Affective Traits, States and Breathlessness

Andreas von Leupoldt & Ysys Denutte

Affiliations:

Health Psychology, University of Leuven, Leuven, Belgium

Corresponding author:

Prof. Andreas von Leupoldt, PhD

Health Psychology

University of Leuven

Tiensestraat 102

B-3000 Leuven (Belgium)

Phone: +32-(0)16-32 60 06

Fax: +32-(0)16-32 61 44

Email: andreas.vonleupoldt@kuleuven.be

Abstract

Purpose of review:

Breathlessness is a prevalent and aversive symptom in various conditions and closely related to affect. Here, we review recent literature from the previous 18 months examining the interactions between affective traits and states with breathlessness.

Recent findings:

Available studies used various qualitative, quantitative and experimental research designs in diverse samples of patients with breathlessness and in healthy individuals. Most studies clearly demonstrated that non-specific forms of negative affective personality traits such as anxiety and depression, disease- or symptom-specific forms such as fear-of-dyspnea and fear-of-physical activity as well as short-lasting negative affective states such as experimentally induced fear were associated with greater breathlessness. Moreover, breathlessness was shown to evoke negative affect, whereas positive affect reduced breathlessness. Different treatment approaches demonstrated concurrent beneficial effects on both negative affect and breathlessness and several potential mechanisms underlying these interactions were suggested.

Summary:

Negative affect is common in diverse patient groups suffering from breathlessness and is related to increased burden due to breathlessness. Future research is required to improve our understanding of the mechanisms underlying these associations together with increased clinical efforts for improved detection and treatment of negative affect in breathless patients.

Keywords: anxiety, depression, emotion, fear, dyspnea

1 Introduction

2
3 Breathlessness (dyspnea) is the subjective experience of breathing discomfort that can vary in
4 quality and intensity. This experience results from interactions between multiple
5 physiological, psychological, social and environmental factors, and can lead to subsequent
6 physiological and behavioral responses [1]. Breathlessness is the main symptom in respiratory
7 diseases such as asthma and chronic obstructive pulmonary disease (COPD), but is also
8 common in other diseases including cardiovascular conditions, cancer, neuromuscular
9 diseases as well as mental disorders [1,2]. Up to 27% of the general population and up to 50%
10 of severely ill patients have been estimated to suffer from breathlessness [2,3], with even
11 greater prevalence rates in palliative care settings [4]. Experiencing breathlessness is highly
12 frightening for many patients, associated with severe disability and significantly reduces their
13 quality of life, which further impacts families, partners and caregivers [5,6]. Not surprisingly,
14 these patients often show high rates of comorbid psychological burden and affect-related
15 disorders such as anxiety and depression are especially common. For example, in patients
16 with COPD, prevalence rates for anxiety and depression of 36% and 40%, respectively [7],
17 have been reported in meta-analyses.

18
19 It is increasingly recognized that breathlessness is a multidimensional experience consisting
20 not only of sensory aspects (e.g., intensity, quality), but also of important affective aspects
21 (e.g., immediate unpleasantness, long-term suffering) [1,2,8–10]. Not surprisingly, many
22 previous studies have demonstrated that affect is closely related to the perception of
23 breathlessness with negative affect typically being associated with greater levels of
24 breathlessness. This holds for long-lasting, non-specific forms of negative affective
25 personality traits such anxiety and depression, for disease- or symptom-specific forms such as

1 fear-of-dyspnea and fear-of-physical activity as well as for short-lasting affective states such
2 as experimentally induced fear. Respective findings were not only observed in patients
3 suffering from breathlessness (e.g., asthma, COPD), but also in healthy individuals and were
4 presented in several previous reviews [8,10–15]. However, both breathlessness as well as
5 negative affect in patients suffering breathlessness remain often under-recognized and under-
6 treated, despite the availability of respective diagnostic instruments and multidisciplinary
7 treatment approaches that also include a focus on negative affect [6,9,12,16].

8
9 Therefore, the aim of the present review is to highlight recent evidence for the interactions
10 between affective traits and states and the experience of breathlessness published in the last
11 18 months. In addition, potential mechanisms underlying these interactions as well as future
12 directions for research and clinical domains will briefly be discussed. To this end, a systematic
13 search of peer-reviewed literature published between July 2018 and December 2019 was
14 conducted in PubMed, restricted to adults and full articles in English. Search terms included
15 ‘breathlessness’, ‘dyspnea’, ‘anxiety’, ‘depression’, ‘disease-specific fear’, ‘disease-specific
16 anxiety’, ‘affective’, ‘emotion’, ‘fear’, ‘mood’ and ‘psycho*’ in several combinations. In
17 addition, reference lists of identified articles were screened, including for articles with ‘in
18 press’ status. Articles were included in the review when providing quantitative or qualitative
19 data on affective traits or states and their interactions with breathlessness together with
20 adequate descriptions of respective measurement procedures.

Recent findings

Non-specific Affective Personality Traits

Several studies using large sample sizes confirmed previous findings that non-specific negative affective personality traits, in particular anxiety and depression, are highly frequent in patients suffering from breathlessness [17**,18*,19**,20**]. The majority of these studies used different validated questionnaires to assess these traits in samples with varying underlying diseases, which might explain the heterogeneity in respective prevalence rates. For example, von Siemens et al. [20**] reported clinically relevant depression levels using the Patient Health Questionnaire-9 (PHQ-9) in 27% of 2255 COPD patients from the COSYCONET multicenter cohort study. Yohannes et al. [17**] observed relevant levels of anxiety and depression using the Depression Anxiety Stress Scales-21 (DASS-21) in 54% and 38% of COPD patients (N=557), respectively, entering a pulmonary rehabilitation program (PR). Similarly, McKenzie et al. [18*] reported elevated levels of anxiety (61%) and depression (57%) in 252 patients with advanced cancer using the Edmonton Symptom Assessment System (ESAS). Depressive symptoms based on the Geriatric Depression Scale (GDS) were also identified by Trevisan et al. [19**] in 52% of 2322 community-dwelling older individuals with breathlessness (modified Medical Research Council dyspnea scale; mMRC > 2) due to multiple chronic conditions including COPD, asthma and cardiac disease.

