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Original Research

Associations of comorbid heart disease and depression/anxiety with multidimensional breathlessness in COPD – A cross-sectional study

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ABSTRACT

Background: Comorbid conditions and breathlessness are associated with poor outcomes in chronic obstructive pulmonary disease (COPD). We evaluated the associations of comorbid heart disease and depression/anxiety with breathlessness in daily life among people with COPD.

Methods: Cross-sectional analysis from the PRAXIS cohort in central Sweden. Data on patient characteristics and the modified Medical Research Council (mMRC) and Dyspnea-12 breathlessness instruments (D-12) were obtained from questionnaires in 2022. Lung function data were collected from record review. Outcome variables were clinically significant breathlessness defined as mMRC≥2 and D-12 total (>2.7), physical (>1.4) and affective (>1.2) scores above published minimal clinical important differences. Associations of heart disease and depression/anxiety with each outcome were analyzed using multivariable Poisson regression adjusted for relevant confounders.

Results: In 522 included patients, mMRC ≥2 was present in 59 % and increased D-12 total, physical and affective domain scores in 69 %, 74 %, and 50 %, respectively. Heart disease was independently associated with mMRC (relative risk ratio [95 % confidence interval] 1.34 [1.17–1.53]), D12 physical domain (1.12[1.02–1.24]) and D-12 affective domain (1.20[1.02–1.42]). Depression/anxiety was independently associated with increased D-12 affective domain (1.25[1.04–1.49]). In addition, previous exacerbations and GOLD stage 3–4 were associated with mMRC and D-12, respectively.

Conclusion: In COPD, comorbid heart disease is associated with both activity-related breathlessness and with physical and affective domains of breathlessness while depression/anxiety is associated with the affective domain of breathlessness. As the influence of different dimensions of breathlessness may differ according to comorbidity the D-12 instrument adds more information when assessing breathlessness in patients with COPD.

1. Introduction

Breathlessness is a cardinal symptom in patients with chronic obstructive pulmonary disease (COPD) [1–3] and is associated with reduced physical capacity and activity, impaired health-related quality of life [4,5], and shorter survival [6,7]. Breathlessness is defined as a

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subjective experience of breathing discomfort, is multifactorial and consists of qualitatively distinct sensations that vary in intensity [8,9]. To reduce breathlessness is a major management target in COPD but patients with COPD suffer from persistent breathlessness despite maximal pharmacological treatment [8,10]. Comorbidities such as heart disease and depression have been suggested to play an important role in persistent breathlessness in this patient group [11], and the importance of optimal treatment of underlying comorbidities has been highlighted [2].

Traditionally, breathlessness has been evaluated mainly using the modified Medical Research Council (mMRC) scale, which measures breathlessness related to physical activity. Clinically significant activity-related breathlessness is often defined as mMRC≥2, corresponding to walking slower than people of the same age or having to stop for breath when walking at one's own pace on level ground, or worse [1,5].

In recent years, it has been emphasized that breathlessness is multidimensional and includes both physical and affective dimensions [12]. The Dyspnea-12 (D-12) questionnaire [13,14] was developed and validated to measure different dimensions of dyspnea experienced in everyday life in COPD as well as in heart disease [15–17]. Different interventions may affect different domains of breathlessness, for example pulmonary rehabilitation has been suggested to mainly improve the affective dimension of breathlessness and symptom mastery although the overall symptom intensity in daily life is relatively unchanged [18].

Recent studies have shown that fatigue and health-related quality of life are both associated with breathlessness as measured by D-12 [19]. However, knowledge of whether the important comorbid conditions heart disease and depression/anxiety are associated with breathlessness and its different dimensions is lacking. The aim of the present study was to investigate and compare the associations of comorbid heart disease and depression/anxiety with activity-related breathlessness and dimensions of breathlessness in daily life in patients with COPD.

2. Material and methods

2.1. Design and data collection

This was a cross sectional analysis of the second COPD cohort of the Swedish PRAXIS study, including 13 hospitals and 76 primary healthcare centers from seven regions in central Sweden. In 2014, a list of all patients 18–75 years old with a diagnosis of COPD (ICD-code J44) was compiled, from which 2310 patients were randomly selected [20–25]. An invitation letter with study information, a letter of consent, and a questionnaire on patient characteristics were sent to the randomly selected patients, resulting in a baseline cohort of 1703 patients for which complementary record review on spirometry was performed (Fig. 1). In 2022, an extended follow-up questionnaire used for the present study was sent to all patients still alive. The follow-up questionnaire collected information on sex, age, weight, height, smoking history, history of COPD exacerbations, comorbid conditions and the Swedish versions of mMRC [26] and D-12(14).

