognition of breathlessness from physicians [97]. Several approaches and algorithms for individuals presenting with chronic breathlessness in primary care have been suggested to improve the diagnostic process.

According to one recent suggestion, the most appropriate initial clinical assessments include detailed history taking, physical examination, complete blood count, spirometry, chest X-ray, and electrocardiogram (figure 10) [137].

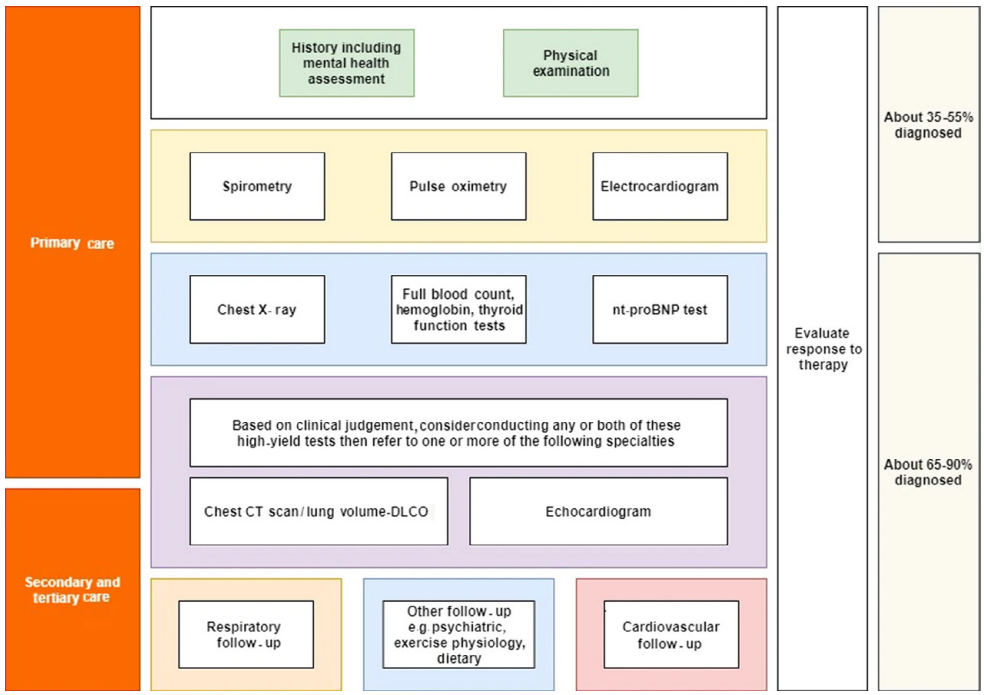

Figure 10: Suggested stepwise approach to individuals presenting with chronic breathlessness in primary care and the proportion where suspected causal diagnosis could be found. From Sunjaya et al. [137]. CC BY 4.0 http://creativecommons.org/licenses/by/4.0/. Published 8 Mars 2022.

The basis of managing breathlessness is to treat the underlying condition adequately and be open to reconsidering the diagnosis, as diagnostic uncertainty is common in this group [138, 140, 141]. Standard treatment options for COPD include inhalation of bronchodilators such as short- and long-acting beta-agonists, muscarinic agonists, and corticosteroids [142]. The basis of asthma treatment relies on inhaled short- and long-acting beta-agonists and ICS [19]. Heart failure treatment commonly includes ACE inhibitors, beta-blockers, MRA inhibitors, and SGLT2 inhibitors [143, 144]. Each other entity underlying breathlessness has its specific therapies, better studied elsewhere. Comorbidities commonly exist, and combinations of treatments are often needed.

The presence of anxiety or depression could enhance the impact and experience of breathlessness [28]. Cognitive behavioural therapy could, in some cases, be indicated

[145]. SSRI, commonly used to treat anxiety and depression, has not been shown to affect breathlessness per se [146]. However, further studies on this topic are needed and ongoing [147]. Benzodiazepines have also been suggested but have not been found to affect breathlessness significantly (figure 8) [148].

The use of opioids to treat breathlessness has been suggested as opioid receptors are present in several areas in the CNS known to be involved with breathlessness perception. Opioids have been used extensively in clinical care [149], but recent randomised controlled trials have shown no significant effects [150-152]. Supplemental oxygen is used routinely for individuals with hypoxia, especially in acute hospital care but it is often also prescribed for home use for individuals with chronic hypoxemia [153]. Oxygen benefits hypoxic users by restoring the mismatch between ventilatory capacity and demand. However, it may not help relieve breathlessness [154]. Air movement around the face seems to be of greater importance for decreasing breathlessness in individuals without hypoxia [155].

Based on the same findings, using a hand-held fan directed towards the face is effective against breathlessness ([156]. Other non-pharmacological interventions shown to have an effect include learning new breathing techniques (breathing retraining) [157] and pulmonary rehabilitation [158]. Structured pulmonary rehabilitation, including exercise and patient education, reduces many of the consequences of breathlessness and is suggested to be part of routine care for chronic breathlessness (figure 8) [158]. Virtual reality has also recently shown some promise for treatment [13].

Aims

Overall aim

This research aimed to study the prevalence, prognosis, underlying conditions, and clinical assessment of chronic breathlessness in the general population, among those with breathlessness and the severely ill.

Specific aims

I. To evaluate the association of breathlessness with chronic obstructive pulmonary disease (COPD) events, cardiac events, and all-cause mortality from middle age throughout life.

II. To evaluate prevalent and overlapping underlying conditions among individuals reporting breathlessness in a general middle-aged population.

III. To compare DES with the mMRC regarding test-retest reliability, concurrent validity, and responsiveness for measuring chronic breathlessness in people with life-limiting illnesses.

IV. To present a protocol for a study exploring the relationship between momentary and recalled breathlessness among individuals with chronic breathlessness.

V. To evaluate the relationship between recalled and momentary ratings of breathlessness and determine the aspect of breathlessness that shows the strongest positive association with recalled breathlessness: the mean, peak, or the most recent rating.

Materials and methods

In this section, different methodological aspects of the studies will be presented. An overview of the studies is shown in table 2. More detailed information can be found in each separate article at the end of this thesis.

Table 2: Overview of the methodological aspects of the included studies.

	Study I **"Men born in 1914"**	**Study II** **"SCAPIS-pilot"**	**Study III** **"Validation of DES"**	**Study V** **"RETRO study"**
Description of population	55-year-old men (at baseline) born in 1914.	Randomly selected middle-aged individuals (55-65)	Individuals with prescribed home oxygen treatment	Adult individuals with self-rated average breathlessness >3 on a 0-10 NRS.
Setting	Malmoe, Sweden	Gothenburg, Sweden	Australia (5 sites)	Karlskrona, Lund and Orebro, Sweden
Study design	Cohort study	Cross-sectional	Secondary analysis from RCT	Observational study with repeated measures design
Year(s) of inclusion	1968-2013	2012	2006-2008	2019-2020

Study I – The cohort "Men born in 1914"

The "Men Born in 1914" cohort started with baseline examinations performed in 1968 in Malmö, Sweden. All men born in even-numbered months in 1914 were invited, and 703 of 809 eligible individuals (87%) participated in the baseline survey. The participants included in 1968, still alive (n=567) and still living in Malmö (n=482),

were asked to be re-examined in 1982-83, 407 agreed (81%). Follow-up lasted until the last of the original 699 participants died in 2013.

Assessments

Baseline measurements in 1968 and follow-up in 1982-83 included mMRC ratings. Spirometry testing, including FEV1 and FVC, was performed on 689 (98.6%) participants in 1968. FEV_1% of predicted was calculated using European reference values [159], and airflow limitation was defined as having an $FEV_1/VC < 0.7$ [160].

BMI was calculated using body weight and height and categorised according to WHO guidelines. Smoking status was classified as "currently smoking", "previously smoking", and "never smoking". Blood pressure was measured at the baseline visit, and hypertension was used on blood pressures >140/90. Bloodwork included lipids, and a cholesterol value above 6,5 was considered dyslipidaemia. The level of physical activity was assessed through self-report.

Outcomes

Primary outcomes were COPD events, cardiac events, and all-cause mortality. "Events" were defined as COPD or cardiac-related hospitalisation, death, or diagnosis. Data on hospitalisation was taken from discharge summaries following hospital care. Death certificates were used to categorise dates and causes of death, and out-patient registries from Swedish hospitals were used for diagnosis. Secondary outcomes were *incident* COPD (no airflow limitation at baseline) and *incident* cardiac events (no previous myocardial infarction at baseline). The role of the trajectory of breathlessness (continuous, remitting, and incident compared to never breathless) was assessed using the breathlessness assessments at both baselines and the follow-up.

Ethics

All participants were informed and gave verbal consent to participate in the study, per research regulations and laws. The Regional Ethical Review Board in Lund, Sweden, approved the study (DNr 1982-111 and 2013-443).

Statistical methods

Pearson's Chi-Square was used to compare categorical variables between groups and one-way ANOVA for continuous variables. For assessing the rates of COPD events, cardiac events, and all-cause mortality, we used the time from baseline assessment to the first of COPD event, cardiac event death, or emigration (n = 4) from Sweden over the entire 44 years of follow-up. Competing-risk regression was used based on Fine and Gray's proportional subdistribution hazards model to analyse the associations between

breathlessness, COPD, and cardiac events [161]. Deaths unrelated to COPD or cardiac disease were defined as competing events. A competing-risk analysis is used when there is a risk of an event occurring that prevents the event of interest from happening. Estimates may be unreliable if competing events are not considered [161, 162]. Competing-risk analyses can be performed using a Cox regression and also with other methods [162]. When using a Cox regression, the translation from the hazard ratio (HR) to cumulative incidence is often interesting. In typical cases, the translation is straightforward as it is a 1:1 relationship between the hazard ratio and the cumulative risk. However, in the presence of competing risks, the relationship is not that simple anymore. The Fine and Gray competing risk regression model was developed to link covariates to cumulative incidence easier than when using cox regression [163]. A downside of this is that the rate (subdistribution hazard ratio [SHR]) calculated with the Fine and Gray model is not as easy to interpret as an HR. [162, 163]. The SHR gives the rate of for example COPD or cardiac events per unit for individuals who are either still alive *or* have already died from another cause [163]. The SHR is the magnitude of the relative change in the rate of COPD or cardiac events associated with the presence of breathlessness. The HR is not comparable to the SHR, and the size of the SHR is of little importance.

The Fine and Gray model relies on two assumptions 1) the time to a COPD or cardiac event is independent between participants, and 2) the difference between breathlessness groups is constant over time [162]. The data has been controlled for these assumptions during the preparations mainly by plotting the Schoenfeld residuals against time [163].

In the study, cox proportional hazards regression was used to analyse the association between breathlessness and all-cause mortality. The results were visualised using cumulative incidence curves and Kaplan-Meyer plots (tested using log-rank test). Adjustments were also performed for possible confounding effects from smoking, diabetes, BMI, level of physical activity, dyslipidaemia, height, hypertension, and FEV1% predicted. Specifically, competing-risk regression with adjustments for confounding effects as described above was used for analysing associations between breathlessness and *incident* COPD events, *incident* cardiac events, and analyses concerning the role of the trajectory of breathlessness. Statistical significance was defined as a two-sided p-value < 0.05. Statistical analyses were conducted using the software package Stata, version 14.2 (StataCorp LP; College Station, TX).

Study II – Prospective observational study (SCAPIS)

The Swedish Cardiopulmonary BioImage Study (SCAPIS) is a prospective observational study of a randomly selected sample from the general population [164, 165]. The current study is a cross-sectional analysis of the pilot part of SCAPIS. Participants were residents in Gothenburg, Sweden, in 2012 and identified from the population registry. They were recruited both from areas with high and with low socioeconomic status. Exclusion criteria for the present analysis were inability to walk for reasons other than breathlessness and missing data on mMRC.

Assessments

Breathlessness was assessed using the mMRC scale. Lung impairment was categorised according to previous studies and ERS/ATS guidelines [166, 167]. Spirometry testing was used to assess the pulmonary pathologies combined with self-report for COPD, asthma, chronic bronchitis (self-reported productive cough for at least three months during the last two years), or other respiratory diseases. ECG or self-report was used for the assessment of cardiac disease. Measurements of weight and height were used to calculate the body mass index (BMI)(weight(kg)/height(m)^2). Aerobic fitness was assessed using a submaximal cycle test (the Ekblom-Bak test) of maximum oxygen uptake (VO_2 max). The values were categorised according to normal values for age and gender [168, 169] and defined as low fitness according to guidelines [168].

Anxiety was defined in the present study as the participant answering "yes, continuously during the last year" to the question 'With stress, we mean feeling tense, agitated, nervous, anxious, or having trouble with sleep because of the situation at work or home. Have you experienced this?'. This method has been used in several previous publications [170].

To identify depression, we used a short form of the DSM-IV CIDI questionnaire [171]. Depression was deemed present if the participant had felt sad, blue, or depressed for two weeks or more in a row in the last 12 months and also reported five of the following: lost interest in things, feeling tired or low on energy, gaining or losing weight, trouble falling asleep, difficulty concentrating, thoughts of death and/or feelings of worthlessness.

We defined anaemia as a hemoglobulin value lower than 110 g/L, representing moderate anaemia [172].

Ethical considerations

The regional ethic committee of Umeå (DNr 2010/228-31) and Gothenburg (DNr 399-16) approved the study. All participants provided written informed consent.

Statistical methods

Multiple logistic regression was used to analyse the associations between breathlessness and the possible underlying contributing conditions. Associations were expressed as odds ratios (OR) with 95% confidence intervals (CI). Analysis was performed separately and merged into groups (respiratory disease, heart disease or chest pain, obesity, and anxiety or depression) per the categories in the study by Johnson et al. [55]. Associations were controlled for confounding effects from age, sex, BMI (for all except obesity), socioeconomic status, and smoking status.

Statistical analyses were conducted using Stata's software, version 14.1 (StataCorp LP; College Station, TX).

Study III – Secondary analysis for validation of DES

We used data from a multi-centre, double-blind, randomised controlled trial. The study's main objective was to compare ambulatory oxygen with medical air for one week in people with chronic breathlessness [21]. We performed a secondary analysis of the data to validate the DES.

Assessments

The baseline was defined as day 1 (two days before randomisation), and assessments continued to day 9, thus including seven treatment days.

The study participant recorded DES, mMRC, and a 0-10 NRS in the evening for each of the nine study days [10]. Research personnel assessed functional status on Days 1, 3, and 9 using the Eastern Cooperative Oncology Group (ECOG) [23, 24].

Ethics

The Southern Adelaide Health Service Human Research Ethics Committee and local research and ethics committees or institutional review boards of all participating sites approved the study. All participants provided written informed consent.

Statistical methods

Baseline patient characteristics were summarised using mean with standard deviation (SD) and median with range or interquartile range (IQR) for continuous variables with normal and skewed distribution, respectively. Categorical variables were expressed as frequencies and percentages. The measurement properties of DES and mMRC were evaluated in concordance with international guidelines for assessing patient-reported outcomes measures [173]. According to the guidelines, validation should include an

assessment of test-retest reliability, concurrent validity, and responsiveness. Reliability is assessed by calculating the correlation between repeated measurements of the same item; the goal is to see if the measurement tool produces similar results if the conditions are the same. Concurrent validity measures how well the ratings from one tool are consistent with those from another, more established tool. Concurrent validity is assessed by measuring the same item simultaneously using different tools and evaluating how well the tools correlate. Responsiveness is a measure of how well the tool detects a change. Assessment of responsiveness is conducted by correlating change measured in other more established tools to the change measured by the tool in question.

Test-retest reliability of DES and mMRC were assessed using ratings on days 1 and 2 (before randomisation). Ratings were cross-tabulated, and test-retest reliability was evaluated using the weighted kappa statistics with linear weights. A kappa value of 0.7 or above is considered good [18, 25]. Concurrent validity (correlations with other relevant measures) was assessed using Kendall's tau B rank correlation coefficient, examining associations between DES and mMRC values and NRS and ECOG scores from day 1. Responsiveness was evaluated by NRS and DES regression slope from Day 1 through 9 for each participant, accounting for correlations. The responsiveness analyses excluded patients with recorded ratings for fewer than half the days (n=11).

Statistical significance was defined as a two-sided p-value < 0.05. Statistical analyses were conducted using Stata's software, version 14.1 (StataCorp LP; College Station, TX).

Study IV – The development of the RETRO study protocol

The focus of the study was the relationship between experienced breathlessness assessed momentarily and the later recalled version. In previous studies, different forms of diaries have been used [122, 174-176]. The momentary assessments have been relatively few, and none included recall. The team consisted of physicians from various specialities, including primary care, palliative medicine, respiratory medicine, clinical memory research, health technology, and psychology. Biostatisticians and programmers from the "Cybercom Group" company also provided support. The team discussed aspects of the study design, including:

- Design and rationale
- Setting and participants
- Recruitment
- Inclusion criteria
- Application-based data collection
- Data storage

- Ethical, methodological, and logistical issues
- Pilot evaluation
- Protocol implementation
- Definitions of breathlessness
- Outcome measures
- Identification of cofactors and other areas of interest
- Statistical analysis plan

Identification of research questions and method

The study aimed to explore the process of recalling breathlessness. Based on previous knowledge from studies and discussions and argumentation within the research group, the primary focus was to examine the impact from the highest, the mean, and the last ratings, but secondary research questions were also developed (table 3).

The study was planned to resemble real life as much as possible and do all assessments in the participant's living environment. An application was developed and made available for the participant's android or iPhone smartphone. The development was carried out in cooperation with the company "Cybercom group" and was repeatedly tested in pilot testing.

Use of mobile ecological momentary assessment (mEMA)

We aimed to collect as much data as possible through the application. We also wanted as many ratings of momentary breathlessness as possible throughout the day. When writing the protocol for the RETRO study, we were unfamiliar with the mEMA terminology. However, through the work with the actual studies and influences from the research community, we realised that our research adheres to these concepts [127, 177, 178]. These studies permit the collection of real-time experiences, behaviours, or moods. Studies using ecological momentary assessment methods have been performed for many decades, but the field has expanded following the growth and availability of personal electronic devices [127, 179]. Most other methods rely heavily on retrospective assessment through questionnaires [179]. Breathlessness is affected momentarily by several aspects, including the current social context, current activity, and mood. Using mEMA, we hope to capture more daily variability than in previous studies.

Table 3: Research question of the RETRO study

1.	**How is the recalled breathlessness intensity for a period (T1) related to**:
1.1.	Experienced breathlessness intensity during T1 measured as:
1.1a	Mean experienced intensity?
1.1b	Peak experienced intensity?
1.1c	Most recent experienced intensity
1.1d	Perceived self-efficacy related to the breathlessness
1.1e	Personality trait of high symptom sensitivity at baseline
1.1f	The experienced trajectory of breathlessness (including constant; variable; increasing; decreasing; quick change)
1.2	Predicted breathlessness intensity for a future period (T2)
2.	**How is the predicted breathlessness intensity for a subsequent period (T2) related to**:
2.1	Experienced breathlessness intensity during T1?
2.2	Recalled breathlessness intensity during T1?
2.3	Experienced breathlessness intensity during T2?
3.	**Which factors are associated with the difference score between:**
3.1	Experienced and recalled breathlessness intensity during T1?
3.2	Predicted and experienced breathlessness intensity during T2?
4.	**How do people think when they recall breathlessness over a defined period (such as 'now', 'last 24 hours' and 'the last week')?** [Qualitative interview study]

Technical aspects

The study begins with participants installing the application on their mobile phones (figure 11) and entering a four-digit code to access and activate the application before starting. Eligibility and baseline data are collected through questionnaires within the application. All questionnaires were in Swedish. The participant sets the daily start and stops times themselves. Sound and homepage notifications alert the participant whenever there is a question to answer in the application. All data is linked to a participant-specific study ID, encrypted, and transferred to a central database whenever there is an internet connection. The data is stored locally on the device in case of no internet connection, and the application will try to resend when the connection is re-

established and stabilised. The database is physically located at the Blekinge Institute of Technology and is used for several other clinical studies per all relevant data security and integrity protocols.

Figure 11: Picture from the application used in the RETRO study. The question is in Swedish and translates to "How intense has your breathlessness been in the last 10-15 minutes? The slider goes from 0-10 anchored to 0 "not at all" and 10 "very".

Clinical sub-study

Apart from the main study, we also planned for a clinical sub-study. The goal was to include as many participants in the sub-study as possible, including a separate written informed consent containing permission for a five-year follow-up of diagnoses, hospitalisation, prescribed medication, and survival. Participants were also invited to participate in an interview and an assessment of cognitive impairment.

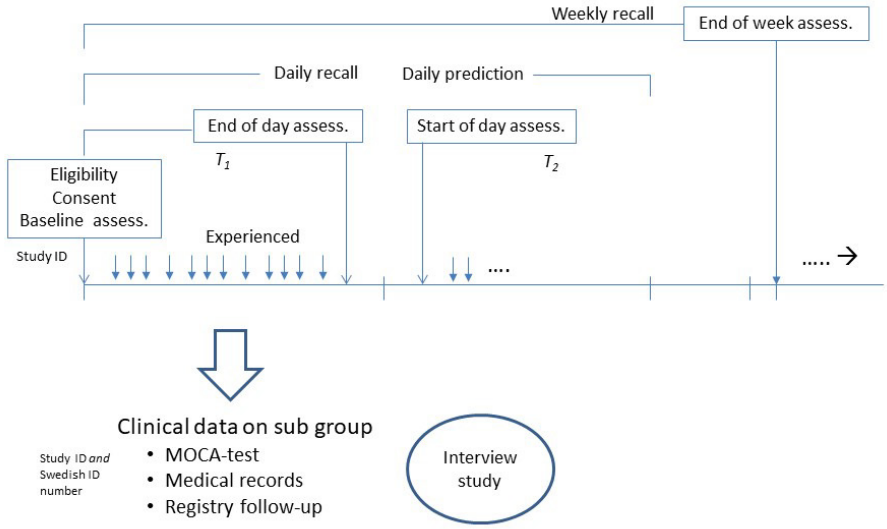

Figure 12: Study outline. The X-axis corresponds to study days. T1 and T2 refer to the period of recall and prediction of breathlessness, respectively. The study is divided into two major parts - one solely application-based, not requiring specific clinical contact, and a clinical and interview sub-study conducted at the participating clinical centres.