Importantly, many studies in patients with various conditions demonstrated that these higher levels of non-specific negative affectivity (e.g., anxiety, depression) were paralleled by higher reports of breathlessness. This was observed in studies including patients with heart failure [21], different cardiorespiratory diagnoses [19**,22,23*], COPD [17**,18*,19**,20**,24–26,27**,28*], cancer [18*,29–31] and neural diseases including Parkinson’s disease [32–33,

34*]. Comparable findings were observed in healthy samples and in general population studies [35,36*]. For example, Currow et al. [36*] demonstrated in a large representative Australian population study that breathlessness (mMRC ≥ 2), and especially longer duration of breathlessness, were associated with higher levels of anxiety and depression as measured with the Generalized Anxiety Disorder Scale-2 (GAD-2) and Patient Health Questionnaire-2 (PHQ-2).

While some of these studies merely reported the co-occurrence of breathlessness and negative affective traits, others demonstrated better characterized and/or gradual associations [17**,18*, 19**,20**,27**,31,36*]. For example, Yohannes et al. [17**] showed that baseline levels of anxiety and depression in COPD patients correlated significantly with breathlessness ratings ($r=0.38$ and $r=0.31$), but only negligibly with spirometrically measured lung function ($r=0.07$ and $r=0.11$). Similarly, Trevisan et al. [19**] observed in older individuals with multiple chronic conditions that increasing levels of breathlessness at baseline (mMRC 1, 2 and >2) related to increasing incidence of possible depression over an average 4-year follow-up period (16% vs 24% vs 27%). In the same vein, von Siemens et al. [20**] demonstrated that the presence of mMRC defined breathlessness in COPD patients increased depression scores by 2.75 points on the PHQ-9, whereas higher exacerbations were associated with a much lower (additional) increase by 1.44 points, while spirometrically measured lung function showed only weak associations. Interestingly, different dimensions of breathlessness such as frequency, impact, and cognitive/affective response were shown to have conditional independent relationships with depression scores and depression items in COPD patients. These findings from network analyses by Schuler et al. [27**] suggest that different dimensions of breathlessness are associated via different paths (e.g., via different symptoms) with depression.

1
2 Notably, a number of studies on the topic of this review presented positive and encouraging
3 findings. Several authors demonstrated that different forms of treatments were not only
4 improving breathlessness, but also symptoms of negative affect (mostly anxiety and
5 depression) next to improvements in several other clinical outcome measures. Respective
6 treatments included varying forms of complexity ranging from implantation of ventricular
7 assist devices in heart failure patients [37], a one-session individualized breathlessness
8 intervention including education and self-management plans in COPD patients [38], a two-
9 month breathing-based walking intervention in COPD patients [39] up to complex, multi-
10 professional and individualized breathlessness services for patients with advanced diseases,
11 for example cancer [40,41**]. However, the majority of studies investigated various forms of
12 multidisciplinary inpatient and outpatient pulmonary rehabilitation programs in COPD
13 patients [17**,27**,42,43,44*], next to those in patients referred to lung transplantation [45]
14 and asthma patients [46]. For example, Yohannes et al. [17**] demonstrated in COPD patients
15 during an 8-week multidisciplinary outpatient PR program significant improvements in levels
16 of anxiety, depression and stress, which were paralleled by significant improvements in
17 breathlessness, especially in those patients with high baseline levels at PR start. Similarly,
18 three separate studies examining the effects of a 3-week multidisciplinary inpatient PR
19 program in COPD patients demonstrated significant pre-post PR improvements in levels of
20 anxiety (GAD-7 scores) and depression (PHQ-9 scores) to be paralleled by improved
21 breathlessness reports using the mMRC or COPD Assessment Test (CAT), respectively
22 [27**,43,44*]. Notably, these parallel improvements in negative affect and breathlessness
23 partly lasted up to 6-months after PR completion [44*].

24
25 *Disease- and Symptom-Specific Affective Personality Traits*

1 In contrast to the large number of studies on non-specific affective personality traits, only a
2 few studies were published during the review period on disease- and symptom-specific
3 affective personality traits in relation to breathlessness. Most of these were conducted in
4 COPD patients [43,44*,47,48]. Two studies used the COPD anxiety questionnaire (CAF) to
5 measure fear-of-dyspnea, fear-of-physical activity, fear-of-disease progression, fear-of-social
6 exclusion and sleep-related worries in COPD patients before and after completion of a 3-week
7 multidisciplinary inpatient PR program [43,44*]. Both studies demonstrated that higher levels
8 of these disease-specific fears were associated with worse PR outcomes including more
9 symptoms and breathlessness as measured with the CAT, St. George's Respiratory
10 Questionnaire (SGRQ) and mMRC, even after controlling for levels of non-specific negative
11 affect. These associations were observed both before and after PR and partly remained stable
12 up to 6-month of follow-up [44*]. Notably, improvements in disease-specific fears were
13 related to improvements in symptom burden in both studies, suggesting potential treatment
14 targets. Similarly, Vardar-Yagli et al. [47] observed high levels of fear-of-movement in 93% of
15 patients with COPD using the Tampa Scale for Kinesiophobia (TSK), which was significantly
16 correlated with higher mMRC breathlessness ratings ($r=0.68$). Mathew et al. [48]
17 demonstrated higher anxiety sensitivity, distress intolerance and anhedonia in current
18 compared to former smokers with COPD. This was paralleled by higher COPD symptom
19 impact (CAT scores) and more catastrophic interpretations of breathlessness as measured with
20 the Breathlessness Catastrophizing Scale (BCS). Two additional experimental studies in
21 healthy samples showed that resistive load induced breathlessness evoked negative affective
22 states including fear, symptoms of panic and partly avoidance behavior [49*,50*]. However,
23 these findings were not related to dyspnea-specific affective traits such as breathlessness
24 catastrophizing (BCS) and fear of suffocation (FoS), which might not be surprising given the
25 relatively low average levels of these traits in both healthy samples.