2.2. Variables

Heart disease was defined as self-reported doctor's diagnosis of angina pectoris, myocardial infarction, heart failure or atrial fibrillation. Depression/anxiety was defined as self-reported conditions with self-reported pharmacological or non-pharmacological treatment for the disorders, during the previous year. An exacerbation was defined as worsening of respiratory symptoms resulting in an emergency visit to primary or secondary care or need for an oral course with corticosteroids or antibiotics, during the previous twelve months. Age was categorized in four groups: <70, 70–74, 75–80 and ≥ 81 years. Body mass index (BMI) was calculated as weight/(height)^2 (kg/m^2) and categorized based on previous knowledge of prognostic values as <22, 22–30, and ≥30 [27]. Smoking status was categorized as never, former, occasional, and current daily smoking. COPD staging was based on the results of dynamic spirometry including forced expiratory volume in 1 s in percent of predicted value (FEV_1 % pred), and categorized according to Global Initiative on Obstructive Lung Disease (GOLD) [1] as stage 1 (FEV_1 % pred≥80 %), stage 2 (50 % ≥FEV_1 % pred<80 %), stage 3 (30 % ≤FEV_1 % pred<50 %) or stage 4 (FEV_1 % pred<30 %). Post-bronchodilator values were used but were substituted with pre-bronchodilator values if post-bronchodilator values were not available. Due to few patients in stage 4, GOLD stages 3 and 4 were combined in the analyses.

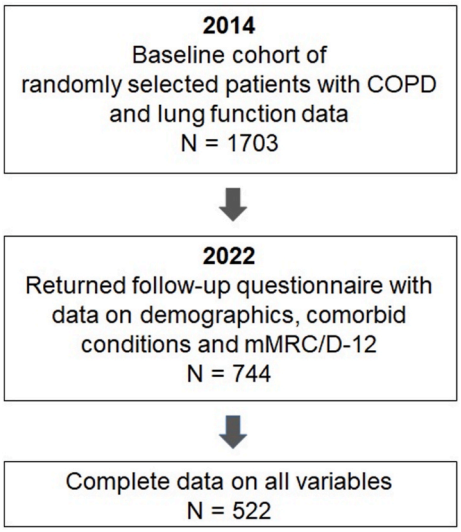

Fig. 1. Participant flow chart. Abbreviations: COPD = Chronic Obstructive Pulmonary Disease, N = Number.

The mMRC breathlessness scale measures activity-related breathlessness in five steps (0–4) from 0 (breathless only with strenuous exercise) to 4 (being too breathless to leave the house or breathless when getting dressed) [5] (Supplemental Fig. S1). The scores were dichotomized with the cut-off mMRC≥2, defining clinically significant breathlessness as walking slower than people of the same age or having to stop for breath when walking at one's own pace on level ground, or worse [5].

The validated Swedish version of D-12 [14] was used to measure breathlessness "these days", in daily life, overall, and in different dimensions. D-12 measures breathlessness by twelve items with descriptors of breathlessness. Each item is rated from 0 to 3 with 0 denoting no- and 3 severe breathlessness. The maximum total score is 36, and a higher score indicates worse breathlessness. The first seven items constitute a physical domain (maximum score 21), and the remaining five items are an affective domain (maximal score 15) (Supplemental Fig. S2). The total and domain D-12 scores were calculated, and we also chose to define clinically relevant increased D-12 total and domain scores as rating above the minimal clinically important differences (MCID). An increased dimension score was defined as a rating above the previously published minimal clinically important differences (MCID) for each D-12 score; 2.7 for the total score, 1.4 for the D-12 physical domain, and 1.2 for the affective domain [17]. The rationale for this definition was to identify patients who had a symptom rating that was likely to be clinically relevant, as one unit's difference in a multi-item scale might not represent a clinical significance in symptoms [26].

2.3. Statistics

Statistical analyses were performed using IBM SPSS version IBM SPSS version 29.0 (IBM Corporation, Armonk, NY) and STATA release 17 (Stata Corp., College Station, TX).