Planned assessments

The study aimed to collect momentary NRS ratings of current breathlessness intensity during wake hours and the recalled intensity of breathlessness each night, morning, and end of the week (figure 12). The momentary assessments used the question 'How intense has your breathlessness been in the past 10–15 minutes?', rated 0 (not at all) to 10 (very). No assessments were recorded during the night.

Several other forms and questionnaires were used as part of the baseline assessment, including the public health questionnaire 15 (PHQ 15) used to screen for somatisation by asking about 15 different somatic symptoms [180], the Grimby-Frändin scale to assess the self-reported level of activity [181], and assessment of the multiple dimensions of breathlessness using MDP [116, 182]. Self-efficacy of breathlessness was assessed using the question *"How confident are you that you can manage breathing difficulty or avoid breathing difficulty during the day"* and rated between 0 (not at all) and 10 (very).

Montreal Cognitive Assessment tool (MoCA) was used to assess participants' cognitive function in the clinical sub-study. The MoCA is a sensitive assessment of cognitive

ability used in routine health care. It briefly assesses memory, orientation, attention, and visuospatial-, executive and verbal functions [183].

Power and sample size

We performed a power analysis based on detecting a clinically and statistically significant difference of 1 point on the 0-10 NRS with at least 80% power. Assuming a pooled SD of 1.81 points, we needed to include at least 30 participants in the main study. This is consistent with the sample sizes from previous studies [122]. We finally aimed at including at least 45 participants with sufficient data (at least two days).

Study V – Mobile ecological momentary assessment study

The study is the first of the planned articles from the RETRO study. The study uses only a part of all data collected within the project. The specific methodology within this study will be presented here.

Research question

This study focused on the relationship between momentarily assessed and recalled breathlessness. What aspect of momentarily assessed breathlessness influences the recalled breathlessness the most?

Assessments

This mEMA study used momentary assessments of breathlessness and recall of breathlessness. The momentary assessments were prompted to the participants once each hour using the question, "how intense has your breathlessness been in the last 10-15 minutes". Recalled breathlessness was collected every morning, evening, and at the end of the study (7 days).

Statistical methods.

Associations between momentary ratings and recalled breathlessness throughout the day were analysed using mixed linear regression with random intercepts and slopes, clustering by participants. This model allows the intercept (mean level of experienced breathlessness) and the slope (change in experienced breathlessness) to vary among participants. Clustering accounted for repeat measurements within participants during the analysis period. The associations were reported as beta coefficients with 95% confidence intervals (CI). A beta coefficient is defined as the mean change in the outcome variable (in this case, the recalled value for the day) for each unit increase of the exposure value (the momentary ratings during the day).

Associations over the seven days were analysed using linear regression. The dependent variable was the recalled breathlessness for the entire study period, and mean peak and end (last recorded) values of breathlessness during the week were the independent variables. The variables were analysed separately and pairwise in multivariate analysis models 1–3 and combined in a final model. The variance inflation factor (VIF) was used to check for multi-collinearity. When assessing the variables for multi-collinearity, low VIF values were found, which indicates that a low level of multi-collinearity is present (highest VIF=3.8).

Coefficients with 95% CI and the corresponding adjusted r^2 value (reflecting the percentage of the variance explained by the model) were presented. The unique contribution of each factor to each model was assessed by calculating the Δr^2 for each factor. The Δr^2 for each factor was computed by subtracting the variable's r^2 values from the r^2 value of the entire model. Significance was defined as two-sided $p<0.05$.

Statistical analyses were conducted using the software package Stata, version 17.2 (StataCorp LP; College Station, TX).

Results

In this chapter, results from the separate studies are reported. Overall populational data for all studies are shown in table 4. Two studies included populational data (Studies I+II), and one (Study IV) was a protocol and did not report any data. The final two studies aimed to find populations with exertional breathlessness (Studies III+V). More detailed information is found in each manuscript at the end of this thesis.

Table 4: Overview of populational data from included studies

	Study I "Men born in 1914"	**Study II** "SCAPIS-pilot"	**Study III** "Validation of DES"	**Study IV+V** "RETRO study"
Total population, n	699	1097	188	84
Male, n (%)	699 (100)	691 (50)	124 (66)	34 (40)
Age, mean (SD)	55	57.7 (4.3)	73.4 (10.1)	64.4 (12.8)
BMI, mean (SD)	24.5 (3.1)	27.3 (4.5)	-	28.2 (5.4)
Smoking, n (%)				
Never	107 (15)	478 (43)	-*	25 (30)
Current	435 (62)	195 (18)	-*	5(6)
Former	157 (22)	424 (39)	-*	53 (64)
mMRC, n (%)				
0	593 (85)	989 (90)	0	2 (2)
1	87 (12)	46 (4)	25 (14)	31 (37)
2	16 (2.3)	33 (3)	47 (26)	22 (26)
3	1 (0.14)	16 (1.5)	81 (16)	29 (35)
4	2 (0.29)	13 (1.2)	29 (44)	

*Smoking was not permitted in this study due to home oxygen.

Study I – Prognostic information from breathlessness

This study included 699 men from the general population in 1968. There was a very high prevalence of smoking by today's measure, as 62% were current smokers, and only 15% had never smoked. All men were 55 years of age at inclusion, and the mean BMI was 24.5. The follow-up continued until 695 (99%) of the population had died, and only four individuals were subsequently lost to follow-up due to emigration (table 4).

We found an increased risk of suffering from a COPD event throughout life among those who reported the presence of any exertional breathlessness at baseline (figure 13a). The adjusted SHR for individuals rating 1 on the mMRC was 2.1 (95% CI, 1.2-3.6) and 7.5 (95% CI 2.6-21.7) for those reporting mMRC ≥ 2 (figure 13a). Breathlessness was also associated with suffering from an *incident* COPD event (individuals with airflow limitation at baseline removed) with an adjusted SHR of 2.2 (95% CI 1.0-4.8).

Occurrence of cardiac events was, however, neither associated with breathlessness level at baseline (SHR for mMRC=1; 0.9 (95% CI 0.8-1.7) and SHR for mMRC ≥ 2; 0.6 (95% CI 0.2-1.7) nor with incident cardiac events (individuals with a cardiac event before baseline) (figure 13b).

A higher level of reported exertional breathlessness was associated with higher all-cause mortality. The hazard ratio (HR) for mMRC=1 was 1.4 (95% CI 1.1-1.7) and 3.4 (95% CI 2.1-5.6) for mMRC ≥ 2 (figure 13c).

Finally, when the impact of the trajectory of breathlessness was assessed, we found that continuous breathlessness was associated with COPD events and all-cause mortality. Incident breathlessness was associated with higher all-cause mortality (HR 2.2 (95% CI 1.5-3.2). After adjustments, the association between incident breathlessness and COPD events was not statistically significant (SHR 1.7 (95% CI 0.8-3.3). The individuals with remitting symptoms were very few and had similar risks as the normal population.

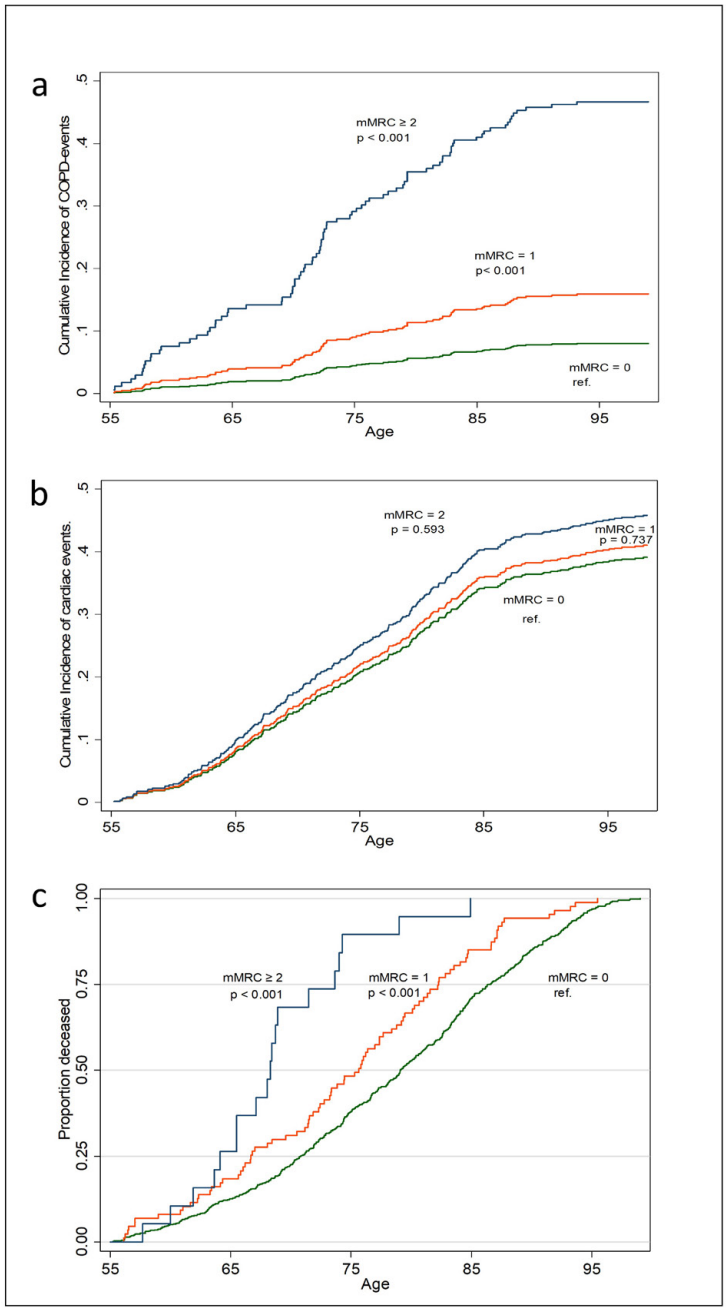

Figure 13: Risk of chronic obstructive pulmonary disease-related events (hospitalisation, our of clinic diagnosis or diagnosis from death certificate) (a), cardiac events (hospitalisation or death certificate) (b), and all-cause mortality (c) per modified Medical Research Council grade from age 55 throughout life. A and b were calculated using competing-risk regression and c using the log-rank test.

Study II – Underlying contributing conditions

In this cross-sectional study from the general population, 1097 individuals were included. Half of them (50%) were females, and the mean age was 57.5 years (SD 4.4). Smoking was quite common as 57% were current or previous smokers. Overweight and obesity were common, and 68% (n=749) had a BMI above or equal to 25. Self-rated exertional breathlessness (mMRC ≥ 1) was present among 9.8% (n=108) individuals (table 4). Breathlessness was more common among women than men and those with lower SES, higher BMI, smoking, and lower aerobic fitness.

Respiratory disease was the most common underlying condition of breathlessness (57%). Anxiety and depression were present among 51% of breathless individuals, and obesity was present among 43%. Among the breathless individuals, 35% had heart disease or chest pain. (table 5)

Table 5: Underlying conditions in the general population with and without exertional breathlessness.

Variable, n (%)	mMRC ≥ 1 n=108	mMRC = 0 n=989	p-value
Chronic airflow limitation (missing = 22)	24 (23)	109 (11)	0.001
Restriction (TLC<LLN) (missing=45)	9 (9.1)	68 (7.1)	0.48
Respiratory disease (missing = 34)	58 (57)	341 (35)	0.001
Asthma (missing =15)	26 (24)	72 (7)	<0.001
COPD (missing = 15)	12 (11.2)	12 (1.2)	<0.001
Chronic bronchitis (missing 41)	21 (20)	60 (6)	<0.001
Heart disease or chest pain (missing = 47)	35 (35)	59 (6)	<0.001
Atrial fibrillation (missing = 17)	2 (2)	7 (0.7)	0.19
Angina pectoris (missing = 22)	30 (30)	38 (4)	<0.001
Coronary heart disease (missing = 21)	4 (4)	15 (1.5)	0.24
Heart failure (missing = 29)	3 (3.8)	5 (0.5)	0.094
Anxiety or depression (missing = 9)	56 (52)	228 (23)	<0.001
Anxiety (missing = 22)	39 (36)	188 (19)	<0.001
Depression (missing = 32)	33 (31)	89 (9)	<0.001
Anemia (missing = 8)	1 (1)	9 (1)	0.96
Obesity	46 (43)	190 (19)	<0.001

The result indicates that overlapping two or several simultaneous underlying conditions were present in 66% of the individuals reporting breathlessness. The most common combination was respiratory disease, anxiety, and/or depression (57%). Respiratory disease and obesity were also prevalent combinations (50%) (figure 13a-c).

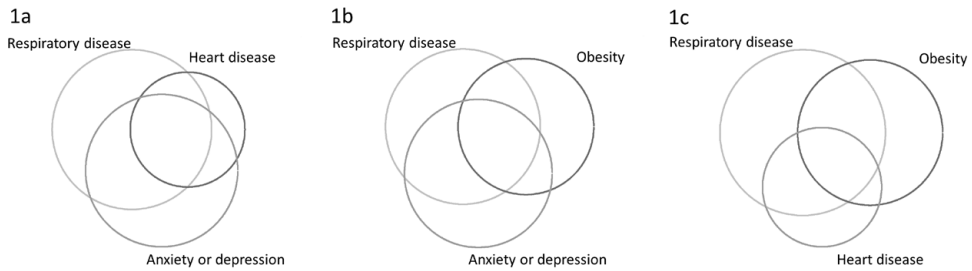

Figure 14: Overlap of underlying conditions among individuals (n=108) reporting exertional breathlessness (mMRC≥1).

Breathlessness was found to be associated with several specific diseases and conditions such as COPD (OR 7.4; 95% CI 3.0-18.5), asthma (OR 3.0 95% CI 1.7-5.2), chronic bronchitis (OR 3.6; 95% CI 2.0-6.6) and having chronic airflow limitation on spirometry (OR 1.8; 95% CI 1.0-3.1). Some factors were independently associated with breathlessness even after adjustment for possible confounding effects. Chronic bronchitis (OR 2.4; 95% CI 1.2-4.8), angina pectoris (OR 7.5; 95% CI 3.9-14.7), obesity (OR 3.6; 95% CI 2.2-6.1) and depression (OR 2.1; 95% CI 1.2-3.9).

We adjusted for aerobic fitness level and found that obesity was still independently associated with breathlessness with an OR of 3.4 (95% CI 1.5-7.6).

Study III – Validation of the dyspnoea exertion scale.

The two previous studies present data from the general population, but in this study, we wanted to explore the measurement properties of mMRC and DES and needed a population where breathlessness was highly prevalent. Subsequently, 188 individuals with known chronic breathlessness (mean mMRC score at baseline = 2.9) were included in these analyses (Table 4). The most common underlying condition was COPD (70%), and nearly 40% had previously been prescribed long-term oxygen therapy. Crosstabulation of mMRC and DES ratings showed that 44% scored the highest category on mMRC, indicating a ceiling effect in this population. Only 6% scored the highest score on DES (figure 14).

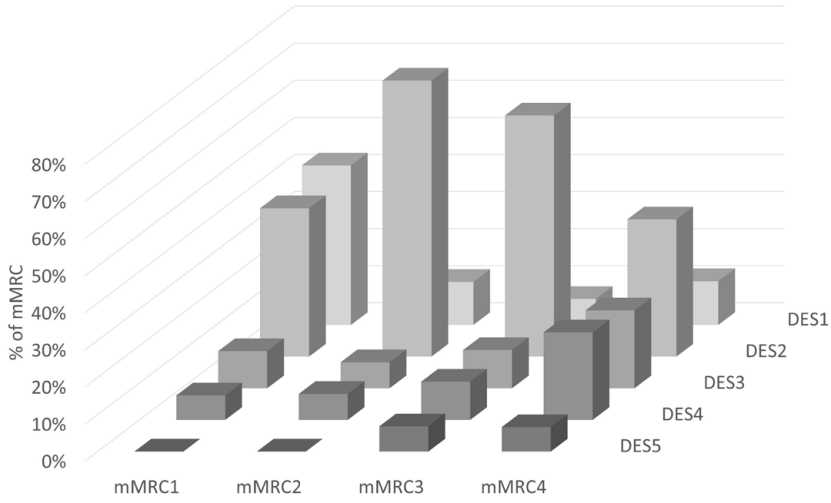

Figure 15: Distribution of modified Medical Research Council (mMRC) scores vs Dyspnoea Exertion Scale (DES) scores.

The analysis of the measurement properties revealed that test-retest agreement was moderate to good for both scales (89% DES; 84% mMRC; p<0.0001), with kappa values of approximately 0.6 for both scales (table 6).

Table 6: Test-retest reliability for DES and mMRC.

	Agreement	**Expected agreement**	**Kappa**	**P-value**
DES	89.12%	72.94%	0.598	<0.0001
mMRC	83.70%	59.01%	0.602	<0.0001

A concurrent validity test showed a stronger correlation between NRS and DES (Kendall's Tau B = 0.32) than between NRS and mMRC (Kendall's Tau B = 0.12). Both scales showed significant but weak associations with ECOG (table 7).

Table 7: Correlation between DES, mMRC, and ECOG scores. For assessment of concurrent validity.

Comparison	Correlation between the scores (Kendall's tau B)
DES vs mMRC	0.32
DES vs NRS	0.32
mMRC vs NRS	0.12
DES vs ECOG	0.23
mMRC vs ECOG	0.30

Finally, both scales showed significant association with change in NRS with r = 0.3 ($p < 0.0001$) for DES and r = 0.16 (p=0.03) for mMRC.

Study IV – The RETRO study

Since Study IV was a protocol study, it did not include any collected data. Results relevant to the protocol construction are discussed here, even though some information is published within Study V.

Out of the data collected from 84 individuals through our mobile phone application, 76 concluded the whole study with complete data. A total of 8121 prompts for momentary breathlessness rating were sent out to the 84 participants, and 6152 were answered within 1 hour (a mean of 7.7 ratings/participant/day). The other 1969 prompts were tagged as missing (compliance rate of 75.8%) (data published within Study V) (figure 15).

Sixty-six per cent of the participants were either moderately or very satisfied with how the application worked, 27% were neutral, and 7% were either somewhat or very dissatisfied. Unfortunately, there was no way to collect more precise motivations within the application.

The RETRO study protocol was prospectively registered with ClinicalTrials.gov (Nr: NCT03468205).

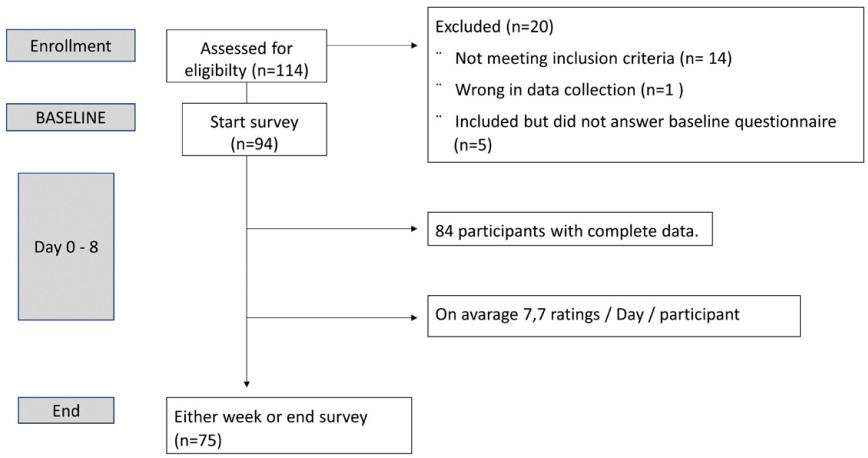

Figure 16: Study design and included participants in the RETRO study

Study V – Comparing momentary and recalled breathlessness.

In this analysis from the RETRO study, all 84 individuals were included, but for the analyses concerning the whole week, only 76 had complete data. The mean age was 64.4 (SD 12.8), and 60% were female. The most common underlying conditions were COPD (40%) and asthma (39%). Only five individuals (6%) were currently smoking, but 64% had previously smoked. Level 1 on the mMRC assessment of exertional breathlessness at baseline was reported by 37%, grade 2 by 26%, and 3 or 4 by 35%. Only 2 % reported no exertional breathlessness (table 4).

The mean value of daytime experienced breathlessness, rated on the 0-10 NRS, was 2.6 (SD 2.2) for the whole study week. The mean daily peak value was 4.8 (SD 1.8), and the weekly peak was 6.8 (SD 1.8). Recalled breathlessness, also using the 0-10 NRS, but recorded each night had a mean value of 3.9 (SD 1.7), and the mean for recall for the whole week was 4.3 (SD 2.2) (figure 16).

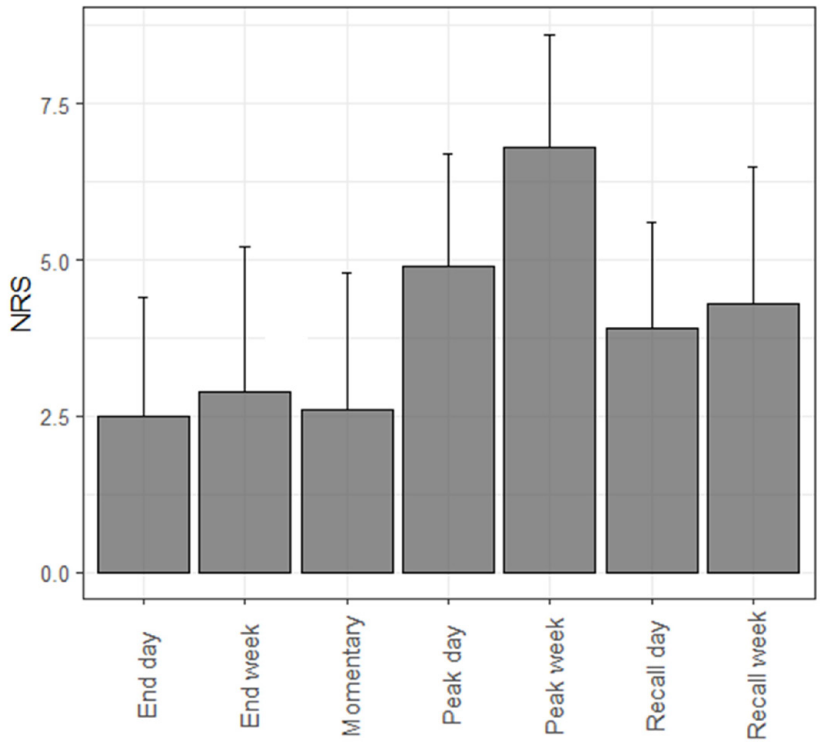

Figure 17: Mean ratings of momentary breathlessness, 0-10 Numerical rating scale (NRS).