Affective States

Next to the studies on long-lasting affective personality traits, several studies examined the interactions between short-lasting affective states and breathlessness. These used cross-sectional questionnaire techniques, qualitative interviews and controlled experimental designs in various samples including patients with acute and chronic respiratory failure [51,52*], hospitalized patients with breathlessness [53,54*], patients with asthma [55], COPD [56*, 57], cancer [58*], functional somatic syndromes [59], pulmonary hypertension [60] as well as obese [61*,62,63] and healthy individuals [49*,50*,64*,65,66,67*,68-72,73*,74]. The most common finding across studies and samples was that breathlessness evoked strong negative affective states characterized by high unpleasantness and anxiety. For example, several studies using the Multidimensional Dyspnea Profile (MDP) questionnaire in patients with respiratory failure requiring non-invasive ventilation [52*], hospitalized patients with breathlessness [54*] and pulmonary hypertension [60] demonstrated that breathlessness most frequently elicited anxiety. Qualitative interviews in some of these patients revealed important additional descriptions of affective responses to breathlessness including frustration, anger, loneliness, fear, traumatic experiences and even fear-of-dying, which were partly related to the experience of non-invasive ventilation [51,53] and described as a vicious circle of breathlessness, anxiety, fear-of-breathlessness and more breathlessness [24,53].

Several experimental studies evoking breathlessness in well-controlled lab settings confirmed these findings. For example, exertional breathlessness induced by cycling tests was shown to elicit unpleasantness and anxiety in individuals with obesity [61*,62,63], asthma [55] and pulmonary hypertension [60]. In this regard, Marines-Price et al. [61*] observed in obese women correlations of Borg ratings of breathlessness with feelings of unpleasantness ($r=0.61$)

1 and states of anxiety ($r=0.50$) as measured on a Visual Analogue Scale (VAS). Similarly,
2 several studies in healthy individuals demonstrated that breathlessness induced by resistive
3 loaded breathing evoked negative affective states such as unpleasantness, arousal, anxiety and
4 panic symptoms [49*, 50*, 64*, 65, 66, 67*, 68, 69, 74]. These effects were even amplified by
5 additional experimental manipulations such as social exclusion [49*, 64*] and increased
6 unpredictability/threat of upcoming breathlessness [68, 74] and were strongest in individuals
7 with high levels of trait anxiety [50*, 70]. Partly, these effects further interfered with cognitive
8 functioning [65, 66, 67*, 68]. For example, in a set of studies Sucec et al. demonstrated that
9 resistive load-induced breathlessness evoked not only negative affective states, but in parallel
10 impaired behavioral and neural performance in different cognitive tasks testing response
11 inhibition, memory and error processing [65, 66, 67*, 68]. Relatedly, two neuroimaging studies
12 using functional Magnetic Resonance Imaging (fMRI) in healthy individuals demonstrated
13 that experimentally induced breathlessness was related to increased state anxiety as measured
14 with the State-Trait Anxiety Inventory (STAI) and amplified the neural processing in affect-
15 related brain areas such as the insula and amygdala [72, 73*].

16
17 Notably, several simple experimental manipulations such as the presence of an observer
18 [49*], a virtual game creating feelings of social inclusion [64*], pleasant acoustic stimulation
19 [71] as well as brief controlled exposures to resistive loaded breathing over five days [67*]
20 did not only elicit more positive affective states than the control manipulations, but in parallel
21 improved breathlessness in healthy samples. Similarly, simple interventions such as listening
22 to music [58*], brief mindfulness exercises [57] and olfactory stimulation with L-menthol
23 [56*] led to improvements in both breathlessness and affective states in patients with cancer
24 and COPD, respectively. These findings encourage future, more systematic studies testing
25 their potential benefits for regular therapeutic use.

Potential Mechanisms for Affect-Breathlessness Interactions

In line with previous reports [8,10–15], the reviewed findings clearly demonstrate strong interactions between affective traits, states and breathlessness. However, it remains difficult to derive unequivocal cause-effect relationships from these findings and often bidirectional and/or circular associations need to be assumed, as reflected by patients' descriptions of the vicious circle of breathlessness, anxiety, fear-of-breathlessness and more breathlessness in qualitative studies [24,53]. Moreover, additional (mediating and moderating) factors are likely involved, which might further vary across patients [9]. An excellent example for this notion provides the prospective study in community-dwelling older individuals with multiple chronic conditions by Trevisan et al. [19**]. Here, worsening of breathlessness (both during the day and the night) over the 4-year follow-up period was associated with more than a threefold increased risk of developing possible depression and a more than doubled risk of worsening pre-existing depressive symptoms. At the same time, the authors observed that persistent pre-existing as well as new incidence of depression doubled the risk of reporting breathlessness over the follow-up period. Thus, this study highlights concurrently two previously hypothesized potential mechanisms of action: 1) breathlessness leads to increased negative affect and 2) negative affect leads to increased breathlessness [12]. The first seems relatively intuitive given that breathlessness (together with other symptoms and burden due to the underlying disease) is usually experienced as highly aversive, thus creating immediate negative affective states, as reflected in several studies described above including experimental studies in healthy individuals. Its frequent and/or chronic experience can subsequently lead to long-term negative affective traits such as anxiety and depression as shown in several other quantitative and qualitative patient studies discussed above. However, the second mechanism is also supported by some of the studies reviewed alongside Trevisan

et al. [19**], for example by the experimental studies demonstrating that changes in affective states can increase as well as decrease breathlessness [49*,64*,67*,75]. While this might partly be related to affect-induced changes in ventilation such as faster and shallower breathing when being anxious [75], other studies found affect-related changes in breathlessness to be independent of ventilatory changes [49*,64*,67*]. This suggests additional linking factors and potential mechanisms [12], which requires intensified future research efforts. However, some of these were also discussed in the review period and are illustrated in figure 1. Briefly, these include factors often found associated with both negative affect and breathlessness such as reduced physical activity [76], persistent smoking behavior [48], inflammation [77] as well as cognitive processes related to learning, memory and expectations [78–80]. Further potentially relevant factors linking affect and breathlessness include sleep disturbances [81], shared genetic risks [82,83] and specific processes in brain function and structure [35,73*,80,84–87].