Cross-tabulation with chi-squared tests were used to present baseline data by sex and for attrition analyses comparing sex and age at baseline in the follow-up population and the excluded patients. Multivariable Poisson regression with robust standard errors was used to study associations of heart disease and depression/anxiety with mMRC ≥2 and with the binarised MCID variables of D-12 and its domains. Poisson regression gives relative risk ratios (RR) as association measure. Multivariable negative binomial regression with robust standard errors was used to study associations with the MCID variables of D-12 and its domains on quantitative scale. Negative binomial regression gives incidence rate ratios (IRR) as association measures, an IRR of 1.20 interprets as 20 % higher D-12 mean in exposed compared to unexposed group. Results were adjusted for sex, age (four groups), BMI (three groups), smoking status (four groups), exacerbations (during the previous twelve months), and GOLD spirometric stages (three groups). The potential confounders were chosen a priori based on previous knowledge [2, 28–31].

In all analyses, $p < 0.05$ was considered statistically significant.

2.4. Ethics

The study was performed in accordance with the principles of the revised Declaration of Helsinki. All participants gave written informed consent. The study was approved by the Regional Ethical Board in Uppsala, Sweden, Dnr 2011/318 (PRAXIS 2014) and the Swedish Ethical Review Authority Dnr 2021–03537 (PRAXIS follow up 2022).

3. Results

A total of 522 patients with COPD (56 % female, mean age 74 years (range 51–85 years) had complete data on mMRC, D-12 and confounders and were included in the analyses (Table 1 and Fig. 1). Of the included patients, 140 (27 %) had comorbid heart disease, 64 (12 %) had comorbid depression/anxiety, and another 37 patients (7 %) had both comorbid heart disease and depression/anxiety (Table 1). Attrition analysis showed that excluded patients were significantly older at baseline but did not differ by sex (Table 2).

In total, 308 (59 %) patients had activity-related breathlessness with mMRC≥2. As for D-12, 359 (69 %), 386 (74 %), and 263 (50 %) had increased total, physical and affective domain scores, respectively. Median (interquartile range (IQR)) for mMRC was 1 (1–2) and median (IQR) for D12 total, physical and affective scores were 7.0 (1.8–16.0), 5.0 (1.0–5.0) and 2.0 (2.0–6.0), respectively (Fig. 2). The prevalence of clinically significantly increased mMRC and D-12 scores were all higher in patients with heart disease and depression/anxiety compared with patients with no heart disease or depression/anxiety, and highest in patients with both conditions (Fig. 3).

The results from the multivariable regression analyses are shown in Table 3 and 4 and Fig. 4. In summary, heart disease was independently associated with mMRC (Relative risk ratio (RR) [95 %CI] 1.34 [1.17–1.53], D-12 physical domain (1.12 [1.02–1.24]) and D-12 affective domain (1.20 [1.02–1.42]) scores. Depression/anxiety was independently associated with increased D-12 affective domain score (1.25 [1.04–1.49]).

In addition to the main explanation variables of heart disease and depression/anxiety, mMRC ≥2 was also independently associated with female sex, obesity, exacerbations and lower lung function. Increased D-12 total and physical scores were associated with obesity, exacerbations, lower lung function, and inversely associated with older age. The affective dimension of D-12 was associated with exacerbations and lower lung function (Table 3). The associations of GOLD stage 3–4 with mMRC and D-12 and of exacerbations with D-12 were stronger than all other investigated associations, including heart disease and depression (Table 3).

Table 1
Patient characteristics.

	Total n = 522(100 %)	Women n = 294 (56 %)	Men n = 228 (44 %)
Heart disease n(%)	177 (34)	87 (30)	90 (39)
Depression or anxiety n (%)	101 (19)	72 (24)	29 (13)
Age (years) n(%)			
<70	125 (24)	78 (27)	47 (21)
70-74	108 (21)	60 (20)	48 (21)
75-79	186 (36)	93 (32)	93 (41)
≥80	103 (20)	63 (21)	40 (18)
Smoking n(%)			
Never	30 (6)	15 (5)	15 (7)
Former	386 (74)	219 (74)	167 (73)
Occasional	26 (5)	16 (5)	10 (4)
Current	80 (15)	44 (15)	36 (16)
BMI (kg/m^2) n(%)			
<22.0	99 (19)	65 (22)	34 (15)
22.0–29.9	286 (55)	153 (52)	133 (58)
≥ 30.0	137 (26)	76 (26)	61(27)
Exacerbations n(%)	193 (37)	118 (40)	75 (33)
GOLD stage n(%)	94 (18)	51 (17)	43 (19)
I	291 (56)	168 (57)	123 (54)
II	117 (22)	65 (22)	52 (23)
III	20 (4)	10 (3)	10 (4)
IV			

Patient characteristics distributed by sex, data presented as frequencies and column percentages. *Abbreviations: BMI = body mass index, GOLD = Global initiative for Chronic Obstructive Lung Disease, n = number.*

Table 2
Patient characteristics in included and excluded patients.