Recalled and experienced breathlessness was statistically significantly associated. The recalled value increased by 0.10 (95% CI 0.08-0.11) units for each unit, increasing an individual rating of experienced breathlessness. The peak and the end values were associated with the recalled value (peak 0.26; 95% CI 0.24-0.28; end 0.10; 95% CI 0.08-0.12). The strongest association with daily recalled breathlessness was the mean value of the experienced ratings. Each unit increase of the mean value resulted in a 0.67 (95% CI 0.64-0.71) unit increase in the recalled value.

Analysis of the data concerning the whole week, show associations with recall from peak (beta=0.97, r^2=0.56, p<0.000), end (beta=0.69, r^2=0.50, p<0.000) and mean (beta=0.91, r^2=0.52, p<0.000) values. A combination of all factors in the multivariate analysis showed that the peak value consistently contributed the most to the models. The mean and end values contribution to the model were reduced when added to the same model. The unique contribution (Δr^2) of the mean was close to zero in the final model, while Δr^2 was 0.11 for the peak. (Table 8)

Table 8: Associations between recalled breathlessness at the end of the week and breathlessness experienced during the week.

	Univariable	**Model 1**	**Model 2**	**Model 3**	**Model 4**
R^2 *	-	r^2=0.66	r^2=0.55	r^2=0.64	r^2=0.66
Mean	0.91 (0.71–1.1), r^2=0.52	-	0.54 (0.20–0.89), Δr^2=0.05	0.49 (0.25–0.72), Δr^2=0.08	0.22 (-0.1–0.55), Δr^2=0.00
Peak	0.97 (0.77–1.16), r^2=0.56	0.65 (0.43–0.87), Δr^2= 0.16	-	0.62 (0.38–0.87), Δr^2=0.12	0.59 (0.35–0.83), Δr^2=0.11
End	0.69 (0.53–0.85), r^2=0.50	0.38 (0.22–0.55), Δr^2=0.1	0.34 (0.07–0.61), Δr^2=0.03	-	0.27 (0.04–0.50), Δr^2=0.02

Variables were analysed separately (univariable) and in different combinations (model 1-4). Estimates were examined using linear regression, N = 76. r^2 = percentage of the variance explained by the model as a whole. Δr^2 = contribution from each factor to the model (r2 for the whole model – r2 for the model without the current factor. *NRS = numerical rating scale, Mean = mean value of momentary breathlessness for the week, Peak = highest recorded momentary breathlessness rating, End = last recorded value of breathlessness before the recall.*

Discussion

Main findings

Prognostication

In Study I, we found that being breathless in middle age was associated with poorer health outcomes in the form of increased COPD events and higher all-cause mortality throughout life. The associations were similar even for individuals reporting low-grade exertional breathlessness (mMRC=1) and individuals who did not have airflow limitation at baseline. Incident and continuous breathlessness were associated with poorer health outcomes. Remitting breathlessness was not associated with increased risks in our study. It is essential to clarify that causality cannot be proven with this study design. Still, the associations seen indicate that the presence of even low-grade breathlessness could signal meaningful prognostic information.

The study did not show a relationship with cardiac events, which was somewhat surprising as previous studies have reported an association [184]. The lack of an association might suggest that much of the association seen in previous studies is mediated through smoking. In this population, where the prevalence of smoking is very high, individuals without breathlessness but smoking are at equally high risk of cardiac events. One other possible explanation might be the use of competing-risk analysis. Previous studies have used Cox regression.

When we used Cox regression on our data set, we saw a statistically significant association between cardiac events and breathlessness as in the other studies. Hypothetically, competing events, such as respiratory complications and death, might mediate much of the association between cardiac events and breathlessness, and when accounting for them, the association disappears. Another explanation could be the risk that competing risk regression might produce results where the competing event precludes the occurrence of the primary event [185]. Therefore, it is essential to adjust for confounding effects not only for the main event but also for the competing event. We used death from a non-cardiac cause as the competing event. If this is somehow strongly associated with breathlessness, an association between cardiac events and breathlessness could be hidden. The fact that we performed a separate cause-specific Cox regression and adjusted both

models for the same factors should prevent this. But as this possible bias cannot be tested, the possibility remains and should be accounted for.

The other findings presented in Study I are in accordance with other studies [36, 186, 187] but add the association with COPD events and the data on different trajectories of breathlessness [186].

Underlying conditions and a high level of overlap

Study II showed that the main underlying conditions among individuals with reported exertional breathlessness from the general middle-aged population were respiratory disease, anxiety or depression, obesity, and heart disease or chest pain. Additionally, the study showed a high level of overlap between conditions. Two or more conditions were present simultaneously in 66% of the breathless participants. Still, the study indicated that obesity was associated with exertional breathlessness even after adjusting to aerobic fitness levels. This finding suggests that another aspect of obesity (the high weight?) is vital for breathlessness regardless of fitness level.

Several other studies have reported that respiratory disease is the most common underlying condition among individuals suffering from exertional breathlessness [55, 188, 189]. High prevalence of heart disease, obesity and anxiety or depression has also been previously reported [55, 189-191]. We found a higher level of overlap than previously reported [189], which might partly be explained by the high prevalence of obesity and anxiety or depression in our populational sample.

There was also a strong association between angina pectoris and breathlessness. The strong association may be due to the similarity in the questions for assessing angina pectoris and the mMRC scale. However, breathlessness and chest pain on exertion is the hallmark of angina pectoris, and a strong association would therefore be expected.

Unexpectedly, chronic airflow limitation on spirometry was not independently associated with breathlessness. Several possible explanations could be given for the lack of association. Firstly, there were many participants with chronic airflow limitation on spirometry but without symptoms and self-reported disease, indicating that airflow limitation might not be that important for the subjective experience of breathlessness. Secondly, mMRC might not detect symptoms in people with high inactivity, which is common in individuals with airflow limitations and the study population [53, 192].

As reported in other studies, chronic bronchitis was independently associated with exertional breathlessness. The association could be due to airway inflammation among individuals with chronic bronchitis but no airflow limitation. Chronic airway inflammation might increase the risk of air trapping during exercise resulting in

exertional breathlessness, as previously reported among individuals with otherwise "asymptomatic" COPD [193].

Breaking through the roof

The main finding from Study III was that DES compared to mMRC had similar test-retest reliability and slightly stronger concurrent validity against an NRS assessment of breathlessness right now. We also showed low responsiveness to change on both scales, limiting their potential for use in clinical trials.

It was also evident that categorising individuals in this population using mMRC introduced some problems. Most importantly, there was an apparent ceiling effect, as 44% of participants rated the highest score, making further population differentiation impossible using only mMRC (figure 15). By using DES, this further differentiation could be performed. On the other hand, DES also had some issues. Most seriously concerning category two, which included many participants from mMRC 2-5, indicating that the DES category might be too broad (or the mMRC categories being too narrow).

Feasibility of mobile phones for data collection

Study IV involved the collection of data using a smartphone application. Results from the study (presented in Study V) show that studying breathlessness in this way is feasible. The compliance level in the study was approximately 75%, which is comparable to previous studies, which have reported compliance rates ranging from 66.9 to 89.3% [178]. Considering most previous studies have been conducted in more healthy and younger populations, the 75% compliance rate was acceptable [178]. The application had excellent overall functionality, apart from some minor errors. Participants in the study found the application to work well when evaluating it at the end, even though there was room for improvement.

The influential peak

Study V showed that the peak rating of momentary breathlessness from one week's data collection had the strongest influence on the recalled severity of breathlessness for that week. For one day, the mean value of breathlessness for that day was more closely related to the recall. The results suggest that the answer when asking someone to recall breathlessness for the last week, a task not uncommon in clinical care, is most closely linked with the highest intensity of breathlessness experienced during that week.

Few other studies exist, but one exploring the peak-end rule after an exercise test revealed the impact of the peak value on the recall [194]. There was no impact from the end value, and the mean value was not tested. Another study on the subject, using a daily recall as experienced and recalling for a longer total time, showed a greater impact from the current (end) breathlessness [122]. Thus, it is logical that the longer the period to be recalled, the more expected influence from the current breathlessness level. These findings are also coherent with basic memory functions. It is easier to remember precisely when the period is short and close in time [131].

The analysis did not reveal any impact on the recall from separate hourly changes of breathlessness. For example, change in breathlessness, from stable and low to high intensity, could be hypothesised to matter for overall recall, but we did not find such associations. Perhaps hourly fluctuations in breathlessness do not count for individuals as long as the change doesn't develop into a peak value.

Strengths and limitations

The general strengths and limitations of the studies will be discussed here.

Strengths in Study I include a very long follow-up time and consistent data, with only a few individuals lost to follow-up. Validation studies have been performed on the involved registries [195], and most causes of death are established through autopsy, which is very uncommon in more modern datasets. Study II relies on extensive data from different sources such as spirometry, blood work, questionnaires, and fitness testing and tests new and unique relationships between obesity and actual aerobic fitness level.

Strengths in Study III include using a very standardised and high-quality cohort with extensive measurements over several days. The population is of adequate size and is relevant in terms of symptom burden for use in the validation of DES and mMRC.

The wide range of competencies in developing the RETRO study protocol (Study IV) strengthens the study. Study V employed reliable and customised software for data collection, which through built-in auditory and visual cues, aids the participants in remembering to enter data. This new method for data collection in this field enabled the reliable gathering of a considerable amount of data from included participants, which would not have been feasible with other methods (such as written diaries). Participants were reminded to rate their breathlessness through auditory and visual cues and could not go back and change or impute values. Electronic journals used have increased compliance in previous studies [196].

Limitations related to study population

Some limitations are also present in these papers. The first and most obvious limitation of Study I is that the cohort consists solely of men, which is an unfashionable way of conducting research. Other studies have reported similar outcomes for males and females [36, 197]. We believe that the completeness, reliability of outcomes, and long follow-up time, as mentioned above, justify the research to be performed in this cohort.

The range of different background variables has also changed considerably since 1968; for example, 64% were current smokers at baseline. In 2021 in Sweden, daily smokers were around six per cent in official numbers [198]**.** This fact will, of course, impact the results. However, a comparison with other populations explored reveals that smoking is common in all these breathless populations (64% were former smokers in Study V). Therefore, some of the results from Study I should still be relevant today for the correct type of population.

Study III, on validation of DES, used a cohort initially intended for a randomised controlled trial on ambulatory oxygen for palliation of breathlessness. Even though several strengths are given from the rigorous procedures associated with this study, it might limit the possibilities for generalisation of the results. Even though it is probable that DES is a valid tool in other populations with severe diseases, differences might occur and need further confirmatory studies.

Using a mobile smartphone in Study V could potentially lead to selection bias due to limiting the study to younger and healthier individuals with the cognitive ability to own and use this technology. However, the included population does show a high symptom burden on mMRC, and they have considerable morbidity with several comorbidities. Sensitivity analysis on excluded participants who did give baseline data showed that those did not differ from the included population. The differences in the use of technology between generations have decreased substantially in later years, both globally [199] and in the population under study [200]. Despite this, it might be important to generalise the results with some caution before more studies from other populations have been conducted. It would also be of great interest to study the breathlessness ratings in more depth. One way could have been to use a structured assessment of activity levels, such as a diary with information about activities performed while becoming breathless, or to use a pedometer or activity watch.

Participants were included in Study V based on breathlessness without considering underlying conditions. The result was a slight overweight of pulmonary diseases in the study population. Either a more random or a more selected (for example only COPD) sample selection would have helped with the generalisability of the results. However,

we aimed to investigate the symptom of breathlessness from a broad generalist perspective and not fall into narrow downpipes limited to only one disease.

Finally, Study V did not include enough participants to perform a thorough subgroup analysis, which is unfortunate. Failure to have enough participants was partly due to the COVID-19 pandemic. Exploring and comparing the relationships between momentary and recalled breathlessness within different subgroups such as COPD and heart failure would have been interesting.

Limitations related to self-report

Several studies included in this thesis rely on self-reported data (Study I-II-V). Self-report might introduce "self-reporting bias", often through participants wanting approval or "social desirability", which could lead to underestimating or overestimating essential aspects. This is especially important concerning subjects that could be sensitive and include, for example, level of physical activity, smoking habits, or dietary intake [201]. Another area prone to self-report bias and unreliable answers is asking about what year something started or how long something has been present (such as pack-years of smoking) [202]. People may not remember such information well. One way to overcome self-reporting bias is using scales and validated questionnaires in relevant populations. In the studies included in this thesis, we have tried to use only appropriate and validated tools, but minor bias introduced through self-report is hard to exclude.

Further, individuals within a general population suffering from a disease or condition might have acquired better knowledge and practice in recalling their history. They might thereby be better at stating risk factors and other events of importance to their condition than healthy individuals for whom that information is perceived as irrelevant, in total that might introduce bias to the data and potentially exaggerate observed associations. The level of recall error could also be different between subpopulations (such as individuals with diabetes compared to individuals with heart failure) within the general population, making it genuinely complex [203]. More information on the role of recall bias is needed to correctly adjust for this in the analyses. Study V explored this type of recall bias. Choosing shorter recall periods and using diaries or other memory tools is vital to overcoming recall bias. Shorter recall periods and use of diaries were used when applicable. Study I and Study II involved spirometry and blood work, objective exercise testing, and validated registries that could validate the data within the studies. In conclusion, several measures have been taken to avoid measurement errors and self-report bias, but it is still plausible that it influences data to some extent. More studies are needed on this topic to correctly adjust and address these issues in the future [204].

Significance

The proposed significance of the findings presented in this thesis will be discussed here. When discussing the significance of the results, it is essential to remember that the study designs cannot prove causality but only show an association.

Having prognostic information

Study I explored the prognostic information given from breathlessness at age 55. A relationship between grading one or higher on the mMRC (independent of pulmonary function) and later development or diagnosis of COPD and earlier death is seen. Thus, early identification of breathlessness could be important in the clinical setting. Identifying breathlessness in an individual could guide the health care personnel into earlier interventions such as smoking cessation, increased physical activity, better control of other risk factors, and perhaps earlier identification and management of an underlying disease. Especially in primary care, this could theoretically improve outcomes for these groups.

Awareness of overlapping conditions

Study II showed that respiratory disease is the most common underlying condition in individuals with exertional breathlessness. The findings could be helpful for primary care physicians in clinical settings working in unselected populations such as the one examined. It is also vital when working with these populations to understand that one sole underlying condition seldom seems present among individuals with breathlessness. In the study population, 66% had two or more, suggesting that even though the health care professional might feel satisfied having found one underlying condition, further assessment and suspicion are needed.

Choosing the right tool

The prominent ceiling effect of mMRC shown in Study III should alert clinicians to choose measurement tools with care. In populations with severe diseases or palliative care, breathlessness might be more prominent than could be detected by the mMRC. One alternative might be to use DES instead in these populations. It might be essential to know that the person in front is breathless even at rest (5 on DES) and not only when dressing or undressing (4 on mMRC) to better understand the true impact of

breathlessness. Such knowledge could help identify and address breathlessness and ease severe suffering present among the patients.

In the research setting, depending on the population, it might be essential to differentiate participants as much as possible to describe populations and aim interventions to the correct group of individuals. However, it is necessary to remember that neither DES nor mMRC were sensitive to change in our Study III and should probably not be used to assess the effect of said intervention.

Improved communication

Much effort in clinical care is given to assessing the effect of interventions such as physical training or medications to increase dosages, try a different drug, continue with more examinations, or decide when to have the subsequent follow-up. In this process, recall of breathlessness is often used as the basis. Study V suggests that peak breathlessness impacts recalled breathlessness one week more than the mean value. Thus, it might be an essential consideration in clinical practice where collecting information covering extended periods, especially in out-patient care, is often necessary. It is unknown what clinical meaning this has and whether medications lowering the peak would be interpreted as more effective than a medication lowering the mean.

In future research, it could be beneficial to be aware of and specify the different aspects of these assessments, including tools used, the period intended to be measured, whether or not there is a need to evaluate the current situation or use a recall and such decision could affect results.

Future Aspects

The research area of breathlessness has developed and expanded in recent years. This section discusses the future research needs identified throughout the thesis. The future research needs are presented as bullet points with a research question followed by a shorter explanatory text.

- **What is the relationship between breathlessness, activity, and fitness?**

Study II (SCAPIS) found that obesity was associated with higher breathlessness in the general population independent of measured fitness level. Future studies should establish the relationship and causal mechanisms for breathlessness, obesity, physical activity, and fitness level. There might be different subpopulations with breathlessness, high or low activity, and high or low fitness levels. The influence of fitness levels on

quality of life and function among equally breathless individuals would be interesting to explore further.

- **Which dimension of breathlessness contributes the most to increased healthcare utilisation?**

Whether different qualities or dimensions of breathlessness contribute equally to care-seeking behaviour is largely unknown. Further research is needed.

- **Which underlying condition is the most strongly associated with breathlessness?**

Study II revealed a high prevalence of overlapping and concurrent morbidity among breathless individuals in the general population. This information raises the question of the relative associations to breathlessness from each underlying condition. It might be possible that different underlying conditions are differently associated with breathlessness.

- **Would a combination of mMRC and DES aid the assessment of breathlessness clinically or in research?**

Study III revealed the potential of combining mMRC and DES into one assessment tool, which could be tested in future research using a Rasch analysis and later in real-life situations. Further research on the optimal questioning and standardisation of the measurements is needed.

- **Will COVID-19 affect the prevalence of chronic breathlessness?**

The prevalence of chronic breathlessness might be affected following the COVID-19 pandemic. Long-term consequences are not known. Evaluation and establishment of methods to assess and research this from a breathlessness perspective, including assessment of multiple dimensions, knowledge of recall bias, and long-term prognostic information from breathlessness deriving from COVID-19, are critical issues [205].

- **What is the situation concerning breathlessness in low-income settings?**

Further studies should assess the prevalence and impact of breathlessness in different populations than those already studied. There is currently a lack of sufficient epidemiological information from other global populations, such as low-income settings [206], urban areas compared to rural areas, among immigrants and the elderly [207]. It is largely unknown whether there is any impact on breathlessness from air pollution, different cooking fuels and methods, different disease panorama (presence of tuberculosis, malaria, or HIV?), and other activity levels (sedentary work or manual labour).

Finally, it is projected that the total burden of "health-related suffering" will increase substantially in the following decades due to the increasing prevalence of pulmonary diseases [208]. Palliative services and relief of suffering have been described as the most neglected aspect of global health [209]. The amount of health-related suffering attributable to breathlessness on a global level is largely unknown and needs to be assessed. Development and implementation of affordable interventions based within primary care are urgently needed. The largest gains from research on breathlessness in future research could be anticipated from low-income settings [210].

- **How do we improve breathlessness identification and management in primary care?**

Only a few older epidemiological studies are performed in a primary care population [89, 90, 211], and more are needed. Primary care is well placed for identifying, diagnosing, and managing most early and late breathlessness cases. However, few primary care studies on these subjects have been completed [212].

While some recently developed guidance concerning the clinician's diagnostic procedure [137], more information on pre-test probability, optimal diagnostic route, and further management is needed. Future studies should adhere to strict and standardised methodology concerning recruitment and definition of breathlessness and preferably have an extended follow-up in relevant registries [94].

- **Could routine screening for persistent breathlessness improve outcomes?**

Assessment and identification of chronic breathlessness in primary care (and elsewhere) seem to be lacking [89, 97]. An intervention aimed at identifying chronic breathlessness and what such an early identification would lead to in practice could give valuable insights [34].

- **Which general symptom gives the most prognostic information?**

Symptoms are the basis for health care seeking in primary care [213]. This thesis shows that breathlessness is associated with poorer health outcomes; however, it is unknown how this association compares to other symptoms such as cough, pain, fatigue, headache, and explained versus unexplained breathlessness [214]. Cohort studies with long follow-up times, such as Study I, could be used to explore the research question.

- **How do we identify and handle cases of under and overdiagnosis of COPD in primary care?**

Study II (SCAPIS) showed several individuals without diagnosis and symptoms but with airflow limitations. The study also revealed individuals with self-reported COPD without any chronic airflow limitation on spirometry. The same has been found in

other studies [138, 139] and might be signs of both over-and underdiagnosis in the study population. Further exploration of those groups and their respective covariates and the development of methods to identify them are needed.

- **How is the momentary level of breathlessness related to clinical outcomes? Is the peak or the mean level of rated momentary breathlessness the most important for these outcomes, or is it the recalled version?**

The studies are only beginning to explore the relationship between experienced and recalled breathlessness. Several questions remain, including the role of expectations of breathlessness on the recall, the role of actual activity level on the recall, and further exploration of the impact of impaired cognitive functions. The clinical meaning of the two different assessments is also unclear.

- **Is there any potential in using hourly ratings of breathlessness as an assessment method in clinical care?**

It would be necessary for future studies to compare momentary ratings to using only recall at the consultation or in combination with methods using standardised exercise stimulus (for example, 6MWT)

Conclusions

Study I

This study shows that exertional breathlessness at 55 years of age is associated with an increased risk of COPD events and increased all-cause mortality throughout life.

Study II

The main underlying contributing conditions among individuals reporting exertional breathlessness were respiratory disease (54%), followed by anxiety or depression (51%), obesity (43%), and heart disease or chest pain (32%). Overlap was common, with 66% having two or more concurrent conditions.