Implications for Future Research and Clinical Practice

The reviewed findings confirmed high rates of negative affective traits in breathless patients which, however, often remain unnoticed by clinicians [12]. This highlights further need to improve their detection in clinical settings, for example by regular routine screenings using available instruments such as PHQ, Hospital Anxiety and Depression Scale (HADS) and GAD for non-specific negative affect [88] and CAF for disease-specific negative affect [44*] and to further refine these instruments for breathless patients. Similarly, several studies showed the strong patient burden due to the affective dimension of breathlessness including anxiety and fear, which suggests to routinely assess this dimension next to sensory aspects of

breathlessness using available multidimensional instruments such as the Dyspnea-12 and MDP [22,54*,89]. Once detected, clinically relevant levels of negative affective traits require treatment, which still occurs only in a minority of patients with breathlessness [12]. Effective evidence-based treatments include PR [90,91], cognitive behavioral and mindfulness-based psychotherapy [92–94] as well as holistic, multidisciplinary breathlessness services [40,41**], while only weak evidence is available for psychopharmacological treatments [95]. Future systematic research is needed to further confirm the effectiveness of the aforementioned simple interventions such as social and acoustic stimulation, to develop and test new treatment formats such as hypoventilation training [96] and to explore why otherwise effective interventions such as exercise training are less successful in certain patient groups [97,98]. Next to necessary future research on potential mechanisms and influencing factors for affect–breathlessness interactions, mechanisms and pathways underlying successful treatments need further study. For example, the respective cause-relationships remain widely unknown as to why some interventions improve both negative affect and breathlessness, whereas others improve breathlessness, but not negative affect [99] and again others increase breathlessness, but reduce negative affect [96]. Finally, more efforts are needed to effectively implement diagnostic and treatment protocols in clinical settings in order to successfully detect and treat negative affect in patients suffering from breathlessness [23*].

Conclusion:

This literature review observed that non-specific forms of negative affective personality traits are common in patients with breathlessness in several disease domains. Together with disease- or symptom-specific negative affective traits these are related to greater breathlessness.

1   Breathlessness can not only induce negative affective states, but also negative affective states
2   can worsen breathlessness, while positive states can improve breathlessness. Several
3   treatment approaches demonstrated beneficial effects on both negative affect and
4   breathlessness and different potential mechanisms underlying these affect-breathlessness
5   interactions were suggested. Future research is required to improve our knowledge on the
6   mechanisms underlying these associations together with increased clinical efforts for
7   improved detection and treatment of negative affect in patients suffering from breathlessness.

References

1. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185:435–452.
2. Laviolette L, Laveneziana P. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J* 2014; 43:1750–1762.
3. Grønseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. *Eur Respir J* 2014; 43:1610–1620.
4. Ekström M, Johnson MJ, Schiöler L, et al. Who experiences higher and increasing breathlessness in advanced cancer? The longitudinal EPCCS Study. *Support Care Cancer* 2016; 24:3803–3811.
5. Hutchinson A, Barclay-Kling N, Galvin K, Johnson MJ. Living with breathlessness: a systematic literature review and qualitative synthesis. *Eur Respir J* 2018; 51(2):1701477.
6. Booth S, Johnson MJ. Improving the quality of life of people with advanced respiratory disease and severe breathlessness. *Breathe* 2019; 15:198–215.
7. Yohannes AM, Baldwin RC, Connolly MJ. Mood disorders in elderly patients with chronic obstructive pulmonary disease. *Rev Clin Gerontol* 2000; 10:193–202.
8. Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol* 2009; 167:53–60.
9. Spathis A, Booth S, Moffat C, et al. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. *NPJ Prim Care Respir Med* 2017; 27:1-6.
10. von Leupoldt A, Dahme B. Psychological aspects in the perception of dyspnea in obstructive pulmonary diseases. *Respir Med* 2007; 101:411–422.
11. Janssens T, Verleden G, De Peuter S, et al. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. *Clin Psychol Rev* 2009; 29:317–327.
12. von Leupoldt A, Kenn K. The psychology of chronic obstructive pulmonary disease. *Curr Opin Psychiatry* 26:458–463.
13. von Leupoldt A, van den Bergh, O, Davenport, PW. Anxiety, depression and panic. In: *Dyspnea: mechanisms, measurement and management*. 3rd ed. Edited by Mahler, DA, O'Donnell, Denis E (editors). Boca Raton: CRC Press; 2014. pp. 129–143.