	Included n = 52	Excluded n = 744
Female sex n(%)	294 (56)	140 (63)
Age n (%)		
<70	125 (24)	45 (20)
70–74	108 (21)	53 (24)
75–79	186 (36)	72 (32)
≥80	103 (20)	52 (23)
Smoking status n(%)		
Never	30 (6)	14 (7)
Former	386 (74)	151 (70)
Occasional	26 (5)	13 (6)
Current	80 (15)	38 (18)
BMI n(%)		
<22	99 (19)	37 (20)
22–29.9	286 (55)	110 (58)
≥30	137 (26)	42 (22)
Exacerbations n(%)	193 (37)	75 (34)
GOLD n (%)		
I	94 (18)	16 (19)
II	291 (56)	46 (54)
III-IV	127 (26)	24 (28)
Heart disease n(%)	177(34)	69 (31)
Depression/anxiety n(%)	101 (19)	40 (18)
mMRC2 ≥2 n(%)	312 (60)	115 (60)
D12 total ≥2.7 n(%)	359 (69)	105 (65)
D12 physical ≥1.4 n(%)	386 (74)	107 (66)
D12 affective ≥1.2 n(%)	263 (50)	77 (48)

Patient characteristics in included and excluded patients, data presented as frequencies and column percentages. *Abbreviations: BMI = body mass index, GOLD = Global initiative for Chronic Obstructive Lung Disease,mMRC = modified Medical Research Council, D-12 = Dyspnea 12, n = number.*

4. Discussion

The main finding of this study is that comorbid heart disease and depression/anxiety are associated with increased risk and severity of breathlessness in patients with COPD. This was found both for activity-related as well as physical and affective dimensions of breathlessness. To make a clinical point, heart disease seems to influence all dimensions of breathlessness, but especially activity-related and physical