Study III

This study shows that compared with mMRC, DES had comparable or better measurement properties in test-retest reliability and concurrent validity. DES could be used as a discriminative tool in this population. Both scales are too insensitive to change to be used as an outcome in clinical trials.

Study IV

This study aimed to design a study to assess the most influential factor in recalling breathlessness for one week. We developed a study using the mobile ecological momentary assessment (mEMA) technique and repeated measures to answer this research question.

Study V

This study shows that the peak of momentary breathlessness ratings more strongly influences the recalled severity of breathlessness over the past seven days than the average or most recent (end) values. Over one day, the mean of momentary breathlessness is the most influential.

Acknowledgements

This will be the most read words of the whole thesis, and rightly so! Many individuals have been involved in big and small ways throughout my (very) many years of education. Thank you all! Of special value for the generation of this thesis are:

Magnus Ekström, my main supervisor. You are a true inspiration, role model and mentor. Somehow you manage to make research feel effortless and fun! I've learned the most valuable things simply by doing what you do, including listening to American rap music and reading 450 pages of Karl Popper simultaneously. Your productivity and astounding knowledge continue to amaze me.

Gunnar Engström, Kjell Torén and Josefin Sundh. My co-supervisors. Thank you for taking me on inspirational journeys through the world of research methodology. Through cohort and observational studies, you helped me explore breathlessness in the past and current generations and gave me valuable advice and an excellent education.

Karen Odberg Pettersson, my first scientific supervisor who introduced me to research. Thank you for taking Gustav and me in and sending us to Nigeria and Uganda. While we mainly wanted adventure, you made us pursue the publication of our studies and made the idea of research stick to my mind.

Ingemar Lilja and Carina Örn, my former and current chief, who have patiently supported me and cleared my clinical schedule when needed, despite a hectic work environment with a lack of resources.

The Research Council of the Region of Blekinge for giving me the time and opportunity to do all of this.

All other researchers in our research group. Thank you, Zainab, for being an inspiration and for proofreading. Thank you, Max and Lucas, for your good cooperation and great football games! Thank you also to Professor David Currow and Professor Miriam Johnson for being very helpful with our studies and including me in your exciting work.

Johanna Söderström. My clinical supervisor during my residency. Thank you for being a mentor clinically and saying the right things with good timing in moments of self-doubt!

Everyone at Jämjö Healthcare central for being skilled professionals and, perhaps more importantly, supportive, kind, and fun friends.

All excellent colleagues on the boards of Blekinge Läkarförening, Distriktsläkarföreningen and Svensk förening för allmänmedicin for giving me a fun and inspirational environment to work within and also some hope for the future.

Friends, colleagues, and family, whom I spent much time with during my educational years mainly in; Ängelholm, Lund, Karlskrona, Stockholm, Göteborg, Lagos, Mbarara, Sao Paolo and especially in Svedala and Estoril. A sincere thank you to all of you for your support and inspiration, but mostly, for all the fun!

Christina and Björn, my parents. Thank you for your love and support. You gave me the possibilities, endurance, curiosity, interest, and motivation to pursue a career in medicine and research. Somehow, I have started to combine biology and pedagogy, each of your special areas, mainly because of your inspiration. And also, thank you to Sara, Artan and Leo for being supportive and positive through all this madness.

Finally, the most important persons behind this thesis. Lina, Alma, Klara and our soon-to-be-born little sister. You fill my life with joy and meaning. Thank you, Lina, for being you and choosing to be with me. You add so much highly needed knowledge, "life skills", and strategic thinking to my life. You challenge me and force me to grow through love and persistence. Now let's get on with our next great adventure!

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Paper I

PLOS ONE

RESEARCH ARTICLE

Breathlessness and incidence of COPD, cardiac events and all-cause mortality: A 44-year follow-up from middle age throughout life

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OPEN ACCESS

Citation: Sandberg J, Engström G, Ekström M (2019) Breathlessness and incidence of COPD, cardiac events and all-cause mortality: A 44-year follow-up from middle age throughout life. PLoS ONE 14(3): e0214083. https://doi.org/10.1371/journal.pone.0214083

Editor: Hajo Zeeb, Leibniz Institute for Prevention Research and Epidemiology BIPS, GERMANY

Received: October 21, 2018

Accepted: March 6, 2019

Published: March 18, 2019

Data Availability Statement: Data cannot be made freely available as they are subject to secrecy in accordance with the Swedish Public Access to Information and Secrecy Act, but can be made available to researchers upon request (subject to a review of secrecy). Requests for data should be made to the corresponding author of this paper or to Medicinska fakulteten, Lunds universitet, Box 117, 221 00 LUND, Swedish Phone: +46-46-222 00 00, email: info@med.lu.se.

Abstract

Background

Breathlessness is prevalent in the general population and may be associated with adverse health outcomes. This study aimed to evaluate the association of breathlessness with Chronic Obstructive Pulmonary Disease (COPD) events, cardiac events and all-cause mortality from middle-age throughout life.

Methods

Breathlessness was measured in 699, 55-year old men residing in Malmö, Sweden using modified Medical Research Council (mMRC). COPD events (hospitalisation, death or diagnosis) cardiac events and all-cause mortality was assessed using The Swedish Causes of Death Register and Hospital Discharge Register. Data was analyzed using Cox- and competing risks (Fine-Gray) regression analysis.

Results

695 (99%) of 699 participants died and four emigrated during follow up. Eighty-seven (12%) had mMRC = 1 and 19 (3%) had mMRC≥2. Breathlessness was associated with COPD events; adjusted Sub-Hazard Ratio 2.1 (95% CI, 1.2–3.6) for mMRC = 1 and 7.5 (2.6–21.7) for mMRC ≥ 2 but not associated with cardiac events when adjusting for competing events and confounding. Breathlessness was associated increased all- cause mortality (Hazard Ratios of 1.4 (1.1–1.7) (mMRC = 1) and 3.4 (2.1–5.6) (mMRC ≥ 2)).

Conclusion

Breathlessness is associated with increased risk of COPD events and increase in all-cause mortality from age 55 until death.

Funding: JS was funded through an unrestricted grant from the Scientific Committee of Blekinge County Council.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Breathlessness is the subjective experience of breathing discomfort.[1] It has a high prevalence across a range of disorders such as chronic obstructive pulmonary disease (COPD) and chronic heart failure and is common among the general public.[2]

The modified Medical Research Council (mMRC) scale is a frequently utilized tool to measure breathlessness in both clinical settings and population studies.[1, 3, 4] It was developed in the 1950's with the main purpose to categorize the functional impact and disability related to breathlessness and is currently recommended by international guidelines for categorizing the severity of COPD.[5]

Breathlessness is associated with mortality both due to cardiovascular diseases and COPD.[6–9] The presence of even mild breathlessness is a predictor of myocardial infarction, heart failure and death, also in people without known heart disease.[7, 8] Among people suffering of COPD, the intensity of breathlessness, measured with mMRC, predicts 5 year mortality better than spirometry values of forced expiratory volume in one second (FEV_1).[10]

The knowledge is limited on the association between breathlessness and future COPD and cardiac events, and on the association with mortality throughout the life span and no previous studies has been conducted using competing events regression(Fine and Gray's). Early detection of people with an increased risk is vital to ensure early treatment measures as well as to give correct information which might enhance willingness to make lifestyle changes or adhere to treatment.

This study aimed to evaluate the association of breathlessness with Chronic Obstructive Pulmonary Disease (COPD) events, cardiac events and all-cause mortality from middle-age throughout life using competing risks regression. Possible differences in associations according to different trajectories of breathlessness will also be explored.

Materials and methods

Study design and population

This study is based upon the "Men Born in 1914" cohort, which started with baseline examinations performed in 1968 in Malmö, Sweden. Invitation to participate went out to all men who were born in even-numbered months in 1914. Out of 809 eligible individuals, 703 (87%) participated in the baseline survey. Four participants were excluded for not answering the mMRC rating at baseline, leaving a total of 699 included participants in the present study. Those still alive and still living in Malmö were asked to be re-examined in 1982–83, and 407 of 482 individuals (81%) agreed. The 297 men who did not participate were either dead (n = 132), had moved away (n = 75) or chose not to participate (n = 90). Follow up lasted until the last participant died in 2013.

Assessments

The mMRC was measured at baseline in 1968 and at follow-up in 1982–83. The mMRC is self-administered with categories 0, "Not troubled by breathlessness, except with strenuous exercise", 1, "Troubled by shortness of breath when hurrying on the level or walking up a slight hill", 2, "Breathless or has to stop for breath when walking at own pace on the level", 3, " Stops for breath after walking about 100 yards (90m) or after a few minutes on the level" and lastly 4 "I am too breathless to leave the house or I am breathless when dressing".[1, 3, 4, 11] Participants were divided into three groups according to the mMRC rating (mMRC = 0, mMRC = 1 and mMRC $\geq$ 2).

Spirometry testing, without prior bronchodilation, was available for 689 (98.6%) participants at baseline. Forced Expiratory Volume in one second (FEV_1) and vital capacity (VC) was measured and used to calculate FEV_1% of predicted using European reference values.[12] Airflow limitation at baseline was defined as having a $FEV_1/VC < 0.7$.[13]

Body mass index (BMI) was calculated using body weight and height and categorized into underweight (≤18.5), normal weight (18.5–25), overweight (25–30) and obese (>30). Smoking status was categorized as "currently smoking", "previously smoking" and "never smoking". Hypertension was defined as a blood pressure above 140/90. Physical activity ranged from "regular hard physical activity", "regular activity", "some physical activity" and "almost inactive". Details of the questionnaires and the assessments have been published elsewhere.[14, 15]

Outcomes

Primary outcomes were COPD events, cardiac events and all-cause mortality. COPD events were defined as the first occurrence of a COPD-related hospitalisation, death or diagnosis. Hospitalisation were established from discharge summaries following hospital care, death from death certificates and diagnosis from out-patient registries from Swedish hospitals. International Classification of Diseases (ICD)-8 (1968–1986; codes 490–492), ICD-9 (1987–1997; codes 490–492 and 496) and ICD-10 (1997–2013; codes J40–J44) were used to establish the COPD event.

Cardiac events were defined as hospitalisation due to myocardial infarction (ICD-9 code 410 and ICD 10 code I21) or death due to ischemic heart disease (ICD 9 codes 410–414; ICD 10 codes I21-I25).

Secondary outcomes were *incident* COPD events using participants without airflow limitation ($FEV_1/VC < 0.7$) at baseline and *incident* cardiac events in people without previous myocardial infarction at baseline.

The trajectory of breathlessness was investigated using data from the follow up examination performed in 1982 and categorised into four groups: Continuous breathlessness (breathlessness present at both baseline and follow-up), remitting breathlessness (breathlessness at baseline but not in 1982) and incident breathlessness (asymptomatic at baseline but breathless in 1982). These groups were compared to the "never breathless" participants (reference category).

The Swedish inpatient registry has been found to be of acceptable validity and good specificity for COPD-disease in epidemiological research and has been active in the south of Sweden for the whole study period.[16].

Statistical analyses

Baseline patient characteristics were expressed as frequencies and percentages and compared between the breathlessness groups using Pearson's Chi-Square for categorical variables and one-way ANOVA for continuous.

COPD events, cardiac events and all-cause mortality were visualised by breathlessness group using Cumulative incidence curves and Kaplan-Meier plots (tested using log rank test). The associations between breathlessness, COPD events and cardiac events were analysed using competing risks regression according to Fine and Gray's proportional subhazards model with non-COPD or non-CE deaths as competing events.[17] Association between breathlessness and all-cause mortality were analysed using Cox proportional hazards regression. The time from baseline assessment to the first of COPD event, cardiac event, death or emigration (n = 4) from Sweden was used to assess the rate of COPD events, cardiac events and all-cause mortality over the total 44 years of follow-up.

All results were adjusted for available potential confounders including smoking, diabetes, BMI, level of physical activity, dyslipidaemia, height, and hypertension. FEV_1%predicted was chosen to adjust for lung function impairment as has been performed in previous similar studies. [6, 9] The COPD events were additionally adjusted for having airflow limitation at baseline ($FEV_1/VC<0.7$) and the cardiac events for having had a previous myocardial infarction (MI) before baseline.

Incident COPD events were analysed among only the participants without airflow limitation ($FEV_1/VC<0.7$) at baseline, and *incident* cardiac events were analysed in only the participants without previous MI at baseline. Because of the lower number of breathless individuals in theses analyses, the breathlessness groups had to be merged to a joint category of mMRC ≥ 1. The same hade to be done when examining the associations between the trajectory of breathlessness (continuous, remitting, incident and never) and COPD events, cardiac events and all-cause mortality using competing risks regression with adjustments for confounding effects as described above.

Statistical significance was defined as two-sided p-value < 0.05. Statistical analyses were conducted using the software package Stata, version 14.2 (StataCorp LP; College Station, TX).

Ethical considerations

All participants were informed and gave verbal consent to participate in the study which were in accordance with research regulations and laws at the period of the study. The study was approved by the Regional Ethical Review Board in Lund, Sweden (DNr 1982–111 and 2013–443).

Results

Patient characteristics

Baseline characteristics of the 699 included men are shown in Table 1. A majority (62%) where current smokers, approximately 40% were hypertensive, 2% diabetic and 43% were overweight or obese. 106 (15%) participants had any grade of breathlessness on the mMRC scale, nine (1%) had had a myocardial infarction, and 144 (21%) participants had airflow limitation ($FEV_1/VC < 0.7$) at baseline. (Table 1)

Thirteen percent (n = 89) experienced a COPD event throughout the follow-up time, mainly through hospitalisation (n = 81), but for a few through diagnosis at out-clinic visits (n = 2), or from death certificates (n = 6, of which 5 were confirmed by autopsy). A cardiac event occurred in 276 participants (39%). (Table 2)

A total of 695 out of 699 participants (99%) died during the follow up, and the remaining four were lost to followup due to emigration. (Table 2)

COPD and cardiac event rates, hazard ratios (HR) and subhazard ratios (SHR) per mMRC grade at age 55 are presented in Table 2. Compared to participants without breathlessness, participants with breathlessness level of mMRC = 1 had an increased risk of COPD event throughout life as shown in Fig 1, the adjusted SHR was 2.1 (95% CI, 1.2–3.6). For the individuals with more breathlessness (mMRC ≥ 2) the risk increased and the adjusted SHR was 7.5 (95% CI, 2.6–21.7).

Breathlessness was not significantly associated with cardiac events when adjusted and calculated with competing risks analyses. Adjusted SHR was 0.9 (95%CI 0.8–1.7) for mMRC = 1 and 0.6(95%CI 0.2–1.7) for mMRC ≥ 2 (Table 2, Fig 2) When using cox-regression (not accounting for competing events) a trend for higher risk, significant for the higher grade of breathlessness was shown with crude HR of 2.7 (95% CI, 1.3–5.6) and adjusted HR of 2.0 (95% CI, 0.9–4.4).

Table 1. Baseline characteristics of 699 participants per modified Medical Research Council (mMRC) breathlessness score at age 55.

Factor	mMRC = 0	mMRC = 1	mMRC≥2	p-value
Subjects (n)	593	87	19	
Body Mass Index (kg/m^2)				<0.001
≤18.5	13 (2.2%)	1 (1.2%)	0 (0.0%)	
18.5–25	327 (55.4%)	43 (50.0%)	7 (36.8%)	
25–30	233 (39.5%)	34 (39.5%)	8 (42.1%)	
>30	17 (2.9%)	8 (9.3%)	4 (21.1%)	
Smoking				0.14
Never	97 (16.4%)	7 (8.0%)	3 (15.8%)	
Former	138 (23.3%)	16 (18.4%)	3 (15.8%)	
Current	358 (60.4%)	64 (73.6%)	13 (68.4%)	
Hypertension	237 (40.0%)	36 (41.4%)	10 (52.6%)	0.53
Diabetes	11 (1.9%)	3 (3.5%)	1 (5.6%)	0.38
Cholesterol (mmol/L), mean (SD)	6.4 (1.1)	6.2 (1.2)	6.2 (0.9)	0.45
Physical activity				0.013
Regular hard	14 (2.4%)	0 (0.0%)	0 (0.0%)	
Regular	82 (14.0%)	7 (8.1%)	0 (0.0%)	
Some	333 (57.0%)	43 (50.0%)	10 (52.6%)	
Inactive	155 (26.5%)	36 (41.9%)	9 (47.4%)	
FEV_1% of predicted, mean % (SD)	90 (40)	90 (20)	80 (20)	0.13
FEV_1/VC mean (SD)	0.77 (0.08)	0.73 (0.1)	0.70 (0.1)	<0.001
Airflow obstruction at baseline (FEV_1/VC <0.7), n (%)	103 (17.7)	31 (36.0)	10 (52.6)	<0.001
Cardiac event before baseline, n (%)	5 (0.8)	3 (3.4)	1 (5.3)	0.039

Data presented as frequency (%) if not otherwise stated. Categorical data compared using Pearson's Chi-square. Continuous data compared using one-way ANOVA. FEV_1 = forced expiratory volume during 1 second; VC = vital capacity; SD = Standard deviation

https://doi.org/10.1371/journal.pone.0214083.t001

Higher mMRC grades were significantly associated with a higher all-cause mortality with a HR of 1.4 (95% CI, 1.1–1.7)) for mMRC = 1 and HR 3.4 (95% CI, 2.1–5.6) for mMRC ≥ 2. (Table 2, Fig 3)

When all 144 individuals with airflow limitation (FEV_1/VC < 0.7) at baseline were removed from analyses, the crude SHR for incident COPD event was 2.4 (95% CI, 1.2–5.0) and 2.2 (95% CI, 1.0–4.8) when adjusted. (Table 3) No association was shown between breathlessness and incident cardiac events (participants with myocardial infarction prior to baseline removed).

Continuous breathlessness (n = 37) was associated with a higher risk of COPD events (SHR 3.2 (95% CI, 1.5–6.7)) and a higher all-cause mortality, HR 2.2 (95%CI,1.5–3.2). Incident breathlessness (n = 80), was associated with COPD events, however not significant after adjustments (SHR 1.7 (0.8–3.3)) and with a higher all-cause mortality, HR 1.5 (95% CI, 1.1–1.9). The participants with remitting symptoms were very few (n = 9) and had similar risks to the not breathless group. (Table 4)

Discussion

Main findings

This study shows that being breathless in the middle age is highly associated with poorer health outcomes throughout life in terms of markedly increased risk of COPD events (hospitalisations, out-patient diagnosis or COPD-related death) and earlier death overall. Interestingly, this study shows that even low-grade breathlessness (mMRC = 1; "when hurrying or walking

Table 2. Association between breathlessness and chronic obstructive pulmonary disease (COPD) events, cardiac events and all-cause mortality.

	mMRC = 0	mMRC = 1	mMRC ≥2
Subjects (n)	593	87	19
COPD events (Fig 1)			
Events, n (n per 1000 person-years)	59 (4.3)	21 (13.1)	9 (42.6)
Crude SHR (95% CI)	1.00	2.7 (1.6–4.4) ¤	7.2 (3.3–16.0) ¤
Adjusted SHR (95% CI) * #	1.00	2.1 (1.2–3.6) §	7.5 (2.6–21.7) ¤
Cardiac events (Fig 2)			
Events, n (n per 1000 person-years)	233 (17.9)	35 (21.2)	8 (31.7)
Crude SHR (95% CI)	1.00	1.1 (0.7–1.5)	1.2 (0.6–2.7)
Adjusted SHR (95% CI) * ^	1.00	0.9 (0.6–1.4)	0.6 (0.2.-1.7)
All-cause mortality (Fig 3)			
Deaths, n (n per 1000 person-years)	589 (42.5)	87 (50.5)	19 (73.1)
Crude HR (95% CI)	1.00	1.5 (1.2–1.9) ¤	3.6 (2.2–5.7) ¤
Adjusted HR (95% CI) /	1.00	1.4 (1.1–1.7) §	3.4 (2.1–5.6) ¤

mMRC = modified Medical Research Council, SHR = Sub Hazard Ratio, HR = Hazard Ratio

/ Adjusted for smoking status (three groups: never, former- and current smokers), FEV1%predicted, body mass index, height and physical activity

* additionally adjusted for hypertension, dyslipidaemia and diabetes

additionally adjusted for airflow limitation at baseline

^additionally adjusted for the presence of cardiac event before baseline

¤ $p<0.001$

§ $p<0.05$

https://doi.org/10.1371/journal.pone.0214083.t002

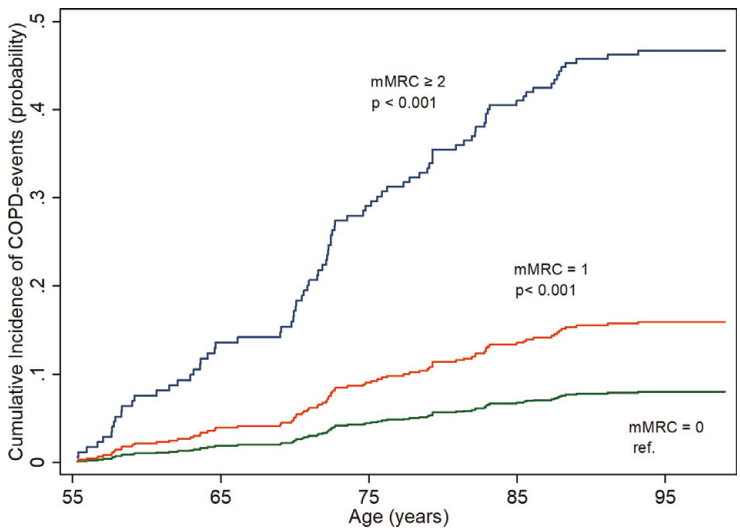

Fig 1. Risk of chronic obstructive pulmonary disease (COPD) events (hospitalisation, out-clinic diagnosis or diagnosis from death-certificate) per modified Medical Research Council (mMRC) grade from age 55 throughout life. Calculated using competing risks regression.