- 1 14. Scano G, Gigliotti F, Stendardi L, Gagliardi E. Dyspnea and emotional states in health
2 and disease. *Respir Med* 2013; 107:649–655.
3
- 4 15. Hayen A, Herigstad M, Pattinson KTS. Understanding dyspnea as a complex
5 individual experience. *Maturitas* 2013; 76:45–50.
- 6 16. Johnson MJ, Fallon M. Chronic breathlessness: time for Cinderella to go to the ball!
7 *Eur Respir J* 2018; 52(3):1801452.
- 8 17. ** Yohannes AM, Dryden S, Hanania NA. Validity and responsiveness of
9 the Depression Anxiety Stress Scales-21 (DASS-21) in COPD. *Chest* 2019; 155:1166–1177.
10 Very interesting study validating the DASS-21 as a tool for measuring anxiety, depression and
11 stress in a large sample of COPD patients undergoing pulmonary rehabilitation. Findings
12 highlight the strong interrelationships between breathlessness and anxiety, depression and
13 stress pre-post rehabilitation.
- 14 18. * McKenzie E, Zhang L, Chan S, et al. Symptom correlates of dyspnea in advanced
15 cancer patients using the Edmonton Symptom Assessment System. *Support Care Cancer*
16 2020; 28:87–98. Interesting study demonstrating cross-sectionally and prospectively that
17 comorbid symptoms including anxiety and depression are associated with greater severity
18 and/or frequency of breathlessness in cancer patients.
- 19 19. ** Trevisan C, Vianello A, Zanforlini BM, et al. The mutual association between
20 dyspnea and depressive symptoms in older adults: a 4-year prospective study. *Aging Ment*
21 *Health* 2019; 1–8. Informative large prospective study in community-dwelling older
22 individuals with chronic conditions showing mutual associations between breathlessness and
23 depression. The main findings highlight that onset, persistence or worsening of breathlessness
24 can increase the risk of developing or worsening depressive symptoms. At the same time,
25 incident or persistent depressive symptoms can increase the risk of breathlessness over 4-
26 years of follow-up.
- 27 20. ** von Siemens SM, Jörres RA, Behr J, et al. Effect of COPD severity and
28 comorbidities on the result of the PHQ-9 tool for the diagnosis of depression: results from the
29 COSYCONET cohort study. *Respir Res* 2019; 20:30. Very informative multicenter study in a
30 large sample of COPD patients demonstrating that breathlessness contributes more strongly to
31 depression scores than exacerbations. In addition, different comorbidities and patient
32 characteristics had a distinct impact on different depression items/problem dimensions.
- 33 21. Auld JP, Mudd JO, Gelow JM, et al. Device-detected congestion is associated with
34 worse patient-reported outcomes in heart failure. *Heart Lung J Crit Care* 2019; 48:208–214.
- 35 22. Sundh J, Bornefalk H, Sköld CM, et al. Clinical validation of the Swedish version of
36 Dyspnoea-12 instrument in outpatients with cardiorespiratory disease. *BMJ Open Respir Res*
37 2019; 6:e000418.
- 38 23. * Kerminen H, Jämsen E, Jäntti P, et al. Implementation of a depression screening

- 1 protocol among respiratory insufficiency patients. *Clin Respir J* 2019; 13:34–42. Very
- 2 informative description of the potential problems to successfully implement a depression
- 3 screening and treatment protocol in an outpatient setting for patients with chronic respiratory
- 4 insufficiency.
- 5 24. Sigurgeirsdottir J, Halldorsdottir S, Arnardottir RH, et al. COPD patients' experiences,
- 6 self-reported needs, and needs-driven strategies to cope with self-management. *Int J Chron*
- 7 *Obstruct Pulmon Dis* 2019; 14:1033–1043.
- 8 25. Zysman M, Burgel PR, Court-Fortune I, et al. Relationship between gender and
- 9 survival in a real-life cohort of patients with COPD. *Respir Res* 2019; 20:191.
- 10 26. Lopes AC, Xavier RF, Ac Pereira AC, et al. Identifying COPD patients at risk for
- 11 worse symptoms, HRQoL, and self-efficacy: A cluster analysis. *Chronic Illn* 2019; 15:138–
- 12 148.
- 13 27. ** Schuler M, Wittmann M, Faller H, Schultz K. The interrelations among aspects of
- 14 dyspnea and symptoms of depression in COPD patients - a network analysis. *J Affect Disord*
- 15 2018; 240:33–40. Very interesting study in a large sample of COPD patients undergoing
- 16 pulmonary rehabilitation suggesting that different aspects of breathlessness are associated via
- 17 different pathways (e.g., different symptoms) to depression. This represents further support for
- 18 the multidimensional concept of breathlessness with advanced network analyses.
- 19 28. * Incalzi RA, Canonica GW, Scichilone N, et al. The COPD multi-dimensional
- 20 phenotype: A new classification from the STORICO Italian observational study. *PloS One*
- 21 2019; 14:e0221889. Interesting cross-sectional findings of an ongoing prospective cohort
- 22 multicentre study trying to identify multi-dimensional COPD phenotypes based on circadian
- 23 rhythms of symptoms such as breathlessness and comorbidities including anxiety and
- 24 depression.
- 25 29. Chow S, Wan BA, Pidduck W, et al. Symptom clusters in patients with breast cancer
- 26 receiving radiation therapy. *Eur J Oncol Nurs* 2019; 42:14-20.
- 27 30. Mosher CE, Secinti E, Hirsh AT, et al. Acceptance and commitment therapy for
- 28 symptom interference in advanced lung cancer and caregiver distress: a pilot randomized trial.
- 29 *J Pain Symptom Manage* 2019; 58:632–644.
- 30 31. Zweers D, de Graaf E, de Graeff A, et al. The predictive value of symptoms for
- 31 anxiety in hospice inpatients with advanced cancer. *Palliat Support Care* 2018; 16:602–607.
- 32 32. Das P, Naing NN, Wan-Arfah N, et al. Depression and quality of life in patients with
- 33 neurological disorder in a Malaysian hospital. *East Asian Arch Psychiatry* 2019; 29:66–70.
- 34 33. Baille G, Perez T, Devos D, et al. Dyspnea is a specific symptom in parkinson's
- 35 disease. *J Park Dis* 2019; 9:785–791.
- 36 34. * Baille G, Chenivresse C, Perez T, et al. Dyspnea: an underestimated symptom in