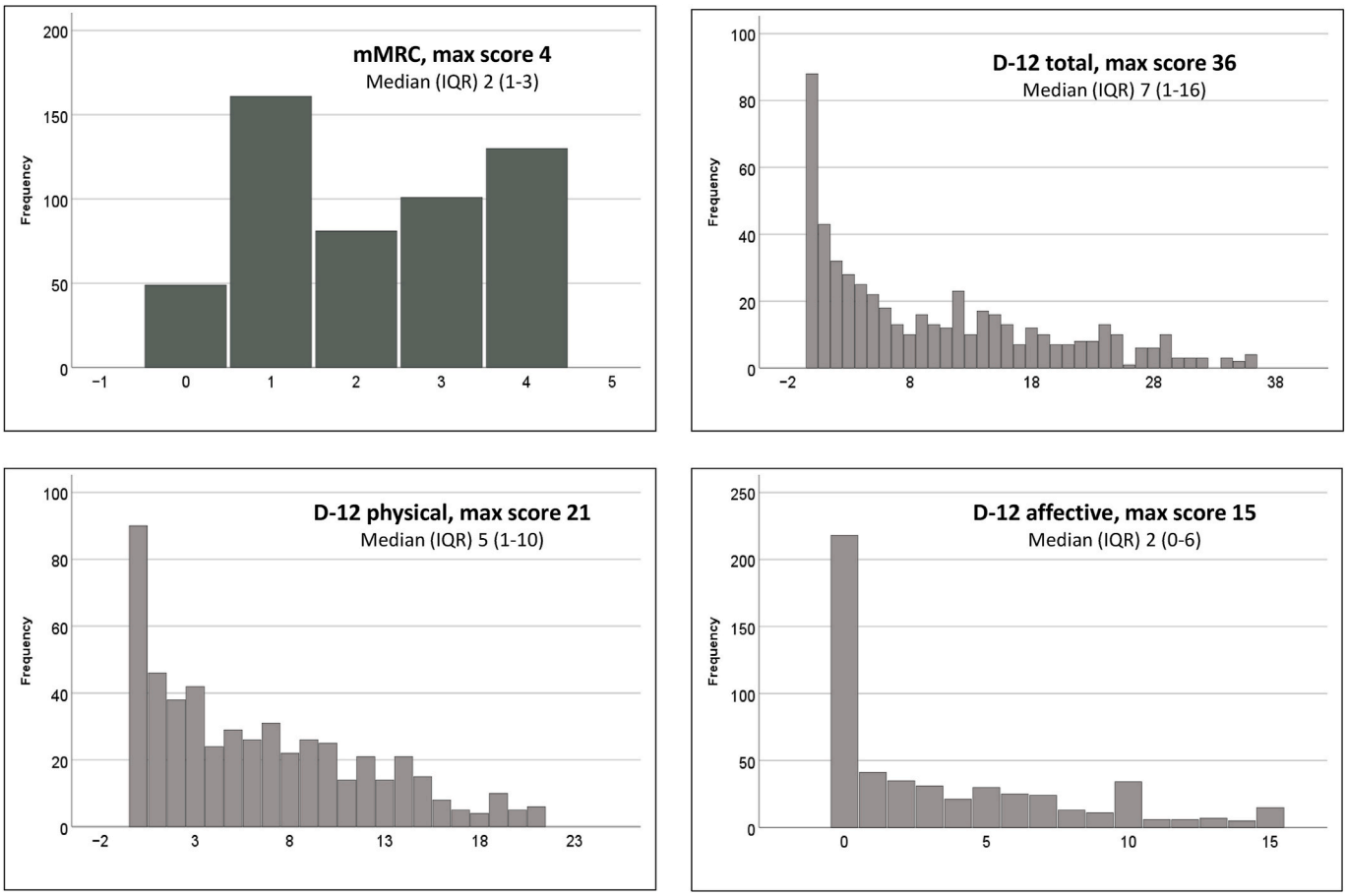

Fig. 2. Distribution of breathlessness in relation to physical activity (mMRC) and daily life (D-12 total-, physical- and affective dimensions) in the studied population.
Abbreviations: mMRC = modified Medical Research Council, D-12 = Dyspnea-12, IQR = Interquartile range.

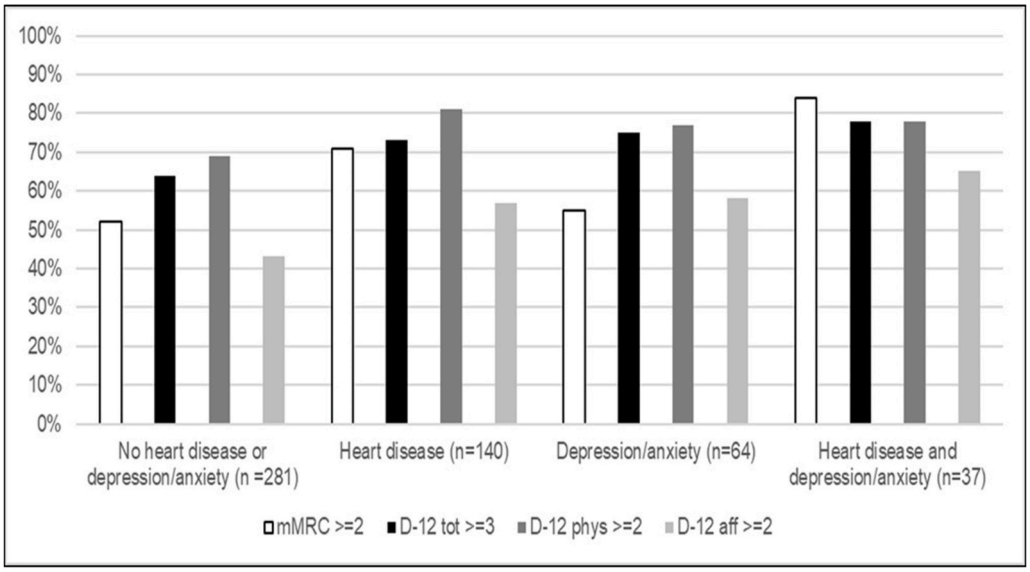

Fig. 3. Daily-life breathlessness in COPD with comorbid conditions
Prevalence of clinically significant breathlessness, defined as mMRC≥2, and D-12 scores minimal clinical important difference from zero, in COPD with comorbid conditions. Abbreviations: COPD = chronic obstructive pulmonary disease, D-12 = Dyspnoea-12, mMRC = modified Medical Research Council.

breathlessness. In contrast, depression/anxiety was associated only with the affective dimension of breathlessness.