https://doi.org/10.1371/journal.pone.0214083.g001

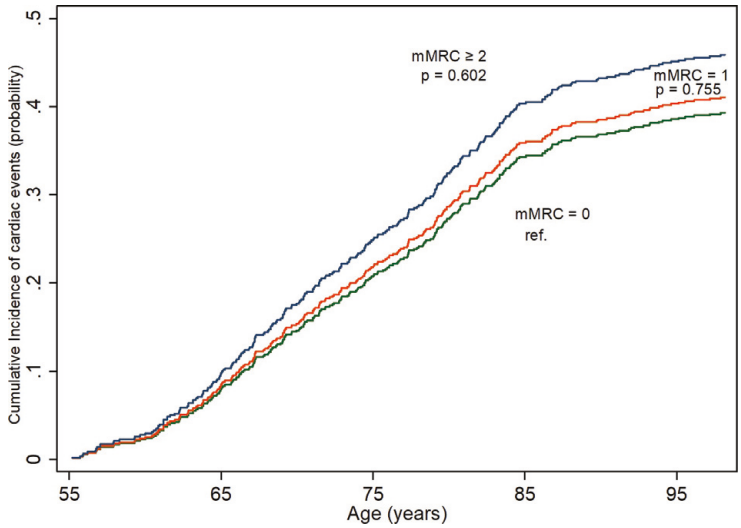

Fig 2. Risk of cardiac events (hospitalisation or death certificates) per modified Medical Research Council (mMRC) grade from age 55 throughout life. Calculated using competing risk regression.

https://doi.org/10.1371/journal.pone.0214083.g002

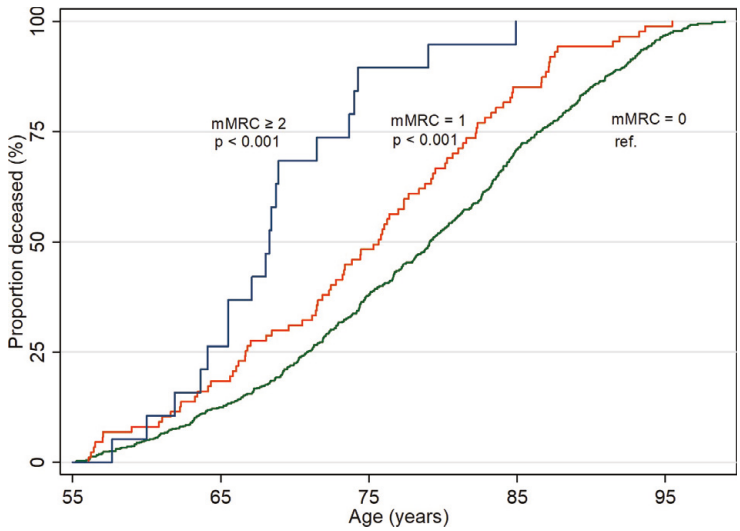

Fig 3. All-cause mortality per modified Medical Research Council (mMRC) grade from age 55 and throughout life. P-values were calculated using log rank tests.

https://doi.org/10.1371/journal.pone.0214083.g003

Table 3. Association between breathlessness and incident chronic obstructive pulmonary disease (COPD) events and incident cardiac events. Analyses were performed in participants with normal lung function or no previous cardiac event at baseline, respectively.

	mMRC = 0	mMRC≥1
Incident COPD events		
Subjects (n)	490	65
Events, n (n per 1000 person-years)	33 (2.8)	10 (8.0)
Crude SHR (95%CI)	1.00	2.4 (1.2–5.0) ¤
Adjusted SHR (95%CI) *	1.00	2.1 (1.0–4.6) §
Incident cardiac events		
Subjects (n)	587	102
Events, n (n per 1000 person-years)	228 (17)	40 (21)
Crude SHR (95%CI)	1.00	1.0 (0.7–1.5)
Adjusted SHR (95%CI) *	1.00	0.9 (0.6-1-3)

mMRC = modified Medical Research Council, SHR = Sub Hazard Ratio

*Adjusted for smoking status (three groups: never, former- and current smokers), FEV1%predicted, diabetes, body mass index, height, hypertension, dyslipidaemia and physical activity

¤ p = 0.014

§ p = 0.056

https://doi.org/10.1371/journal.pone.0214083.t003

up a steep hill") is associated with higher rate of COPD events and overall mortality even after adjustments for potential confounders. When individuals with airflow limitation (FEV_1/VC<0.7) at baseline were removed, a risk increase for incident COPD-diagnosis remained although not significant when fully adjusted. This could be due to lack of power. The finding indicates that low-grade breathlessness has a prognostic value for future incident COPD and death and could be a risk factor for COPD even when lung function is normal. Breathlessness seems to be an independent risk factor for both COPD-events and all-cause mortality as the findings are all adjusted for lung function as well as other risk factors.

Associations between breathlessness and future cardiac events were weak and not significant. A significant trend for higher risks of cardiac events and mortality with increasing breathlessness was found when using Cox regression but when using competing risks analysis, the association disappeared. This was further reinforced when adjusting for confounding effects from smoking status FEV1%predicted, diabetes, body mass index, height, hypertension, dyslipidaemia, physical activity and having had a myocardial infarction already at baseline. These findings are interesting as they contradict previous studies which has shown an association between breathlessness and myocardial infarction.[7] Our findings may indicate that the increased risk shown previously might be mediated in large by respiratory complications and death and when accounting for these by using competing risks regression the risk increase does not remain. It might also be possible that there are missing cases of sudden cardiac death which may not have been categorised as myocardial infarction, however almost all causes of deaths were established from autopsy which should reduce this weakness.

The results in this study strengthens findings from previous studies, [6–8, 18] with larger study populations but shorter follow-up times and mostly focusing on mortality and none specifically on COPD events. We also found that continuous, chronic breathlessness is the most associated with poor health outcomes and that participants with remitting breathlessness returned to the risk of the normal population. This is consistent with the only other report, to our knowledge, on this topic.[6]

Table 4. Incidences and associations between breathlessness (mMRC>1) and chronic obstructive pulmonary disease (COPD) events, cardiac events and all-cause mortality by trajectory of breathlessness using data from baseline and follow-up in 1982–83.

	Never breathlessness	Continuous breathlessness	Incident breathlessness	Remitting breathlessness
Subjects (n)	272	37	80	97
COPD events				
Events n (n per 1000 person-years)	25 (3.2)	14 (18.0)	14 (7.3)	2 (8.2)
Crude SHR (95% CI)	1.00	5.3 (2.7–10.2) ¤	2.1 (1.1–4.1) §	2.8 (0.6–12.4)
Adjusted SHR (95% CI) * #	1.00	3.2 (1.5–6.7) §	1.7 (0.8–3.3)	2.5 (0.5–12.7)
Cardiac events				
Events, n (n per 1000 person-years)	102 (13.9)	17 (20.5)	37 (20.6)	2 (8)
Crude SHR (95%CI)	1.00	1.4 (0.8–2.3)	1.4 (1.0–2.3)	0.5 (0.1–2.3)
Adjusted SHR (95% CI) * ^	1.00	1.2 (0.7–2.1)	1.4 (0.9–2.2)	0.5 (0.1–2.3)
All-cause mortality				
Deaths n (n per 1000-person years)	272 (35.3)	37 (42.9)	80 (39.5)	9 (34.2)
Unadjusted HR (95% CI)	1.00	2.3 (1.6–3.3) ¤	1.4 (1.1–1.9) §	1.08 (0.6–2.1)
Adjusted HR (95% CI) /	1.00	2.2 (1.5–3.1) ¤	1.5 (1.1–1.9) §	1.0 (0.5–2.0)

mMRC = modified Medical Research Council, SHR = Sub Hazard Ratio, HR = Hazard Ratio

/ Adjusted for smoking status (three groups: never, former- and current smokers), FEV1%predicted, body mass index, height and physical activity.

*Additionally adjusted for diabetes, hypertension and dyslipidaemia

additionally adjusted for airflow limitation at baseline

^additionally adjusted for the presence of cardiac event before baseline

¤ $p < 0.001$

§ $p < 0.05$

https://doi.org/10.1371/journal.pone.0214083.t004

Strengths and limitations

This is a prospective longitudinal study with a very long follow up of middle aged individuals followed throughout life, regarding breathlessness and its relationship with COPD events, cardiac events and overall mortality. A strength compared with previous studies is that this study accounted for competing risks which has not been done before. The outcome data is very reliable as the registries have been active with near complete coverage for the whole study period, Validation studies has been performed [16] and most fatal events are based upon autopsy results (5 out of 6 COPD deaths). Limitations of this study include that only males were studied. However, previous studies which included both men and women showed similar associations between genders for the association between breathlessness and all-cause mortality [18, 19] It is also possible that milder COPD events which never required hospital admission have been missed, since almost all the COPD-incidence is based on hospital discharge summaries, and diagnoses from primary care facilities were not available.

The long follow-up gives a lot of strengths to this study but at the same time adds a risk of changes within the baseline characteristics over time which would affect risks. Many of the participants were smokers at baseline but had quit smoking at follow-up which could lead to an underestimation of the associations between breathlessness and mortality as that risk factor were adjusted for but actually had disappeared.

Limitations also include that we were not able to adjust for socioeconomic factors as data did not exist as well as the low number of participants with remitting breathlessness which makes estimates less reliable.

Implications

This study further showcases the need for the clinician to take prompt interest in patients with even a low grade self-reported breathlessness with or without reduced lung function. Patients presenting with chronic breathlessness has a wide variety of underlying diagnoses, but the majority is respiratory.[20, 21] Our study further highlights the need to establish a diagnosis in these patients and ensure intervention such as smoking cessation, increased physical activity, control of other risk factors and medication. Future research should focus on how to better and earlier identify patients with breathlessness as well as how to intervene in the most effective way when these individuals presents in, most commonly, a primary care setting. There is also a need for further research with larger populations on the associations between breathlessness and cardiac events, as our study showed no association when accounting for competing events.

Conclusion

In conclusion, this study shows that presence of breathlessness at 55 years of age is associated with an increased risk of COPD events and increase in all-cause mortality throughout life.

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Paper II

BMJ Open Respiratory Research

Underlying contributing conditions to breathlessness among middle-aged individuals in the general population: a cross-sectional study

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To cite: Sandberg J, Ekström M, Börjesson M, *et al*. Underlying contributing conditions to breathlessness among middle-aged individuals in the general population: a cross-sectional study. *BMJ Open Resp Res* 2020;**7**:e000643. doi:10.1136/bmjresp-2020-000643

Received 19 May 2020
Revised 2 September 2020
Accepted 2 September 2020

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ABSTRACT

Introduction Breathlessness is common in the general population and associated with poorer health. Prevalence, frequencies and overlap of underlying contributing conditions among individuals reporting breathlessness in the general population is unclear. The aim was to evaluate which conditions that were prevalent, overlapping and associated with breathlessness in a middle-aged general population.

Method Cross-sectional analysis of individuals aged 50–65 years in the Swedish CArdioPulmonary bioImage Study pilot. Data from questionnaire, spirometry testing and fitness testing were used to identify underlying contributing conditions among participants reporting breathlessness (a modified Medical Research Scale (mMRC) score ≥1). Multivariate logistic regression was used to identify independent associations with breathlessness.

Results 1097 participants were included; mean age 57.5 years, 50% women and 9.8% (n=108) reported breathlessness (mMRC ≥1). Main underlying contributing conditions were respiratory disease (57%), anxiety or depression (52%), obesity (43%) and heart disease or chest pain (35%). At least one contributing condition was found in 99.6% of all participants reporting breathlessness, while two or more conditions were present in 66%.

Conclusion In a middle-aged general population, the main underlying contributing conditions to breathlessness were respiratory disease, anxiety or depression, obesity and heart disease or chest pain with a high level of overlap.

Key messages

- What is the frequency and overlap of underlying conditions contributing to breathlessness in the general population?
- The most common underlying conditions contributing to breathlessness is respiratory disease, anxiety or depression, obesity and heart disease with a large degree of overlap.
- This study is the first population-based study on contributing causes to breathlessness and presents new information on the relationships between breathlessness and underlying contributing condition.

INTRODUCTION

Breathlessness is defined as the subjective experience of breathing discomfort and affects 10%–25% of middle aged and elderly people in the general population.[1–4] Breathlessness is the main reason for 1%–3.9% of primary care consultations across several European countries and is also present in a high proportion of people seeking care for other reasons.[5 6] Presence of self-reported breathlessness, often measured using the modified Medical Research council (mMRC) scale, indicates a poorer prognosis, lower quality of life, higher rate of hospitalisation and is strongly associated with mortality.[5 7–14]

Several conditions have been shown to cause breathlessness. Pulmonary disease cause breathlessness through several mechanisms such as increased central respiratory neural drive, vagal influences on respiratory sensation and afferent inputs from respiratory muscles.[15 16] Breathlessness is also caused by heart diseases such as heart failure, valvular disease and ischaemic heart disease.[15 17] Obese individuals in the community have increased risk of activity-related breathlessness.[18] It is suggested that the increased breathlessness due to obesity is caused largely by the extra workload and the following extra respiratory demand.[19 20] Low aerobic fitness may contribute to breathlessness[15 21] but has been shown to correlate poorly with reported breathlessness during exercise testing.[22] However, the relationship between aerobic fitness, obesity and breathlessness has not been explored using standardised testing. Psychological conditions such as anxiety or depression are more common in individuals reporting breathlessness and may also contribute to breathlessness through reduced

respiratory sensory gating and increased awareness of breathing problems.[23]

Although the prevalence and severity of breathlessness has been assessed at the population level, knowledge on the frequencies of underlying conditions contributing to breathlessness in the general public is scarce. One previous study, using self-report, examined the underlying contributing conditions and showed that respiratory disease was the most common entity, reported by 62% of participants with breathlessness.[24] Other studies examining the underlying contributing conditions among breathless individuals performed in hospital and pulmonary clinical settings showed that 53% of breathless individuals was given a respiratory diagnosis, and 16% was attributed to heart disease, the remaining 31% had other underlying conditions.[15]

Diagnoses known to cause breathlessness often coexists. Most notably chronic obstructive pulmonary disease (COPD) and heart disease as they share risk factors, but also COPD and anxiety or depression as well as COPD and obesity.[25] The overlap of contributing causes of breathlessness in a general population has not been systematically evaluated.

The primary aim of the present paper was to evaluate which conditions that were prevalent and overlapping as well as the frequency of these conditions among individuals reporting breathlessness in a middle-aged general population. Secondary aims were to explore associations between underlying contributing conditions and breathlessness and to explore the relationship between obesity and breathlessness when adjusting for fitness level.

METHODS

Design and population

This was a cross-sectional analysis of individuals aged 50–65 years in the Swedish Cardiopulmonary bioImage Study (SCAPIS) pilot. This was the pilot part of the larger SCAPIS cohort that was designed as a prospective observational study of a randomly selected sample from the general population. The study design is detailed elsewhere.[26 27] Participants were resident in Gothenburg, Sweden, in 2012 and identified from the population registry. They were recruited both from areas with high and with low socioeconomic status. Exclusion criteria for the present analysis were inability to walk for other reason than breathlessness and missing data on mMRC.

Assessments and definitions

Breathlessness was assessed using the mMRC scale, which is frequently used to measure the physical disability and functional impact of breathlessness in population studies.[7 28–30] The mMRC is a self-administered assessment of exertional breathlessness categorised as: 0 (not troubled by breathlessness except on strenuous exercise), 1 (short of breath when hurrying or walking up a slight hill), 2 (walks slower than contemporaries on the level because of breathlessness or has to stop for breath when walking at own pace), 3 (stops for breath after walking 100 m or after a few minutes on the level) and 4 (too breathless to leave the house or breathless when dressing or undressing). In the present study, breathlessness was defined as an mMRC score of 1 or more.[14 18]

Spirometry testing was used to assess the presence of chronic airflow limitation (defined as postbronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) below the fifth percentile (lower limit of normal (LLN)) or restriction (total lung capacity <LLN). Spirometry including plethysmography was performed using Jaeger Master Screen equipment (Hoechberg, Germany) according to European Respiratory Society/American Thoracic Society (ERS/ATS) standards.[31] For FEV_1 and FVC, the postbronchodilator values 15 min after inhalation of 400 µg of salbutamol was used. All lung function measures were expressed as absolute value and percentage of predicted using European references.[32–35]

The categorisation of lung impairment was performed according to previous studies and ERS/ATS guidelines.[31 36] Self-report was used for COPD, asthma, chronic bronchitis (self-reported productive cough for at least 3 months during each of the two last years) or other respiratory disease. Respiratory disease was defined as presence of any of COPD, asthma, chronic bronchitis, other respiratory disease or chronic airflow limitation or restriction on spirometry testing. Heart disease was assessed by self-report of physician diagnosed myocardial infarction, having had a percutaneous coronary intervention, coronary bypass or valvular surgery, presence of atrial fibrillation/flutter on ECG or self-reported angina pectoris (defined as answering yes to the question 'do you experience chest pain when walking fast or uphill?' or 'do you experience chest pain when walking on the level at normal walking speed?' and answering yes to the question 'Does the chest pain disappear if you stop or slow down?).

Measurement of weight and height were used to calculate the body mass index (BMI) (weight (kg)/height $(m)^2$). Overweight was defined as having a BMI between 25.0–29.9 and obesity as having 30 or higher. Obesity was chosen as a main factor as it was considered a more specific cause of breathlessness than overweight as almost half of this population was overweight.[18]

Aerobic fitness was assessed using a submaximal cycle test (the Ekblom-Bak test) of maximum oxygen uptake (VO_2 max) and assessed according to normal values for age and gender as performed and validated in previous studies.[37 38] Participants with a diagnosed heart condition or taking beta-adrenergic blockers were excluded from the fitness testing and additional subjects did not participate due to various other reasons such as pain, obesity, perceived inability to perform the test or ongoing illness (n=441). A subgroup of 656 individuals remained for assessment with the fitness test. Low fitness was defined as having a VO_2 max of 28 mL/kg/min or less for men aged 50–59 years, 23 mL/kg/min or less for men aged 60 years or higher, 26 mL/kg/min or less for women aged

50–59 years or 22 mL/kg/min or less for women aged 60 years or higher.[37]

Anxiety was defined as the participant answering 'yes, continuously during the last year' to the question 'With stress we mean feeling tense, agitated, nervous, anxious or having trouble with sleep because of the situation at work or at home, have you experienced this?', this method has been used in several previous publications.[39]

Depression was assessed by asking if the participant had felt sad, blue or depressed for 2 weeks or more in a row in the last 12 months, and if yes, also answering yes to five out of seven yes or no questions concerning losing interest in things, feeling tired or low on energy, gaining or losing weight, trouble falling asleep, trouble concentrating, thoughts of death and feelings of worthlessness. The questionnaire questions concerning depression are an adaptation of the short form Composite International Diagnostic Interview for the Diagnostic and Statistical Manual of Mental Disorders version 5 I questionnaire.[40]

Anaemia was categorised as having a haemoglobulin level in blood of lower than 110 g/L, which is the cut-off level for moderate anaemia according to the WHO.[41]

Statistical analyses

Patient characteristics were tabulated by presence of breathlessness (mMRC ≥1) and displayed using frequencies and percentages for categorical data as well as mean and SD for continuous variables.[6 15 17]

Respiratory disease (COPD, asthma, chronic bronchitis, other respiratory disease, chronic airflow limitation or restriction on spirometry), heart disease or chest pain (heart failure, atrial fibrillation, angina pectoris and coronary heart disease), obesity, anxiety and depression were selected as underlying contributing conditions to breathlessness. These were selected based on subject matter knowledge from mechanistic and population studies.[1–3 24 42–47]

The associations between breathlessness and the possibly underlying contributing conditions were analysed using multiple logistic regression, with associations expressed as ORs with 95% CIs. The conditions were analysed both separately and merged into the main underlying condition groups (respiratory disease, heart disease or chest pain, obesity and anxiety or depression) in accordance with the categories in the study by Johnson *et al*.[24] Associations were analysed and controlled separately for possible confounding from age, sex, BMI (for all except obesity) socioeconomic status and smoking status and shown in table 1. Regression analysis was not performed on variables with too few cases (atrial fibrillation, coronary heart disease and anaemia). To look for independent associations between the conditions and breathlessness, we added a second analysis model as shown in table 2. Chronic airflow limitation, chronic bronchitis and angina pectoris were chosen to be included as they were deemed to be the most specific and most objective measures from the larger groups.

Table 1 Associations between underlying conditions and breathlessness

	mMRC ≥1 versus 0	
Factor	**Crude OR (95% CI)**	**Adjusted OR (95% CI)***
Respiratory disease	2.5 (1.6 to 3.7)	2.0 (1.3 to 3.2)
Chronic airflow limitation (FEV_1 <LLN)	2.4 (1.4 to 3.9)	1.8 (1.0 to 3.1)
Asthma	4.0 (2.4 to 6.6)	3.0 (1.7 to 5.2)
COPD	10.1 (4.4 to 23.2)	7.4 (3.0 to 18.5)
Chronic bronchitis	3.8 (2.2 to 6.5)	3.6 (2.0 to 6.6)
Heart disease or chest pain	8.3 (5.1 to 13.5)	6.9 (4.0 to 11.9)
Angina pectoris	10.4 (6.1 to 17.8)	9.3 (5.1 to 17.2)
Heart failure	7.7 (2.0 to 29.0)	6.6 (1.3 to 33.3)
Anxiety or depression	3.5 (2.4 to 5.3)	3.3 (2.1 to 5.1)
Anxiety	2.4 (1.6 to 3.7)	2.2 (1.4 to 3.5)
Depression	4.3 (2.7 to 7.0)	3.3 (2.0 to 5.4)
Other		
Obesity†	3.1 (2.0 to 4.7)	2.7 (1.8 to 4.2)

OR and 95% CIs.
Analysed as separate variables.
*Adjusted for age, sex, body mass index (BMI), socioeconomic status and smoking status, as applicable. Obesity=BMI >30; BMI <30 is the reference value.
†Not adjusted for BMI.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume for 1 s; LLN, lower limit of normal; mMRC, modified Medical Research Council.