- 1 Parkinson's disease. *Parkinsonism Relat Disord* 2019; 60:162–166. Important study
- 2 highlighting in a well powered sample that breathlessness is a frequent symptom in
- 3 Parkinson's disease, which is related to disease severity and greater anxiety and depression.
- 4 35. Herzog M, Sucec J, Van Diest I, et al. Reduced neural gating of respiratory sensations
- 5 is associated with increased dyspnoea perception. *Eur Respir J* 2018; 52(1):1800559.
- 6 36. * Currow DC, Chang S, Reddel HK, et al. Breathlessness, anxiety, depression, and
- 7 function-The BAD-F Study: a cross-sectional and population prevalence study in adults. *J*
- 8 *Pain Symptom Manage* 2020; 59:197-205. Large representative Australian population study
- 9 highlighting associations between intensity and duration of breathlessness and anxiety,
- 10 depression and functional status in the general population.
- 11 37. Lee CS, Mudd JO, Lyons KS, et al. Heart failure symptom biology in response to
- 12 ventricular assist device implantation. *J Cardiovasc Nurs* 2019; 34:174–182.
- 13 38. Qian MYY, Politis J, Thompson M, et al. Individualized breathlessness interventions
- 14 may improve outcomes in patients with advanced COPD. *Respirol* 2018; 23:1146–1151.
- 15 39. Lin F-L, Yeh M-L, Lai Y-H, et al. Two-month breathing-based walking improves
- 16 anxiety, depression, dyspnoea and quality of life in chronic obstructive pulmonary disease: a
- 17 randomised controlled study. *J Clin Nurs* 2019; 28:3632–3640.
- 18 40. Brighton LJ, Miller S, Farquhar M, et al. Holistic services for people with advanced
- 19 disease and chronic breathlessness: a systematic review and meta-analysis. *Thorax* 2019;
- 20 74:270–281.
- 21 41. ** Maddocks M, Brighton LJ, Farquhar M, et al (2019) Holistic services for people
- 22 with advanced disease and chronic or refractory breathlessness: a mixed-methods evidence
- 23 synthesis. *Health Serv Deliv Res* 2019; 7. Important mixed-methods evidence synthesis
- 24 including meta-analytic methods and stakeholder surveys on the benefits of holistic
- 25 breathlessness services. Main findings highlight that breathlessness services are highly valued
- 26 by recipients, lead to significant improvements in the distress caused by breathlessness and
- 27 depression and that beneficial outcomes are independent of patient diagnosis, lung function,
- 28 health status, and baseline breathlessness/anxiety/depression.
- 29 42. Kubincová A, Takáč P, Kendrová L, et al. The effect of pulmonary rehabilitation in
- 30 mountain environment on exercise capacity and quality of life in patients with chronic
- 31 obstructive pulmonary disease (COPD) and chronic bronchitis. *Med Sci Mon* 2018; 24:6375–
- 32 6386.
- 33 43. Reijnders T, Schuler M, Wittmann M, et al. The impact of disease-specific fears on
- 34 outcome measures of pulmonary rehabilitation in patients with COPD. *Respir Med* 2019;
- 35 146:87–95.
- 36 44. * Janssens T, Van de Moortel Z, Geidl W, et al. Impact of disease-specific fears on

- 1 pulmonary rehabilitation trajectories in patients with COPD. *J Clin Med* 2019; 8:1460.
- 2 Informative well powered prospective study in COPD patients undergoing inpatient
- 3 pulmonary rehabilitation. The main findings on different disease-specific fears highlight their
- 4 trajectory over pre-, post- and 6-months after rehabilitation as well as their interactions with
- 5 symptom burden.
- 6 45. Pehlivan E, Balci A, Kilic L, Kadakal F. Preoperative pulmonary rehabilitation for
- 7 lung transplant: effects on pulmonary function, exercise capacity, and quality of life; first
- 8 results in Turkey. *Exp Clin Transplant* 2018; 16:455–460.
- 9 46. Sahin H, Naz I. Comparing the effect of pulmonary rehabilitation in patients with
- 10 uncontrolled and partially controlled asthma. *J Asthma* 2019; 56:87–94.
- 11 47. Vardar-Yagli N, Calik-Kutukcu E, Saglam M, et al. The relationship between fear of
- 12 movement, pain and fatigue severity, dyspnea level and comorbidities in patients with chronic
- 13 obstructive pulmonary disease. *Disabil Rehabil* 2019; 41:2159–2163.
- 14 48. Mathew AR, Yount SE, Kalhan R, Hitsman B. Psychological functioning in patients
- 15 with chronic obstructive pulmonary disease: a preliminary study of relations with smoking
- 16 status and disease impact. *Nicotine Tob Res* 2019; 21:686–690.
- 17 49. * Herzog M, Sucec J, Van Diest I, et al. The presence of others reduces dyspnea and
- 18 cortical neural processing of respiratory sensations. *Biol Psychol* 2019; 140:48–54.
- 19 Informative experimental study in healthy individuals demonstrating that the mere presence
- 20 of an observer can reduce breathlessness and threat as well as the neural processing of
- 21 respiratory sensations.
- 22 50. * Benke C, Krause E, Hamm AO, Pané-Farré CA. Predictors of behavioral avoidance
- 23 during respiratory symptom provocation. *Behav Res Ther* 2019; 112:63–67. * Informative
- 24 experimental study in healthy individuals demonstrating that greater negative affective
- 25 personality traits can predict the avoidance of breathlessness during a symptom provocation
- 26 task using resistive loads and breath holding. This highlights the potential role of fearful
- 27 avoidance for breathless patients with low levels of physical activity.
- 28 51. Iosifyan M, Schmidt M, Hurbault A, et al. “I had the feeling that I was trapped”: a
- 29 bedside qualitative study of cognitive and affective attitudes toward noninvasive ventilation in
- 30 patients with acute respiratory failure. *Ann Intensive Care* 2019; 9:134.
- 31 52. * Morélot-Panzini C, Perez T, Sedkaoui K, et al. The multidimensional nature of
- 32 dyspnoea in amyotrophic lateral sclerosis patients with chronic respiratory failure: air hunger,
- 33 anxiety and fear. *Respir Med* 2018; 145:1–7. Informative study demonstrating that
- 34 breathlessness in ALS patients is strongly related to fear and anxiety, partly due to experiences
- 35 with non-invasive ventilation.
- 36 53. Banzett RBB, Sheridan AR, Baker KM, et al. “Scared to death” dyspnoea from the
- 37 hospitalised patient’s perspective. *BMJ Open Respir Res* 2020; 7:e000493.