Anxiety, depression and obesity were also included, and all the factors were added into the same model together with the background variables, age, sex, socioeconomic status, smoking status and physical fitness and presented in table 2.

No values were imputed, and analyses were by complete cases only. Analysis of concurrent conditions were performed by tabulation and visualised using Venn diagram software.[48] Missing data were visualised in table 3. Statistical significance was defined as two-sided p value <0.05. Statistical analyses were performed with Stata V.14.2.

RESULTS

After excluding participants with inability to walk for other reason than breathlessness (n=14; 1.2%), 1097 participants were included. Baseline characteristics, spirometry values and underlying contributing conditions of the participants are shown in table 3. The mean age was 57.5 (SD 4.4) years and 57% were former or current smokers. Overweight and obesity were highly prevalent in this population and 68% (n=749) had a BMI >25. Low aerobic fitness was present among 77 out of the 656 assessed with fitness testing (12%).

Table 2 Multivariable analysis of independent associations between underlying contributing conditions and breathlessness

Factor	mMRC ≥1 versus 0 Adjusted OR (95% CI)*
Chronic airflow limitation (FEV_1 <LLN)	1.6 (0.8 to 3.1)
Chronic bronchitis	2.4 (1.2 to 4.8)
Angina pectoris	7.5 (3.9 to 14.7)
Anxiety	1.3 (0.7 to 2.3)
Depression	2.1 (1.2 to 3.9)
Obesity	3.7 (2.2 to 6.1)

OR and 95% CIs.
*Adjusted for age, sex, socioeconomic status, smoking status, aerobic fitness and all other factors in table. Obesity=body mass index (BMI) >30; BMI <30 is the reference value.
FEV_1, forced expiratory volume for 1 s; LLN, lower limit of normal; mMRC, modified Medical Research Council.

Breathlessness was present in 9.8% (n=108) of participants and more common among women than men and among participants with low Socioeconomic status (SES), with higher BMI, lower aerobic fitness and among people with higher smoking exposure (table 3).

The main underlying contributing conditions among individuals reporting breathlessness were respiratory disease (57%) followed by anxiety or depression (51%), obesity (43%) and heart disease or chest pain (35%) as shown in table 3. Four participants with breathlessness (0.4%) were not categorised as having any known contributing condition.

Overlap of underlying contributing conditions to breathlessness was common; two or more concurrent conditions were present in 66% of the participants reporting breathlessness (figure 1A–C). Respiratory disease and anxiety or depression was the most common combination (57% of individuals reporting breathlessness) followed by respiratory disease and obesity (50% of individuals reporting breathlessness).

All main conditions were more prevalent in the groups reporting breathlessness compared with the group without breathlessness. Associations between the main underlying contributing conditions and breathlessness are shown both crude and adjusted for age, sex BMI, socioeconomic status and smoking status in table 1. Breathlessness was associated with several respiratory conditions such as COPD (OR 7.4; 95% CI 3.0 to 18.5), asthma (OR 3.0; 95% CI 1.7 to 5.2), chronic bronchitis (OR 3.6; 95% CI 2.0 to 6.6) and having chronic airflow limitation on spirometry (OR 1.8; 95% CI 1.0 to 3.1). It was also associated with heart disease, mainly angina pectoris (OR 9.3; 95% CI 5.1 to 17.2) and with obesity (OR 2.7; 95% CI 1.8 to 4.2), anxiety (OR 2.2; 95% CI 1.4 to 3.5) and depression (OR 3.3; 95% CI 2.0 to 5.4) (table 1).

The final model is shown in table 2. The factors remaining as independently associated with breathlessness after adjusting for background variables (age, sex, socioeconomic status and pack-years) as well as the other factors in table 2 were chronic bronchitis (OR 2.4; 95% CI 1.2 to 4.8), angina pectoris (OR 7.5; 95% CI 3.9 to 14.7), obesity (OR 3.6; 95% CI 2.2 to 6.1) and depression (OR 2.1; 95% CI 1.2 to 3.9). Obesity was independently associated with breathlessness even after additional adjustment for aerobic fitness level (n=656) (OR 3.4; 95% CI 1.5 to 76).

DISCUSSION

Main findings

The main underlying contributing condition among middle-aged individuals reporting breathlessness were respiratory disease (57%) followed by anxiety or depression (51%), obesity (43%) and heart disease or chest pain (35%). Overlap was common with 66% having two or more concurrent contributing conditions. Obesity was associated with reported breathlessness even after adjusting for aerobic fitness level.

What this study adds

The present study adds to the previous knowledge in several ways. First, it describes the frequency of conditions among breathless individuals in the general population. Second, it is performed in a general population and uses both spirometry and fitness testing in addition to self-report. Third, we showed an association between obesity and breathlessness, which remained even after adjusting for aerobic fitness level which, to the author's knowledge, has not been controlled previously in a general population.[18 49] This finding suggests that the high weight itself is an important factor for increased breathlessness even among obese individuals with normal aerobic fitness levels.

Several previous studies have reported similar findings of pulmonary disease as the most common entity contributing to breathlessness followed by heart disease and obesity.[6 15 24] Anxiety, depression and respiratory disease coexisted to a very large degree in our study supporting previous results.[50 51]

We found a high degree of overlap between conditions contributing to breathlessness, more than what was reported in the study by Pratter *et al* which, however, was performed on a population of care seeking individuals. Our findings are in line with the literature on diagnoses coexisting with COPD, where high rates of concurrent COPD and either coronary heart disease (30%), heart failure (63%) or depression (20%–60%) were reported.[15 25] In our study, there was a high prevalence of obesity and of anxiety or depression among participants reporting breathlessness, which is one explanation for the high proportion of individuals with several concurrent conditions.[15]

Table 3 Characteristics of 1097 people from the middle-aged general population by presence of breathlessness

Variable	With breathlessness (mMRC ≥1) n=108	Without breathlessness (mMRC=0) n=989	P value
Age, mean years (SD)	59.1 (4)	57.5 (4)	<0.001
Female, n (%)	71 (66)	477 (48)	0.001
Low socioeconomic status, n (%)	80 (74)	461 (47)	<0.001
BMI, kg/m^2, mean (SD)	30.2 (6)	26.9 (4)	<0.001
Pack years of smoking, mean years (SD)	16.9 (30)	9.3 (13.6)	<0.001
Smoking status, n (%)			0.069
Never	37 (34)	441 (45)	
Current	26 (24)	169 (17)	
Former	45 (42)	379 (38)	
Fitness- Ekblom-Bak (mL/min/kg), mean (SD) (missing=441)	30.7 (7)	35.4 (7)	<0.001
Low aerobic fitness*, n (%) (missing=441)	14 (33)	63 (10)	<0.001
FEV_1, L (SD) (missing=15)	2.6 (0.6)	3.3 (0.75)	<0.001
FEV_1, % of predicted (SD)	84 (23)	102 (23)	<0.001
FVC, L (SD) (missing=15)	3.5 (0.8)	4.2 (1)	<0.001
FVC, % of predicted (SD)	88 (24)	103 (24)	<0.001
FEV_1/FVC (SD) (missing=22)	0.75 (0.1)	0.78 (0.6)	<0.001
FEV_1/FVC, % of predicted (SD) (missing=22)	93 (14)	98 (8)	<0.001
Chronic airflow limitation (FEV1 <LLN), n (%) (missing=22)	24 (23)	109 (11)	0.001
Restriction (TLC <LLN) (missing=45)	9 (9.1)	68 (7.1)	0.48
Respiratory disease, n (%) (missing=34)	58 (57)	341 (35)	0.001
Asthma, n (%) (missing=15)	26 (24)	72 (7)	<0.001
COPD, n (%) (missing=15)	12 (11.2)	12 (1.2)	<0.001
Chronic bronchitis, n (%) (missing=41)	21 (20)	60 (6)	<0.001
Heart disease or chest pain, n (%) (missing=47)	35 (35)	59 (6)	<0.001
Atrial fibrillation/flutter, n (%) (missing=17)	2 (2)	7 (0.7)	0.19
Angina pectoris, n (%) (missing=22)	30 (30)	38 (4)	<0.001
Coronary heart disease, n (%), (missing=21)	4 (4)	15 (1.5)	0.24
Heart failure, n (%) (missing=29)	3 (3.8)	5 (0.5)	0.094
Anxiety or depression, n (%) (missing=9)	56 (52)	228 (23)	<0.001
Anxiety, n (%) (missing=22)	39 (36)	188 (19)	<0.001
Depression, n (%) (missing=32)	33 (31)	89 (9)	<0.001
Anaemia, n (%) (missing=8)	1 (1)	9 (1)	0.96
Obesity, n (%)	46 (43)	190 (19)	<0.001

Obesity=BMI>30.
*Subcohort with measured exercise capacity using the Ekblom-Bak test (n=656), defined as having a score of 28 or less for men aged 50–59 years, 23 or less for men aged 60 years or higher, 26 or less for women aged 50–59 years or a score of 22 or lower for women aged 60 years or higher.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume during 1 s; FVC, functional vital capacity; LLN, lower limit of normal; mMRC, modified Medical Research Council; TLC, total lung capacity.

Angina pectoris was shown to be strongly and independently associated with breathlessness, this might in part be explained by the questioning and symptomatology that is similar to the mMRC questions. Chronic airflow limitation was however not independently associated with breathlessness. This might be explained by the fact that we found many participants with pathology on spirometry but without both self-reported disease and no breathlessness on the mMRC. Problems with the mMRC scale in detecting symptoms in this group has been previously discussed and includes the fact that mMRC measures the functional impact of breathlessness that might not be the same as pathological breathlessness. Also, the mMRC might not register symptoms at all in the case of high inactivity, which is common in many populations worldwide, including the present one.[3 52]

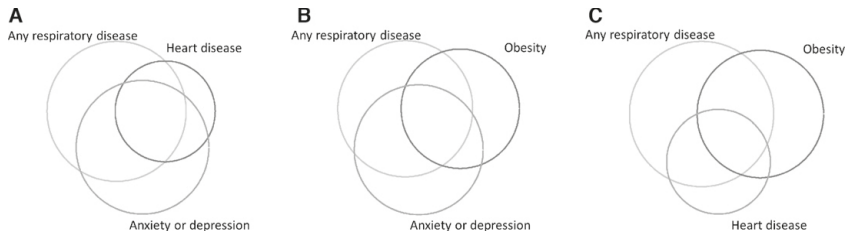

Figure 1 (A) Overlap between respiratory disease, heart disease or chest pain and anxiety or depression among participants reporting breathlessness (score ≥1 on the modified Medical Research Council scale), n=108. Respiratory disease (n=58) is defined as self-reported disease and/or presence of pathology on spirometry, heart disease or chest pain (n=35) is self-reported previous disease, self-reported angina or atrial fibrillation on ECG, anxiety or depression (n=56) is either self-reported symptoms of depression or of anxiety. (B) Overlap between respiratory disease, obesity and anxiety or depression among participants reporting breathlessness (score ≥1 on the modified Medical Research Council scale), n=108. Obesity (n=43) is defined as a body mass index >30. (C) Overlap between respiratory disease, obesity and heart disease or chest pain among participants reporting breathlessness (score ≥1 on the modified Medical Research Council scale), n=108. heart disease or chest pain (n=35) is defined as self-reported previous disease, self-reported angina or atrial fibrillation on ECG.

Chronic bronchitis was found to be independently associated with breathlessness. The same trend has been observed elsewhere.[53 54] One hypothesis for this is that among the individuals with symptoms of chronic bronchitis, there are individuals with normal spirometry but with chronic airway inflammation resulting in both symptoms of chronic bronchitis and increased risk for air trapping resulting in breathlessness during exercise as has been shown to be common among individuals with asymptomatic COPD.[55]

Strengths and limitations

Strengths of the present study include that the measurements used, such as mMRC, spirometry testing and aerobic fitness testing, have a high validity and are relevant and detailed.[9 14] The relationship between obesity and breathlessness was explored using additional data on aerobic fitness level, which has not been performed previously.

Potential limitations of the study include the relatively few cases of breathlessness in the population that were handled by analysing larger categories of possible underlying conditions to breathlessness. It would have been interesting to be able to also analyse the data using an ordinal regression analysis to explore the impact on breathlessness severity from the different conditions. Since the number of individuals on each individual mMRC level was low, the results were considered to be too imprecise. We hope that the present study can be of use as a foundation for more detailed analysis in future larger datasets. No data were available on intensity, multiple dimensions of breathlessness or symptom duration that would have strengthened the findings and given interesting information. Data on aerobic fitness were only available for a subcohort, which was unfortunate and a limitation to the study. There was also a known selection bias due to individuals with reports of obvious heart disease or taking beta-adrenergic blockers being excluded from aerobic fitness testing. However, it is probable that the excluded group would have a low fitness level due to their known illness. Another limitation was some uncertainty of the reliability of diagnoses that are part of the primary endpoints, mainly due to the use of self-report for main diagnoses.

Implications

This study reports the main underlying contributing conditions among individuals with breathlessness as well as the most common concurrent conditions in a sample of the middle-aged general population. The clinical evaluation of breathlessness in a population of unselected patients presenting with breathlessness, such as in primary care should focus on respiratory disease, anxiety or depression, obesity and heart disease. Future research is needed on this area using larger datasets and more detailed data to further explore the role of chronic bronchitis, angina pectoris, ischaemic heart disease, obesity and aerobic fitness to breathlessness.

Conclusion

The main underlying contributing conditions among individuals reporting breathlessness were respiratory disease (54%) followed by anxiety or depression (51%), obesity (43%) and heart disease or chest pain (32%). Overlap was common with 66% having two or more concurrent conditions. Independent associations with breathlessness were found for chronic bronchitis, asthma, angina pectoris, depression and obesity.

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Funding Wallenberg Foundation, the Swedish Research Council (VR), VINNOVA and the Swedish Council for Working Life, Health, and Welfare (FORTE). In addition, there was support from the Sahlgrenska University Hospital, strategic grants from ALF/LUA (Avtal om Läkarutbildning och Forskning) in Western Sweden and from the Sahlgrenska Academy at University of Gothenburg. JS was funded by an unrestricted grant from the Blekinge Council of Science. ME was supported by unrestricted grants from the Swedish Respiratory Society, the Swedish Heart-Lung Foundation and the Swedish Research Council (DNr: 2019-02081). AR is supported by AFA Insurance.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by the regional ethic committee of Umeå (DNr 2010/228-31) and Gothenburg (DNr 399-16). Written informed consent was provided by all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data cannot be made freely available as they are subject to secrecy in accordance with the Swedish Public Access to Information and Secrecy Act but can be made available to researchers upon request (subject to a review of secrecy). Requests for data should be made to the corresponding author of this paper. A prerequisite for access to data is a permission from a Swedish Ethical Committee. More information can be found at http://scapis.org/.

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Paper III

Brief Methodological Report

Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness

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Abstract

Background. Although chronic breathlessness is common in life-limiting illnesses, validated feasible instruments to measure *functional impact* of the symptom in this population are scarce. We aimed to validate the Dyspnea Exertion Scale (DES) compared with the modified Medical Research Council (mMRC) breathlessness scale for test-retest reliability, concurrent validity, and responsiveness in people with life-limiting illness.

Methods. A total of 188 participants, 66% males, with chronic breathlessness, mostly (70%) because of chronic pulmonary disease (chronic obstructive pulmonary disease) self-reported evening scores of mMRC, DES, Numerical Rating Scale (NRS), and Eastern Cooperative Oncology Group during nine days.

Results. About 44% ($n = 81$) scored the highest score on mMRC indicating a ceiling effect not seen with DES. Both scales had moderate-to-good test-retest agreement (89% DES; 84% mMRC; $P < 0.001$ for both). Analyses for concurrent validity showed that higher DES and mMRC scores were correlated with higher NRS breathlessness intensity scores and Eastern Cooperative Oncology Group scores throughout the nine days. In longitudinal analyses, DES ($r = 0.30$; $P < 0.001$) was more responsive to change in NRS score during nine days than the mMRC ($r = 0.16$; $P = 0.03$).

Conclusion. Compared with mMRC, DES had comparable or better measurement properties in terms of test-retest reliability and concurrent validity and could be used as a discriminative tool in this population, but both scales are too insensitive to change to be used as an outcome in clinical trials. J Pain Symptom Manage 2018;56:430–435.

Key Words

Breathlessness, measurement, Medical Research Council breathlessness scale, Dyspnea Exertion Scale (DES), mMRC, DES, validation

Introduction

Chronic breathlessness is common and causes major suffering in patients with life-limiting illness.[1] It is associated with increased morbidity and mortality, including worse quality of life and increased dependency on health services.[2,3] Nearly all people with life-limiting cardiac or respiratory disease will experience chronic breathlessness late in their disease trajectory, becoming persistent and triggered by minimal exertion, or present even at rest.[1,3–5]

There are few validated unidimensional instruments that measure the *functional impact* in people with chronic breathlessness useful for categorizing patients and for prognosis purposes.[1,6] Although measures of exercise-induced breathlessness may be applicable in the early more stable phases of pulmonary disease, arguably these are less relevant in later stages when breathlessness is triggered by minimal movement or even at rest without an obvious precipitant.[6] Existing measures are mostly disease specific (cancer, chronic obstructive pulmonary disease [COPD], or motor

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Accepted for publication: May 2, 2018.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2018.05.002

neuron disease) and designed for use in a research, rather than clinical, setting.[7] Routine clinical assessment of chronic breathlessness is important to identify and manage this often-neglected symptom.[7,8]

The modified Medical Research Council (mMRC) breathlessness scale is a widely used measure of the presence and severity of breathlessness in relation to physical activities (Table 1).[2,9–12] It was developed in the 1950s with the main purpose to categorize disability because of breathlessness in research. It is still the most used instrument across both clinical and research settings. The mMRC scale is discriminative but not responsive to change enough to be useful as outcome in clinical trials. It is recommended by international guidelines for categorizing the severity of COPD.[13] It strongly predicts increased hospitalization, reduced quality of life and mortality. mMRC is a better predictor of death than the degree of airflow limitation.[14,15]

However, the mMRC scale is only weakly associated with physiological and functional measures of impairment and is poorly responsive to change over time and in relation to therapy, perhaps because it only has five categories.[16,17] In patients with severe illness, there might be a risk of a ceiling effect (defined as >15% of respondents selecting the highest score category[18]) as many patients, despite varying levels of symptom and disability, are likely to be in the worst category.[19]

The Dyspnea Exertion Scale (DES; Table 1) was developed from the mMRC scale for use in people with advanced cancer. DES may offer better face validity than mMRC for people with severe COPD who have breathlessness at rest or with minimal exertion.[19] DES was presented within an MD thesis and has never been published as a peer-reviewed article or compared formally against the mMRC. The relative merits of mMRC and DES for measuring exertion-related chronic breathlessness because of life-limiting illness are unknown.[6,19]

The aim of this study was to compare DES with mMRC in terms of test-retest reliability, concurrent validity, and responsiveness for measuring chronic breathlessness in people with life-limiting illnesses.

Methods

Study Design and Population

This was a secondary analysis of a multicenter, double-blind, randomized controlled trial of ambulatory oxygen compared with medical air for one week in people with chronic breathlessness.[20]

Participants ($n = 239$) were recruited between April 2006 and March 2008 from outpatient pulmonary, palliative care, and primary care clinics in Australia (five sites), U.S. (two sites), and U.K. (two sites). Only data from the Australian participants were available for this analysis ($n = 188$).

Eligible participants were aged 18 years and older; with a life-limiting illness who did not qualify for long-term oxygen therapy; partial pressure of oxygen in arterial blood >7.3 kPa breathing ambient air; mMRC ≥3 at screening despite optimal disease management; life-expectancy longer than one month; and stable medication for at least the previous week. Exclusion criteria included current smoking; a respiratory or cardiac event in the previous seven days; anemia (hemoglobin <100 g/L); partial pressure of carbon dioxide in arterial blood <8 and > 6.7 kPa; or cognitive impairment (Mini-Mental State examination score <24 points).[21]

Assessments

Baseline was defined as Day 1 (two days before randomization) and assessments continued to Day 9, thus including seven treatment days.

DES (using the question "What is your breathlessness like right now?"), mMRC ("What is your best exertional performance today?"), and a 11-point Numerical Rating Scale (NRS) ("How is your breathlessness right now?") between 0 (not breathless at all) and 10 (breathlessness as bad as you can imagine)

Table 1
DES and mMRC Breathlessness Scale

DES	mMRC Scale
1 = I am able to walk at my own pace on the level without getting out of breath	0 = Not troubled by breathlessness, except with strenuous exercise.
2 = I become breathless if I walk around the house or on the hospital ward on the level at my own pace	1 = Troubled by shortness of breath when hurrying on the level or walking up a slight hill
	2 = Breathless or has to stop for breath when walking at own pace on the level
	3 = Stops for breath after walking about 100 yards (90 m) or after a few minutes on the level
3 = I become breathless if I move around in bed or get out of bed	4 = Breathless when dressing or undressing
4 = I become breathless on talking	
5 = I am breathless at rest	

DES = Dyspnea Exertion Scale; mMRC = modified Medical Research Council.

were recorded by the study participant in the evening for each of the nine days.[10]

Functional status was assessed by research personnel on Days 1, 3, and 9 using Eastern Cooperative Oncology Group (ECOG).[22,23] ECOG was categorized as asymptomatic (0), symptomatic but ambulatory (1), symptomatic, <50% in bed during the day (2), symptomatic, >50% in bed but not bedbound (3), and bedbound (4).[22]

Statistical Analyses

Baseline patient characteristics were summarized using mean with SD and median with range or interquartile range for continuous variables with normal and skewed distribution, respectively. Categorical variables were expressed as frequencies and percentages.