- 1 54. * Stevens JP, Sheridan AR, Bernstein HB, et al. A multidimensional profile of dyspnea
2 in hospitalized patients. *Chest* 2019; 156:507–517. Informative study providing a
3 multidimensional portrait of breathlessness in a general population of hospitalized patients,
4 which highlights the sensations and affective responses these patients experience.
- 5 55. Good J, Dogra S. Subjective responses to sprint interval exercise in adults with and
6 without exercise-induced bronchoconstriction. *J Asthma* 2018; 55:1059–1067.
- 7 56. * Kanezaki M, Terada K, Ebihara S. Effect of Olfactory Stimulation by L-Menthol on
8 Laboratory-Induced Dyspnea in COPD. *Chest* 2020. Interesting study demonstrating that
9 olfactory stimulation with L-menthol might be an effective adjunct therapy for reducing
10 breathlessness and anxiety in COPD patients, which might optimize benefits of IMT or PR.
- 11 57. Perkins-Porras L, Riaz M, Okekunle A, et al. Feasibility study to assess the effect of a
12 brief mindfulness intervention for patients with chronic obstructive pulmonary disease: A
13 randomized controlled trial. *Chron Respir Dis* 2018; 15:400–410.
- 14 58. * Peng CS, Baxter K, Lally KM. Music intervention as a tool in improving patient
15 experience in palliative care. *Am J Hosp Palliat Care* 2019; 36:45–49. Encouraging study
16 demonstrating that a simple music intervention can lead to improvements in anxiety,
17 depression and dyspnea in palliative care patients.
- 18 59. Van Den Houte M, Van Oudenhove L, Bogaerts K, et al. Relationship between
19 different experimental measures of distorted symptom perception in functional syndrome
20 patients. *Psychosom Med* 2019; 81:441–448.
- 21 60. Boucly A, Morélot-Panzini C, Garcia G, et al. Intensity and quality of exertional
22 dyspnoea in patients with stable pulmonary hypertension. *Eur Respir J* 2020; 55(2):1802108.
- 23 61. * Marines-Price R, Bernhardt V, Bhammar DM, Babb TG. Dyspnea on exertion
24 provokes unpleasantness and negative emotions in women with obesity. *Respir Physiol*
25 *Neurobiol* 2019; 260:131–136. Informative experimental study demonstrating correlations
26 between exertional breathlessness and negative affective states in obese women.
- 27 62. Balmain BN, Weinstein K, Bernhardt V, et al. Multidimensional aspects of dyspnea in
28 obese patients referred for cardiopulmonary exercise testing. *Respir Physiol Neurobiol* 2020;
29 274:103365.
- 30 63. Bernhardt V, Bhammar DM, Marines-Price R, Babb TG. Weight loss reduces dyspnea
31 on exertion and unpleasantness of dyspnea in obese men. *Respir Physiol Neurobiol* 2019;
32 261:55–61.
- 33 64. * Herzog M, Sucec J, Vukovic M, et al. Experimental social rejection increases
34 dyspnoea perception and neural processing of respiratory sensations in healthy subjects. *Eur*
35 *Respir J* 2019; 53:1801409. Informative experimental study in healthy individuals using a
36 virtual ball tossing game to induce feelings of social inclusion vs. exclusion. Social exclusion

- 1 led to increased resistive load-induced breathlessness and negative affective state.
- 2 65. Sucec J, Herzog M, Van den Bergh O, et al. The effect of dyspnea on recognition
3 memory. *Int J Psychophysiol* 2020; 148:50–58.
- 4 66. Sucec J, Herzog M, Van Diest I, et al. The impairing effect of dyspnea on response
5 inhibition. *Int J Psychophysiol* 2018; 133:41–49.
- 6 67. * Sucec J, Herzog M, Van den Bergh O, et al. T The effects of repeated dyspnea
7 exposure on response inhibition. *Front Physiol* 2019; 10:663. Informative experimental study
8 in healthy individuals highlighting that resistive load-induced breathlessness is paralleled by
9 increased negative affect and impaired performance in a cognitive test. These effects improve
10 after daily, brief controlled exposure to resistive loads over 5-days, which might be relevant to
11 support treatments.
- 12 68. Sucec J, Herzog M, Van Diest I, et al. The impact of dyspnea and threat of dyspnea on
13 error processing. *Psychophysiology* 2019; 56:e13278.
- 14 69. Benke C, Krause E, Hamm AO, Pané-Farré CA. Dynamics of defensive response
15 mobilization during repeated terminations of exposure to increasing interoceptive threat. *Int J*
16 *Psychophysiol* 2018; 131:44-56.
- 17 70. Tan Y, Vandeput J, Qiu J, et al. The error-related negativity for error processing in
18 interoception. *NeuroImage* 2018; 184:386–395.
- 19 71. Sharma P, Hall L, Morris NR, et al. Experimental modulation of mood by acoustic
20 stimulation and its effect on exertional dyspnoea. *Thorax* 2019; 74:707–710.
- 21 72. Chan PYS, Wu YT, Hsu AL, et al (2019) The effect of anxiety on brain activation
22 patterns in response to inspiratory occlusions: an fMRI study. *Sci Rep* 9:15045.
- 23 73. * Stoeckel MC, Esser RW, Gamer M, von Leupoldt A. Breathlessness amplifies
24 amygdala responses during affective processing. *Psychophysiology* 2018; 55:e13092.
25 Informative fMRI study in healthy individuals suggesting an important role of the amygdala
26 for mediating the interactions between breathlessness and affective states.
- 27 74. Tan Y, Van den Bergh O, Qiu J, von Leupoldt A. The impact of unpredictability on
28 dyspnea perception, anxiety and interoceptive error processing. *Front Physiol* 2019; 10:535.
- 29 75. Kato A, Takahashi K, Homma I. Relationships between trait and respiratory
30 parameters during quiet breathing in normal subjects. *J Physiol Sci* 2018; 68:369–376.
- 31 76. Hanania NA, O'Donnell DE. Activity-related dyspnea in chronic obstructive
32 pulmonary disease: physical and psychological consequences, unmet needs, and future
33 directions. *Int J Chron Obstruct Pulmon Dis* 2019; 14:1127–1138.
- 34 77. Ryan R, Spathis A, Clow A, Booth S. Breathlessness and inflammation: potential
35 relationships and implications. *Curr Opin Support Palliat Care* 2016; 10:242–248.