The measurement properties of DES and mMRC were evaluated in concordance with international guidelines for the evaluation of patient-reported outcome measures.[24] Test-retest reliability of DES and mMRC was assessed using ratings on Days 1 and 2 (before randomization). Ratings were cross-tabulated, and test-retest reliability was assessed using the weighted kappa statistics with linear weights. A kappa value of 0.7 or above is considered good.[18,24] Concurrent validity (correlations with other relevant measures) was assessed using Kendall's Tau B rank correlation coefficient, looking at associations between DES and mMRC values and NRS and ECOG scores, all from Day 1. Responsiveness was assessed by the regression slope of NRS and DES over time from Day 1 to 9 for each individual participant, accounting for correlations. Patients with recorded ratings for fewer than half the days were excluded ($n = 11$) from the responsiveness analyses. Statistical significance was defined as a two-sided P-value <0.05. Statistical analyses were conducted using the software packages, Stata, version 14.1 (StataCorp LP, College Station, TX).

Results

Patient Characteristics

Table 2 shows baseline characteristics of the 188 included participants; 66% were males, and the most common cause of breathlessness was COPD (70%). Nearly 40% of the participants had previously been prescribed long-term oxygen therapy. The mean DES and mMRC scores at baseline were 2.3 and 2.9, respectively (Table 2).

Score Distribution and Reliability

The distribution of mMRC on DES scores and their inter-relation is shown in Fig. 1. Of all respondents, 44% scored the highest category (4) on mMRC, indicating a ceiling effect in this setting, whereas only 6% scored the highest category (5) on DES. Most of the responses categorized as mMRC 2–4 scored DES at Category 2. Nine individuals (6.6%) scored the highest category on mMRC and the lowest (1) on DES at the same time (Fig. 1).

The relationship between both scales and the NRS rating is shown in Figs. 2a and 2b. Test-retest agreement was moderate to good for both scales (89% DES; 84% mMRC; $P < 0.0001$) with kappa values of approximately 0.6 for both scales (Table 3; Fig. S1a and b; Fig. S2a-c).

Table 2
Baseline Characteristics

Variable	All ($n = 188$)
Age, mean (SD)	73.4 (10.1)
Gender (%)	
Male	124 (66)
Missing	1 (0.5)
Causes of breathlessness (%)	
COPD	131 (70)
Primary lung cancer	24 (13)
Other causes	36 (19)
PaO_2, kPa, mean (SD)	10.1 (1.6)
$PaCO_2$, kPa, mean (SD)	5.2 (0.5)
Oxygen treatment (%)	38.8 (4.4)
DES ($n = 177$), %	
1	33 (19)
2	86 (49)
3	27 (15)
4	25 (14)
5	6 (3)
Missing	9
mMRC ($n = 182$), %	
1	25 (14)
2	47 (26)
3	29 (16)
4	81 (44)
Missing	6
ECOG ($n = 181$), %	
1	52 (28)
2	80 (42)
3	49 (26)
Missing	7

COPD = chronic obstructive pulmonary disease; PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; DES = Dyspnea Exertion Scale; mMRC = modified Medical Research Council; ECOG = Eastern Cooperative Oncology Group.

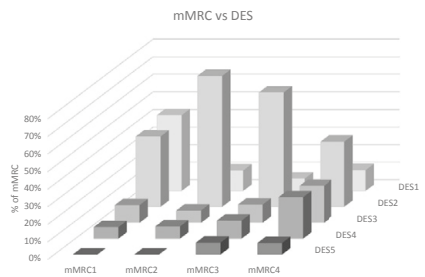

Fig. 1. Distribution of modified Medical Research Council (mMRC) scores vs. Dyspnea Exertion Scale (DES) scores.

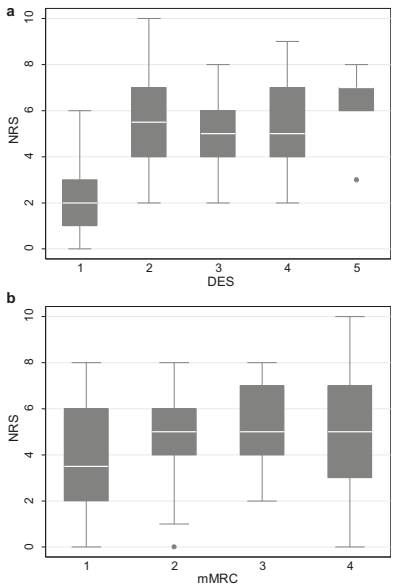

Fig. 2. (a) Distribution of Dyspnea Exertion Scale (DES) scores per Numerical Rating Scale (NRS) scores of breathlessness. (b) Distribution of modified Medical Research Council (mMRC) scores per NRS scores of breathlessness.

Concurrent Validity

Both DES and mMRC were correlated with NRS breathlessness intensity scores and ECOG scores (Table 4). All correlations were highly statistically significant but overall weak. The NRS was correlated more strongly with the DES (Kendall's Tau B 0.32) than the mMRC (Kendall's Tau B 0.12).

Responsiveness

The change in DES and NRS scores over the nine-day period is shown in Fig. 3. The change scores for both scales were approximately normally distributed. The mean change is less than zero in each case, indicating an overall tendency for both breathlessness scores to decrease during the study period. A change in DES was associated with change in NRS, $r = 0.3$ ($P < 0.0001$) (Fig. 3a). The mMRC also showed a statistically significant association with change in NRS, $r = 0.16$ ($P = 0.03$) (Fig. 3).

Table 3
Test-Retest Reliability of DES and mMRC

Scale	Agreement (%)	Expected Agreement (%)	Kappa	*P*
DES	89.12	72.94	0.598	<0.0001
mMRC	83.70	59.01	0.602	<0.0001

DES = Dyspnea Exertion Scale; mMRC = modified Medical Research Council.
Agreement and expected agreement for ratings of breathlessness between two days. Test-retest reliability assessed using the weighted kappa statistics with linear weights.

Table 4
Associations Between DES and mMRC Values and NRS and ECOG Scores

Comparison	Correlation Between the Scores (Kendall's Tau B)
DES vs. mMRC	0.32
DES vs. NRS	0.32
mMRC vs. NRS	0.12
DES vs. ECOG	0.23
mMRC vs. ECOG	0.30

DES = Dyspnea Exertion Scale; mMRC = modified Medical Research Council; NRS = Numerical Rating Scale; ECOG = Eastern Cooperative Oncology Group.
Associations were measured using Kendall's Tau B ranging from 1 (all rankings are the same) to −1 (all rankings are the reverse of the other).

Discussion

In this first validation study in people with life-limiting illnesses, DES, compared with mMRC, had similar test-retest reliability and slightly stronger concurrent validity against an NRS for breathlessness right

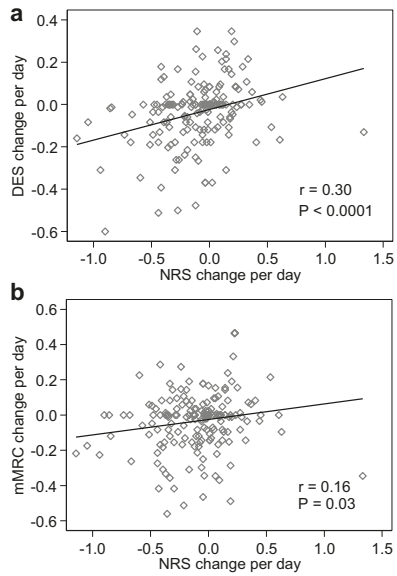

Fig. 3. (a) Change in Dyspnea Exertion Scale plotted against change in Numerical Rating Scale (NRS) scores of breathlessness. (b) Change in modified Medical Research Council plotted against change in NRS scores of breathlessness.

now. Both scales were relatively unresponsive to change. The need of an instrument more adapted to this setting than mMRC is highlighted by that 44% of the participants were in the highest mMRC category. DES differentiated the group of patients with mMRC 4, and increasing DES scores were more closely correlated to increasing breathlessness intensity (NRS scores) compared with increasing mMRC scores. This study also identified potential problems with both scales as the comparative distribution shows that most mMRC values 3−5 equate to DES 2 values, indicating that the DES category may be too broad or the mMRC categories too narrow. Furthermore, the response options 2−5 on DES are not mutually exclusive. The participant may both be breathless when walking around the house as well as when getting out of bed, and Category 2 might be the first one that applies to most respondents. Compared with mMRC, DES was somewhat more responsive to changes in breathlessness intensity (NRS scores), but both are still relatively unresponsive, and correlations were weak. Although DES might be more useful than mMRC for description and discrimination in this population, both scales likely have insufficient responsiveness to be used as endpoints in clinical trials.

Strengths of this study include the use of a quality data set with a large cohort of patients with life-limiting illness and chronic breathlessness in a randomized controlled trial, with standardized longitudinal collection of clinically relevant data during nine days.

Potential limitations were that the eligibility criteria of the randomized controlled trial may limit the generalizability to all patients with life-limiting disease, which should be evaluated in further studies in this setting. The questions were not asked precisely the same, with different temporal references, which might affect the small difference in responsiveness that was shown.

Full understanding of the impacts of chronic breathlessness requires a multidimensional measurement in research,[25,26] but in clinical practice among people with life-limiting illness, it might be more useful to focus on simple and unidimensional measurements.

This study has important implications for practice and research. For clinicians, DES is a discriminative tool that could be used for assessing symptom prevalence and functional impact of breathlessness to describe and select patient populations in clinical care and research. Both scales are insufficiently responsive to be used as an outcome measure of therapy, but DES had better score distribution in severe illness with less ceiling effect. Further research should focus on the optimal questioning and standardizing the use to ensure a better distribution. In the light of the problems showed with both scales, perhaps a combination of the two scales could prove useful to give a better distribution and differentiation of patients.

In conclusion, compared with mMRC, DES had comparable or better measurement properties in terms of test-retest reliability and concurrent validity and could be used as a discriminative tool in this population, but both scales are too insensitive to change to be used as an outcome in clinical trials.

Disclosures and Acknowledgments

The authors thank Professor Emeritus Martin Bland at Department of Health Sciences, University of York, for his work with the statistical analysis as well as all participating staff and patients. J. S. was funded by an unrestricted grant from the Scientific Committee of Blekinge County Council. M. E. was supported by unrestricted grants from The Swedish Society of Medicine, the Swedish Respiratory Society, the Swedish Heart-Lung Foundation (grant number: 20150895), the Scientific Committee of Blekinge County Council, the Wera and Emil Cornell Foundation, and the Swedish Society for Medical Research.

Ethical approval: The study was approved by the Southern Adelaide Health Service Human Research Ethics Committee as well as local research and ethics committees or institutional review boards of all participating sites. All participants provided written informed consent.

The authors declare no conflicts of interest.

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Appendix

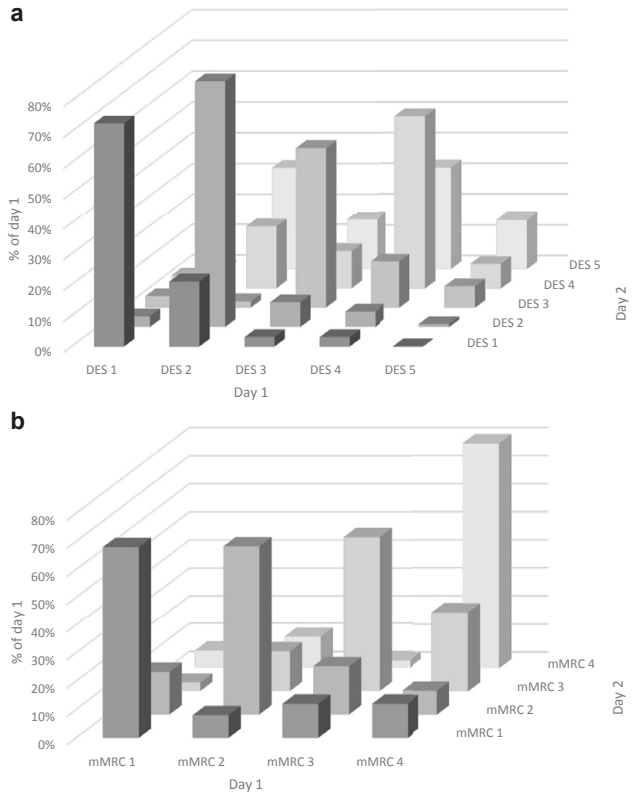

Fig. S1. (a) Change in Dyspnea Exertion Scale (DES) between Day 1 and 2. (b) Change in modified Medical Research Council (mMRC) between Day 1 and 2.

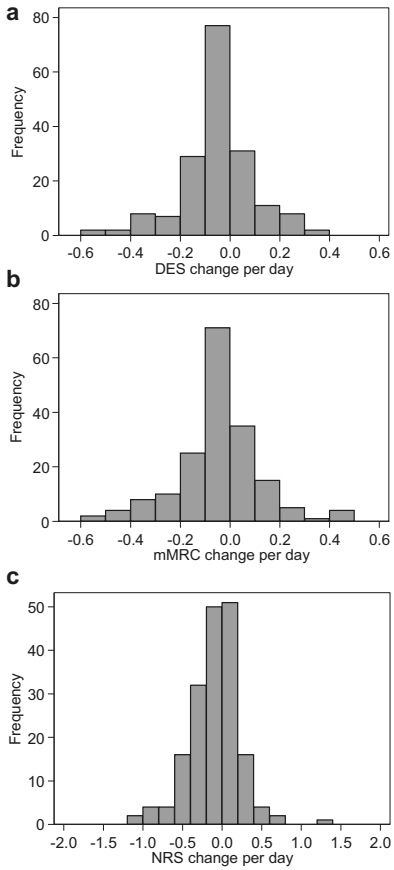

Fig. S2. (a) Distribution of the Dyspnea Exertion Scale (DES) slope to assess responsiveness. (b) Distribution of modified Medical Research Council (mMRC) slope to assess responsiveness. (c) Distribution of Numerical Rating Scale (NRS) slope to assess responsiveness.

Paper IV

BMJ Open Respiratory Research

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

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To cite: Sandberg J, Lansing R, Anderberg P, *et al*. Relating Experienced To Recalled breathlessness Observational (RETRO) study: a prospective study using a mobile phone application. *BMJ Open Resp Res* 2019;**6**:e000370. doi:10.1136/bmjresp-2018-000370

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2018-000370).

Received 9 October 2018
Revised 5 December 2018

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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.

Key messages

- Novel method of collecting data in this field—continuously in daily life through a mobile phone application.
- Investigating previously poorly understood areas of the experience and recall of breathlessness.
- Multidimensional approach to breathlessness.
- Easy to expand or modify study procedure for use in other settings.
- One limitation might be the low level of control of included participants in the general cohort.

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.[4 5] 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.[9] Lack of communication and understanding of the patient's symptoms lead to poor concordance, inappropriate treatment decisions and influence the patients adherence with treatment.[9–11] 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.[12 13] 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.[12 13] Studies evaluating the 'peak-end rule' in breathlessness have previously shown contradictory results between groups.[14] The current intensity of breathlessness is the measure shown to be the most associated with the recalled intensity.[15] 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.[15]

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.

Box 1 Research questions

Three types of breathlessness measures evaluated: experienced (at a time point), recalled (remembered) and predicted (future) breathlessness. The main research questions are:

1 How is the recalled breathlessness intensity for a time period (T1) related to:

1.1 Experienced breathlessness intensity during T1 measured as:
1.1a Mean experienced intensity?
1.1b Peak experienced intensity?
1.1c Most recent experienced intensity?
1.1d Perceived self-efficacy related to the breathlessness?
1.1e Personality trait of high symptom sensitivity at baseline?
1.2 Predicted breathlessness intensity for a future time period (T2)?

2 How is the predicted breathlessness intensity for a subsequent time period (T2) related to:

2.1 Experienced breathlessness intensity during T1?
2.2 Recalled breathlessness intensity during T1?
2.3 Experienced breathlessness intensity during T2?
3 Which factors are associated with the difference score between:
3.1 Experienced and recalled breathlessness intensity during T1?
3.2 Predicted and experienced breathlessness intensity during T2?

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

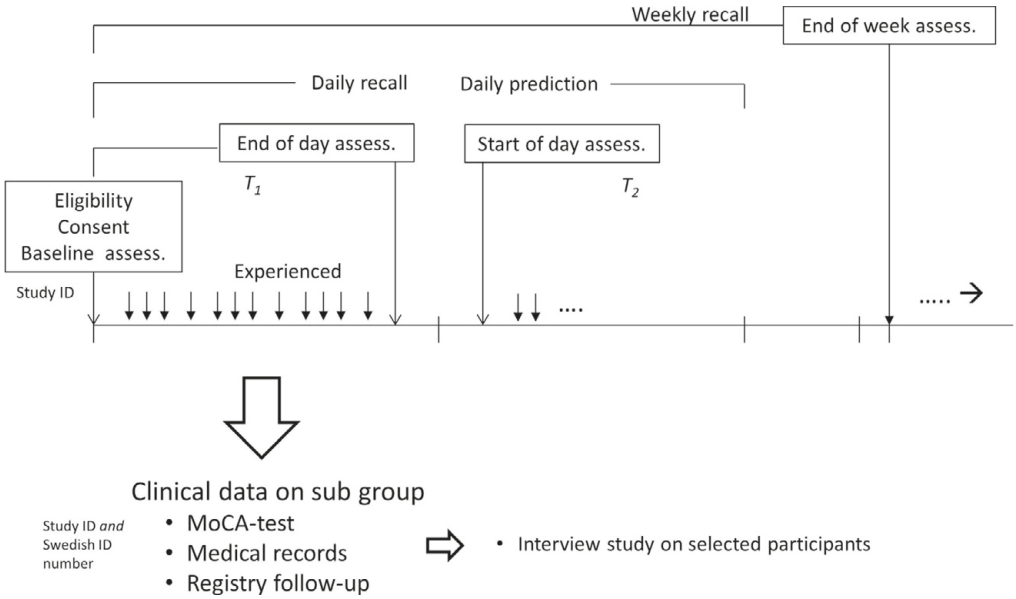

Figure 1 Overview of the timing of planned assessments, starting with eligibility, consent and baseline assessments then continuing with several daily prompts asking on intensity of breathlessness as well as morning, evening and weekly assessments including daily recall and daily predictions as well as a weekly recall.

participants by research staff or through the advertising. Baseline data will be recorded when starting the application and individual daily start and stop times will be set. At regular intervals during each day, the application will cue the participant, using sound and homepage notifications, to self-rate the intensity of breathlessness during the last 10–15 min. Each cue can be ignored or filled in later. Recall of breathlessness during the preceding night or day and additional measurements are rated in the application each morning and, for the whole week at the end of each week in the study (figure 1). The participant can quit the application at any time and will be asked to complete the cessation/exit assessments for the completed part of that week. If any problems or questions arise during the study period, there is a help section within the application with an email address to the primary investigators. All application data, linked to the participant-specific study ID, is encrypted and transferred to a central database in real time via the internet connection. If no internet connection is available at the time of transfer or if for some reason the data transfer is interrupted, the data will be stored locally on the device and the application will try to resend when the connection is re-established and stabilised. The data will also be kept on the device until the end of the study as a safeguard to create a redundancy.

Clinical substudy

A subset of participants at the study centres will be asked to participate in a clinical substudy. In addition to the information regarding the main application-based study, these participants will receive specific information about the substudy on paper and be asked to give their written informed consent to participate. Data including demographics, diagnoses, measures of pulmonary and cardiac function, treatments and hospitalisations will be obtained from medical records and national registries with up to 5 years follow-up of diagnoses and hospitalisations (Patient Registry), dispensed medications (Prescribed Drug Registry) and survival (Causes of Death Registry). Participants in the clinical substudy will be assessed for cognitive impairment at the beginning of the study. Some participants will also be invited to take part in a semistructured qualitative interview focusing on their experience of breathlessness and specifically how they cognitively recall breathlessness over different time periods such as 'now', 'last 24 hours' or 'last week'. This group of participants will also be interviewed shortly about their experiences on using the mobile application. A separate study protocol and analysis plan will be developed before starting the qualitative substudy.

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)	X					
Modified personality trait of symptom sensitivity (PHQ-15)[16]	X					
Mental state (anxiety/depression) (0–10 NRS)	X				X	X
Self-perceived overall well-being (0–10 NRS)	X				X	X
Self-efficacy regarding breathlessness (online supplementary appendix 1c)	X			X	X	X
Breathlessness (0–10 NRS)						
Modified Medical Research Council[25–28]	X					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]	X			X	X	X
Emotional responses related to breathlessness during the time period (MDP)[6 29]	X				X	X
Intensity during the past week (0–10 NRS)	X				X	X
Predicted intensity for the coming week (0–10 NRS)	X					
Predicted intensity for the coming day (0–10 NRS)	X			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.[19] It has been validated in numerous diseases, including cognitive impairment related to dyspnoea, COPD and heart failure.[20–22]

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*.[15] 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 characteristics 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.[23] 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://ltblekinge.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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Acknowledgements The authors would like to thank Håkan Lövkvist PhD, Clinical Studies Sweden, Unit for Medical Statistics and Epidemiology, Skåne University Hospital, Lund, Sweden, for valuable help concerning the statistical methods.

Contributors ME and JS contributed to the conception and drafting of the article. All authors contributed to the study design and revised the article for important intellectual content and approval of the version to be published.

Funding Jacob Sandberg was funded by an unrestricted grant from the Scientific Committee of Blekinge County Council. Magnus Ekström was supported by unrestricted grants from The Swedish Society of Medicine, the Swedish Respiratory Society, the Swedish Heart-Lung Foundation, the Scientific Committee of Blekinge County Council, the Wera and Emil Cornell Foundation, and the Swedish Society for Medical Research.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Paper V

Received: 12 January 2022 | Accepted: 31 May 2022

DOI: 10.1111/resp.14313

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology
APSR
WILEY

Comparing recalled versus experienced symptoms of breathlessness ratings: An ecological assessment study using mobile phone technology

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Funding information
Hjrt-Lungfonden; Region Blekinge; Svenska Sllskapet for Medicinsk Forskning; Vetenskapsradet, Grant/Award Number: 2019-02081

Associate Editor: Amanda J. Piper; **Senior Editor:** Lutz Beckert

Abstract

Background and objective: Recall of breathlessness is important for clinical care but might differ from the experienced (momentary) symptoms. This study aimed to characterize the relationship between momentary breathlessness ratings and the recall of the experience. It is hypothesized that recall is influenced by the *peak* (worst) and *end* (most recent) ratings of momentary breathlessness (peak-end rule).