- 1 78. Van Diest I. Interoception, conditioning, and fear: The panic threesome.
2 Psychophysiology 2019; 56:e13421.
- 3 79. Sandberg J, Ekström M. Differences between experienced and recalled breathlessness:
4 a review. Curr Opin Support Palliat Care 2019; 13:161–166.
- 5 80. Marlow LL, Faull OK, Finnegan SL, Pattinson KTS. Breathlessness and the brain: the
6 role of expectation. Curr Opin Support Palliat Care 2019; 13:200–210.
- 7 81. Lee SH, Kim KU, Lee H, et al. Sleep disturbance in patients with mild-moderate
8 chronic obstructive pulmonary disease. Clin Respir J 2019; 13:751–757.
- 9 82. Lehto K, Pedersen NL, Almqvist C, et al. Asthma and affective traits in adults: a
10 genetically informative study. Eur Respir J 2019; 53(5):1802142.
- 11 83. Zhu Z, Zhu X, Liu C-L, et al. Shared genetics of asthma and mental health disorders: a
12 large-scale genome-wide cross-trait analysis. Eur Respir J 2019; 54(6):1901507.
- 13 84. Stoeckel MC, Esser RW, Gamer M, et al. Dyspnea catastrophizing and neural
14 activations during the anticipation and perception of dyspnea. Psychophysiology 2018; 55.
- 15 85. Reijnders T, Troosters T, Janssens W, et al. Brain activations to dyspnea in patients
16 with COPD. Front. Physiol. 2020; 11:7.
- 17 86. Spilling CA, Bajaj M-PK, Burrage DR, et al. Contributions of cardiovascular risk and
18 smoking to chronic obstructive pulmonary disease (COPD)-related changes in brain structure
19 and function. Int J Chron Obstruct Pulmon Dis 2019; 14:1855–1866.
- 20 87. Abdallah SJ, Faull OK, Wanigasekera V, et al. Opioids for breathlessness:
21 psychological and neural factors influencing response variability. Eur Respir J 2019;
22 54(3):1900275.
- 23 88. Baker AM, Holbrook JT, Yohannes AM, et al. Test performance characteristics of the
24 air, GAD-7, and HADS-Anxiety screening questionnaires for anxiety in chronic obstructive
25 pulmonary disease. Ann Am Thorac Soc. 2018; 15:926-934.
- 26 89. Williams MT, Johnston KN. Multidimensional measurement of breathlessness: recent
27 advances. Curr Opin Support Palliat Care 2019; 13:184–192.
- 28 90. Osadnik CR, Singh S. Pulmonary rehabilitation for obstructive lung disease.
29 Respirology 2019; 24:871–878.
- 30 91. Gordon CS, Waller JW, Cook RM, et al. Effect of pulmonary rehabilitation on
31 symptoms of anxiety and depression in COPD: a systematic review and meta-analysis. Chest
32 2019; 156:80–91.
- 33 92. Pollok J, van Agteren JE, Esterman AJ, Carson-Chahhoud KV. Psychological therapies
34 for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database

- 1 Syst Rev 2019; 3(3):CD012347
- 2 93. Heslop-Marshall K, Baker C, Carrick-Sen D, et al. Randomised controlled trial of
3 cognitive behavioural therapy in COPD. *ERJ Open Res* 2018; 4(4):00094-2018.
- 4 94. Farver-Vestergaard I, O'Toole MS, O'Connor M, et al. Mindfulness-based cognitive
5 therapy in COPD: a cluster randomised controlled trial. *Eur Respir J* 2018; 51(2):1702082.
- 6 95. Pollok J, van Agteren JE, Carson-Chahhoud KV. Pharmacological interventions for the
7 treatment of depression in chronic obstructive pulmonary disease. *Cochrane Database Syst*
8 *Rev* 2018; 12(12):CD012346.
- 9 96. Meuret AE, Ritz T, Wilhelm FH, et al. Hypoventilation therapy alleviates panic by
10 repeated induction of dyspnea. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018; 3:539–
11 545.
- 12 97. Cavalheri V, Burtin C, Formico VR, et al. Exercise training undertaken by people
13 within 12 months of lung resection for non-small cell lung cancer. *Cochrane Database Syst*
14 *Rev* 2019; 6(6):CD009955.
- 15 98. Peddle-McIntyre CJ, Singh F, Thomas R, et al. Exercise training for advanced lung
16 cancer. *Cochrane Database Syst Rev* 2019; 2(2):CD012685.
- 17 99. Kako J, Morita T, Yamaguchi T, et al. Fan therapy is effective in relieving dyspnea in
18 patients with terminally ill cancer: A parallel-arm, randomized controlled trial. *J Pain*
19 *Symptom Manage* 2018; 56:493–500.

20
21
22

Figure 1:
Schematic illustration of the interactions between negative affective traits, states and breathlessness with potential influencing factors and mechanisms

Key points:

- Non-specific forms of negative affective personality traits such as anxiety and depression are common in patients suffering from breathlessness.
- Non-specific as well as disease- or symptom-specific negative affective traits are typically related to increased levels of breathlessness.
- Breathlessness evokes negative affective states and negative affective states can worsen breathlessness, while positive affective states can improve breathlessness.
- Several treatment approaches demonstrated concurrent beneficial effects on both negative affect and breathlessness.
- Future research is required on the precise mechanisms underlying these affect-breathlessness associations together with increased clinical efforts for improved detection and treatment of negative affect in patients suffering from breathlessness.

1   **Acknowledgements:**

2

3   *Financial support and sponsorship:*

4   AvL is supported by research grants from the Research Foundation – Flanders (FWO), Belgium
5   (GOA4516N and GOA3718N), by an infrastructure grant from the FWO and the Research Fund
6   KU Leuven, Belgium (AKUL/19/06; I011320N), and by the “Asthenes” long-term structural
7   funding Methusalem grant (METH/15/011) by the Flemish Government, Belgium.

8

9   *Conflicts of interest:*

10   none