Methods: This study used mobile ecological momentary assessment (mEMA) for assessing breathlessness in daily life through an application installed on participants' mobile phones. Breathlessness ratings (0–10 numerical rating scale) were recorded throughout the day and recalled each night and at the end of the week. Analyses were performed using regular and mixed linear regression.

Results: Eighty-four people participated. Their mean age was 64.4 years, 60% were female and 98% had modified Medical Research Council (mMRC) ≥ 1. The mean number of momentary ratings of breathlessness provided was 7.7 ratings/participant/day. Recalled breathlessness was associated with the *mean*, *peak* and *end* values of the day. The *mean* was most closely associated with the daily recall. Associations were strong for weekly values: *peak breathlessness* (beta = 0.95, $r^2 = 0.57$); *mean* (beta = 0.91, $r^2 = 0.53$); and *end* (beta = 0.67, $r^2 = 0.48$); $p < 0.001$ for all. Multivariate analysis showed that *peak breathlessness* had the strongest influence on the breathlessness recalled at the end of the week.

Conclusion: Over 1 week, recalled breathlessness is most strongly influenced by the *peak breathlessness*; over 1 day, it is *mean breathlessness* that participants most readily recalled.

KEYWORDS
breathlessness, dyspnoea symptoms, mEMA, mobile ecological momentary assessment, peak-end rule, recall of symptoms

INTRODUCTION

Chronic breathlessness frequently affects the daily life of individuals with diseases such as congestive heart failure, asthma and chronic obstructive pulmonary disease (COPD).[1] It is associated with increased use of health services, hospitalizations and premature mortality.[2–4]

In clinical practice, patient recall of recent breathlessness intensity is often used to assess the severity of conditions, establish the need for further examination and evaluate response to therapy. However, recall of symptom severity may not accurately reflect the patient's experiences across the time span in question.[5–11] The process of reporting symptoms involves complex tasks, including recalling, summarizing and communicating past experiences.[6,12,13] There

is a wide variation in how patients approach this task, making interpretation of reported symptoms challenging.[12,14]

The 'peak-end rule' is related to a cognitive bias that influences the recall of past events.[6,13,15] The rule states that the highest (peak) and most recent (end) intensity of a symptom during a specified time period has the most influence on the recalled symptom level. The peak-end rule impacts the recall of a variety of situations such as painful procedures,[12,13,16–19] events evoking emotion,[20–24] exercise[25] and episodes of mental effort.[26] However, the peak-end rule seems to have a lower effect on the recall of more complex life experiences.[19,27–29] It is largely unknown which factors affect recall of breathlessness.[30–32] Recall of breathlessness after exercise seems to differ from the recall of pain by being context-dependent[30] and less affected by the peak-end rule.[5,7,9,33]

A previous study using paper diaries showed that the intensity of breathlessness on the study day was the most important contributor to variations in recalled scores.[34] More recently, mobile ecological momentary assessments (mEMA) for data collection have been shown to be both more reliable and lead to better compliance than paper diaries.[35–40]

This study aimed to evaluate the relationship between recalled and experienced (momentary) ratings of breathlessness and determine whether the *mean*, *peak* or the *most recent* momentary rating has the strongest influence on the recall.

SUMMARY AT A GLANCE

Recall of breathlessness is essential for clinical care but might differ from the momentary symptoms. This study reports that the peak momentary breathlessness most strongly influences recalled breathlessness over the past 7 days. Recall for 1 day was influenced the most by the *mean breathlessness value* for that day.

METHODS

The Relating Experienced To Recalled Breathlessness Observational (RETRO) study is an observational study with longitudinal data collection for 1 week (7 days), using an application installed on participants' mobile phones for data collection (mEMA). A detailed description of all methods has been published.[41] An mEMA STROBE checklist[38] is in the supplementary material.

Population and design

Inclusion criteria were age ≥ 18 years with a self-reported breathlessness intensity ≥3 on a 0–10 numerical rating scale (NRS) during the preceding 14 days, not related to an acute infection such as an upper respiratory tract infection or pneumonia. Participants needed to be clinically stable, regularly use a smartphone or tablet with internet access and be able to read and complete baseline assessments on the device.

From March 2018 to April 2020, participants were recruited via notice in a local newspaper; at primary care facilities in Lund and Karlskrona; at pulmonary clinics in Karlskrona and Örebro; and by invitation letter to patients of the Karlskrona pulmonary clinic. Potential participants installed an application on their personal smartphone and, if eligible, continued to a baseline questionnaire. All questionnaires were in Swedish. The participants were asked to respond to repeated questions each waking hour of the day as well as each morning and evening for 7 days. At the end of 7 days, or if choosing to drop out, participants were presented with an end of study questionnaire (Figure 1). No training of participants was needed.

Assessment

Baseline characteristics included age, sex, height, weight, smoking habits and physician diagnoses. Breathlessness in the week before the study was assessed using the modified Medical Research Council (mMRC) breathlessness scale[42] and a 0–10 NRS ('How intense has your breathlessness been during the previous week'). The mMRC is a 5-point ordinal measure of exertional breathlessness from 0 ('I only get breathless with strenuous exercise') to 4 ('I am too breathless to leave the house' or 'I am breathless when dressing'). The mMRC responses 3 and 4 were merged due to a recording error. The NRS[43,44] is widely used and validated for the assessment of breathlessness.[45–48]

Underlying conditions were reported by selecting them from a pre-defined list. Momentary breathlessness was assessed using the question 'How intense has your breathlessness been in the past 10–15 min?', rated from 0 (no breathlessness) to 10 (worst imaginable breathlessness).[41]

Recalled breathlessness was assessed each evening using the NRS ('How intense has your breathlessness been during this day?') and at the end of the 7 days using the question 'How intense has your breathlessness been during the past week?'.

Statistical analysis

Outcomes were the *recalled breathlessness at the end of the day* and *recalled breathlessness for the week*. The exposure was the momentary breathlessness reported at times throughout the day. Momentary breathlessness was analysed as:

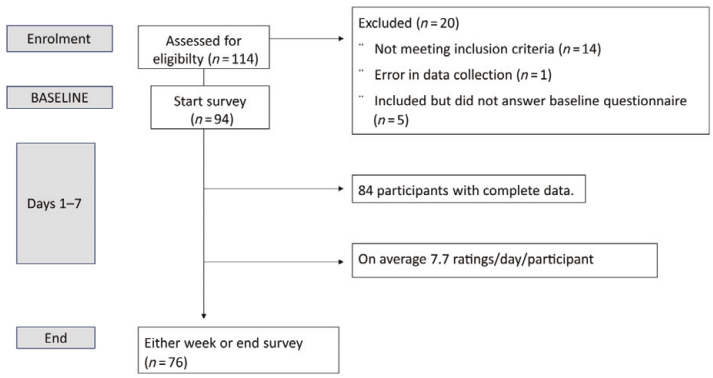

FIGURE 1 Study design and the inclusion of participants

- The difference in breathlessness intensity between momentary ratings and the *mean* value for that day, assessing for impact on recall from a change in breathlessness;
- The *mean* of an individual's momentary breathlessness ratings for each day;
- The *mean* momentary breathlessness ratings for all of the 7 days;
- The *peak* value for each day defined as the highest reported momentary value of breathlessness;
- The *peak* value for the whole 7-day study period;
- The last recorded (*end*) momentary breathlessness rating of each day; and
- The last recorded (*end*) momentary breathlessness rating of the entire study period.

Associations between momentary and recalled breathlessness ratings throughout the day were analysed using mixed linear regression with random intercepts and slopes, with clustering by participant. This model allows the intercept (mean level of momentary breathlessness) and the slope (change in momentary breathlessness) to vary among participants. Clustering accounted for repeated measurements within participants' responses during the analysis period.

Associations were reported as beta coefficients with 95% CIs. A beta coefficient is defined as the mean change in the outcome variable (the recalled value for the day) for each unit increase of the exposure value (the momentary breathlessness measures recorded during the day).

Associations over the 7 days were analysed using linear regression. The recalled breathlessness for the entire study period was the dependent variable, and *mean, peak* and *end* (last recorded) values of momentary breathlessness during the week were the independent variables. The variables were analysed separately and pairwise in multivariate analysis models 1–3 and combined in a final model. The variance inflation factor (VIF) was used to check for multi-collinearity. Low VIF values were found, indicating that the risk of multi-collinearity was low (highest VIF = 3.8).

Beta coefficients with 95% CI and the corresponding adjusted r^2 value (reflecting the percentage of the variance explained by the model) are presented. The unique contribution of each factor to each model was assessed by calculating the Δr^2 for each factor by subtracting the variable's r^2 values from the r^2 value of the entire model. Significance was defined as two-sided $p < 0.05$.

A power analysis performed before the enrolment began[41] determined that a minimum of 30 participants was needed to obtain a power of 80%, consistent with the sample size of Meek et al.[34] We aimed for at least 45 participants providing data for at least 2 days. The statistical analysis plan was designed in collaboration with a biostatistician.

Statistical analyses were conducted using the software package Stata, version 14.2 (StataCorp LP, College Station, TX).

RESULTS

Participants

A total of 114 people downloaded the application, of whom 30 were excluded from the analysis based on: not meeting the eligibility criteria ($n = 14$); not completing the baseline questionnaire ($n = 5$); a technical error with the mobile phone application ($n = 1$); and not responding to enough daily prompts or not providing recall information ($n = 10$). Excluded individuals who contributed baseline data did not differ substantially from those included in age, sex or breathlessness level. The final study population comprised 84 individuals. A total of 8121 prompts for momentary breathlessness rating were sent out to the 84 participants, and 6152 were answered within 1 h (a mean of 7.7 ratings/participant/day). The other 1969 prompts were tagged as missing (compliance rate of 75.8%). Seventy-six individuals completed the whole data collection period, including the end-of-study assessment (Figure 1).

TABLE 1 Baseline characteristics of the 84 study participants experiencing daily breathlessness

Characteristic	Value (%)
n	84
Age, mean (SD)	64.4 (12.8)
Female, *n* (%)	50 (60)
BMI, mean (SD)	28.2 (5.4)
Smoking status, *n* (%)	
Never	25 (30)
Former	54 (64)
Occasionally	2 (2)
Regular daily smoking	3 (4)
Breathlessness past week (0–10 NRS), mean (SD)	5.2 (1.8)
mMRC past week, *n* (%)	
0	2 (2)
1	31 (37)
2	22 (26)
3–4	29 (35)
Asthma, *n* (%)	33 (39)
COPD, *n* (%)	34 (40)
Heart failure, *n* (%)	7 (8)
Atrial fibrillation, *n* (%)	9 (11)
Coronary heart disease, *n* (%)	7 (8)
Cancer, *n* (%)	11 (13)
Diabetes, *n* (%)	9 (11)
Hypertension, *n* (%)	33 (39)
Stroke, *n* (%)	2 (2)

Note: Data were self-reported by participants.
Abbreviations: COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council; NRS, numerical rating scale.

The mean age of the study population was 64.4 (SD 12.8); 60% were female; and the main underlying diagnoses were COPD (40%) and asthma (39%). A total of 30% of the participants had never smoked (Table 1). Breathlessness during the preceding week was reported on the mMRC scale by 98% (grade 1 [37%], grade 2 [26%] or grades 3 and 4 [35%]).

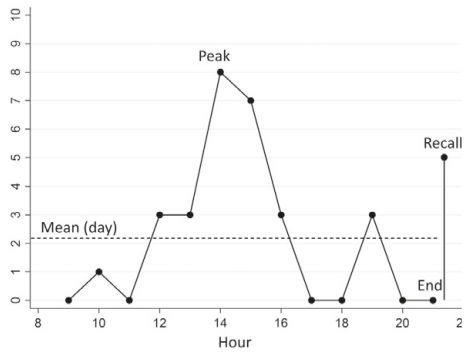

FIGURE 2 Momentary breathlessness ratings and recalled rating of one illustrative participant over a single day with added mathematical mean value and labels for values of special interest (peak and end). Values were calculated similarly over the 7-day study period

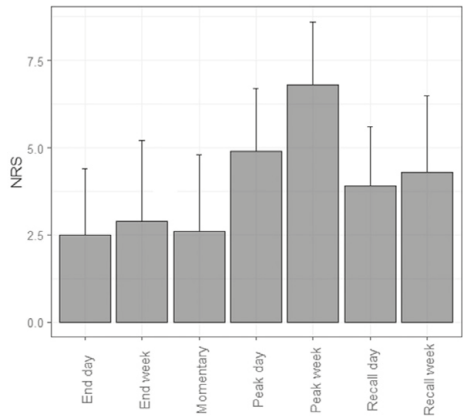

FIGURE 3 Mean numerical rating scale (NRS) values of momentary breathlessness severity of the entire cohort throughout the 7-day study

Breathlessness data

The ratings from one illustrative participant are presented in Figure 2. The mean value of momentary breathlessness ratings throughout the day for the study period was 2.6 (SD 2.2) on the 0–10 NRS, the mean *daily peak value* was 4.8 (1.8) and the mean *weekly peak value* was 6.8 (SD 1.8). The mean *daily recalled value* was 3.9 (SD 1.7), and the mean *weekly recalled value* was 4.3 (SD 2.2; Figure 3).

Analysis of daily ratings

We observed a significant association between momentary and recalled breathlessness in univariate analyses (Table 2). For each unit increase in an individual rating of momentary breathlessness, the recalled rate for *the day* increased by 0.10 (95% CI 0.08–0.11) units. The mean of the ratings for the day showed the strongest association with the recalled severity for that day, with each unit increase of the mean resulting in a 0.67 (95% CI 0.63–0.71) unit increase in recalled severity. The *recalled value* showed an association with the *peak value* (beta value 0.28 [95% CI 0.26–0.30]). The end value was also positively associated with the recalled value but to a lesser degree. Multivariate analysis with peak and end was similar to univariate findings. Change in momentary breathlessness from the group

mean showed no association with recalled breathlessness (Table 2).

Analysis of the ratings over the week

Associations between momentary and recalled breathlessness for *the week* are shown in Table 3. Significant associations were revealed for the *peak value* (beta = 0.97, $r^2 = 0.56$, $p < 0.000$), the *mean momentary breathlessness* (beta = 0.91, $r^2 = 0.52$, $p < 0.000$) and the *end value* (beta = 0.69, $r^2 = 0.50$, $p < 0.000$). The relationship was strongest with the *peak value*. The *mean*, *peak* and *end values* were combined pairwise in multivariate models 1–3 and then combined all together for model 4 analysis (Table 3). The peak value consistently made the highest contribution to the models. The association between *mean* and *recalled values* was reduced when combined in the model with the *peak* and *end values*. The unique contribution (Δr^2) of the *mean* to model 4 was close to zero ($\Delta r^2 = 0.00$) and $\Delta r^2 = 0.11$ for the *peak value* (Table 3).

TABLE 2 Relationship between recalled breathlessness at the end of the day and momentary breathlessness ratings during that day (beta coefficients and corresponding 95% CI)

Factor	Univariate analysis Beta (95% CI)	Multivariate analysis Beta (95% CI)
Momentary	0.097 (0.08–0.11)	-
Change	0.00 (−0.02–0.02)	-
Mean	0.67 (0.63–0.71)	-
Peak	0.28 (0.26–0.30)	0.26 (0.2–0.28)
End	0.16 (0.14–0.18)	0.10 (0.08–0.12)

Note: Estimates were analysed using mixed linear regression with random intercepts and slopes, accounting for repeated measurements. $n = 84$.
Abbreviations: Change, difference in breathlessness from the mean value, calculated by subtracting each reported value from the individual mean for that day; end, last recorded breathlessness rating before recall; NRS, numerical rating scale; peak, highest recorded momentary breathlessness rating.

Findings were similar when adjusting the associations for age and sex.

DISCUSSION

The main finding of the study was that the peak momentary breathlessness over the course of 7 days was closely linked with the recalled breathlessness severity for that same period. The findings suggest that the impact of peak breathlessness on recalled breathlessness is stronger than the impact from the *mean* or the *end values* for 1 week. Recall for 1 day seemed to be influenced the most by the *mean breathlessness value* for that day.

This study contributes novel information on interpretation of self-reported breathlessness levels over 1 day or 1 week. Compared to other studies with a similar methodology, we have collected many more breathlessness ratings and used verifiable real-time measures.[39,40,49]

Similar to our results, recall of breathlessness after an exercise test has been shown to reflect the impact of peak breathlessness but not the last recorded value.[33] In our study, we found that the impact of the peak value was stronger when using a 7-day recall period compared to a daily recall (where the mean value had the strongest association). This could be explained by basic memory functions, suggesting that a shorter recall period decreases bias.[15,34] No association was found between recall and change in breathlessness (Table 2). This indicates that hourly changes in breathlessness do not impact the recall for that day to any large degree.

A change of 1 point in the *peak* or the *mean value* influenced the weekly recall by a margin of close to 1 point. This corresponds to a large clinically important change as predefined in the protocol.[41] A change in mean breathlessness of 1 point for the day influenced the recall with an increase of 0.67 points, which corresponds to a moderate change.

Strengths of this study include the use of mEMA as a novel tool to investigate this research question using data captured in real time. The use of mEMA also gives better

TABLE 3 Relationship between the recalled breathlessness at the end of the week and the momentary breathlessness ratings during that week (beta coefficients, corresponding 95% CI, r^2 and Δr^2)

Factor	Univariate Beta (95% CI)	Model 1 Beta (95% CI)	Model 2 Beta (95% CI)	Model 3 Beta (95% CI)	Model 4 Beta (95% CI)
R^2 for the whole model	-	$r^2 = 0.66$	$r^2 = 0.55$	$r^2 = 0.64$	$r^2 = 0.66$
Mean	0.91 (0.71 to 1.1), $r^2 = 0.52$	-	0.54 (0.20 to 0.89), $\Delta r^2 = 0.05$	0.49 (0.25 to 0.72), $\Delta r^2 = 0.08$	0.22 (−0.1 to 0.55), $\Delta r^2 = 0.00$
Peak	0.97 (0.77 to 1.16), $r^2 = 0.56$	0.65 (0.43 to 0.87), $\Delta r^2 = 0.16$	-	0.62 (0.38 to 0.87), $\Delta r^2 = 0.12$	0.59 (0.35 to 0.83), $\Delta r^2 = 0.11$
End	0.69 (0.53 to 0.85), $r^2 = 0.50$	0.38 (0.22 to 0.55), $\Delta r^2 = 0.1$	0.34 (0.07 to 0.61), $\Delta r^2 = 0.03$	-	0.27 (0.04 to 0.50), $\Delta r^2 = 0.02$

Note: Variables were analysed separately (univariate) and together in different combinations (models 1–4). Estimates were analysed using linear regression, $N = 76$.
Abbreviations: Δr^2, contribution from each factor to the variance of the model (r^2 for the whole model − r^2 for the model without the current factor). A higher Δr^2 corresponds to a higher contribution to that model; end, last recorded value of momentary breathlessness before recall; mean, mean value of momentary breathlessness ratings for the week; NRS, numerical rating scale; peak, highest recorded momentary breathlessness rating; r^2, percentage of the variance explained by the whole model.

compliance than paper diaries[35] and prevents participants from manually changing or adding responses afterwards.[37] This is the first study of its kind and adds new knowledge based on reliable and consistent use of a 0–10 NRS.

Limitations include the lack of data concerning activities performed when reporting breathlessness, limiting in-depth interpretation. Our choice to include participants with breathlessness with different aetiology may limit generalizability in disease-specific groups but, at the same time, improves generalizability among unselected populations. The size of the study population limits the possible subgroup analysis of differences between disease groups. Future studies on more selected populations are needed.

This study was conducted in Swedish, and confirmatory studies using other languages are needed. Selection bias due to participants with mobile phones being younger or healthier could be an issue, but mobile use disparities between generations have decreased substantially in recent years for 65–75-year-olds.[36,50]

The study suggests that *peak breathlessness* has an impact on recalled breathlessness. This might be an important consideration in clinical practice where it is often necessary to collect information covering more extended periods, especially in outpatient care. Future research should focus on the clinical relevance of these findings and the relationships with treatment outcomes and survival. For example, would a treatment that reduced the peak breathlessness be more important than one lowering the mean?

In conclusion, recalled severity of breathlessness over the past 7 days was more strongly linked to the *peak momentary breathlessness* in that period than to average or most recent (end) values. Recall for 1 day was influenced the most by the *mean breathlessness value* for that day.

AUTHOR CONTRIBUTION

Jacob Sandberg: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Josefin Sundh:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); supervision (supporting); writing – review and editing (equal). **Peter Anderberg:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); software (supporting); writing – review and editing (equal). **David C. Currow:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (equal). **Miriam Johnson:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (equal). **Robert Lansing:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (equal). **Magnus Ekström:** Conceptualization (lead); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (lead); project administration (supporting); resources (equal); supervision (lead); validation (equal); visualization (supporting); writing – review and editing (lead).

ACKNOWLEDGEMENTS

The authors thank the nurses at the pulmonary outpatient clinic at Blekinge Hospital for helping with the recruitment of participants, Dr Mahmood Ahmadi for his invaluable contributions to data collection and the biostatisticians at 'Clinical studies Sweden—South' (a part of the southern healthcare regions in Sweden) for support and advice.

Research funding: The study was supported by unrestricted grants from the Scientific Committee of the Region of Blekinge, the Swedish Heart-Lung Foundation and Swedish Society for Medical Research. Magnus Ekström was supported by the Swedish Research Council (DNr: 2019-02081).

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

HUMAN ETHICS APPROVAL DECLARATION

The Regional Ethical Review Board in Lund approved the study procedures (DNr 2017/149). All participants provided written informed consent prior to enrolment. Participation could be discontinued at the discretion of the participant, in which case, no further data were collected. All research was performed in accordance with relevant guidelines and regulations.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Sandberg J, Sundh J, Anderberg P, Currow DC, Johnson M, Lansing R, et al. Comparing recalled versus experienced symptoms of breathlessness ratings: An ecological assessment study using mobile phone technology. Respirology. 2022. https://doi.org/10.1111/resp.14313