To our knowledge, this is the first study to evaluate associations of comorbid conditions with different dimensions of breathlessness. Heart disease and depression have previously been shown to be associated with persistent exertional breathlessness as measured by mMRC [2,11,

Table 3
Multivariable Poisson regression of associations with breathlessness.

	mMRC ≥2	D-12 total ≥2.7	D-12 phys ≥1.4	D-12 aff ≥1.2
	AdjustedRR (95 % CI)	AdjustedRR (95 % CI)	AdjustedRR (95 % CI)	AdjustedRR (95 % CI)
Heart disease	**1.34 (1.17 to 1.53)**	1.10 (0.98–1.23)	**1.12 (1.02 to 1.24)**	**1.20 (1.02 to 1.42)**
Depression or anxiety	1.08 (0.92–1.26)	1.12 (0.99–1.28)	1.04 (0.92–1.11)	**1.25 (1.04 to 1.49)**
Female sex	**1.19 (1.03 to 1.36)**	1.00 (0.89–1.12)	1.01 (0.91–1.11)	0.96 (0.81–1.13)
Age (years)				
<70	Ref	Ref	Ref	Ref
70-74	0.83 (0.67–1.03)	**0.81 (0.69 to 0.95)**	**0.86 (0.75 to 0.99)**	0.81 (0.63–1.04)
75-79	1.01 (0.85–1.22)	**0.83 (0.73 to 0.95)**	**0.88 (0.78 to 0.99)**	0.86 (0.70–1.06)
≥80	1.05 (0.86–1.28)	**0.83 (0.71 to 0.97)**	**0.84 (0.72 to 0.97)**	0.90 (0.71–1.13)
Smoking				
Never	0.99 (0.69–1.40)	0.92 (0.66–1.29)	0.85 (0.63–1.15)	0.86 (0.56–1.34)
Former	1.13 (0.90–1.42)	1.13 (0.94–1.35)	1.06 (0.91–1.23)	1.04 (0.81–1.34)
Occasional	0.99 (0.67–1.46)	1.01 (0.74–1.36)	0.94 (0.71–1.25)	0.80 (0.50–1.29)
Current	Ref	Ref	Ref	Ref
BMI (kg/m^2)				
>22.0	0.93 (0.77–1.13)	0.96 (0.82–1.12)	0.94 (0.82–1.09)	1.03 (0.84–1.26)
22.0–29.9	Ref	Ref	Ref	Ref
≥ 30.0	**1.32 (1.14 to 1.53)**	**1.19 (1.06 to 1.34)**	**1.17 (1.06 to 1.30)**	1.12 (0.92–1.35)
Exacerbations	**1.33 (1.16 to 1.51)**	**1.47 (1.32 to 1.63)**	**1.36 (1.24 to 1.49)**	**1.86 (1.57 to 2.21)**
GOLD stages				
I	Ref	Ref	Ref	Ref
II	**1.34 (1.05 to 1.71)**	**1.33 (1.09 to 1.63)**	**1.26 (1.05 to 1.50)**	1.18 (0.90–1.55)
III-IV	**1.68 (1.31 to 2.16)**	**1.53 (1.25 to 1.88)**	**1.40 (1.17 to 1.68)**	**1.60 (1.21 to 2.12)**

Results from Poisson regression, adjusted for sex, age (four groups), BMI (three groups), smoking status (four groups), exacerbations or not previous year and GOLD spirometric stages (three groups). *Abbreviations: BMI = body mass index, CI = confidence interval, D-12 = Dyspnoea-12, GOLD = Global initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, RR = relative risk ratio*

Table 4
Multivariable negative binomial regression of associations with breathlessness.

	D-12 total	D-12 phys	D-12 aff
	Adjusted IRR (95 % CI)	Adjusted IRR (95 % CI)	Adjusted IRR (95 % CI)
Heart disease	1.26 (1.06–1.51)	**1.25 (1.07 to 1.47)**	**1.26 (1.01 to 1.58)**
Depression or anxiety	1.18 (0.96–1.45)	1.09 (0.91–1.31)	**1.37 (1.05 to 1.78)**
Female sex	0.99 (0.82–1.18)	1.01 (0.86–1.19)	0.94 (0.74–1.19)
Age (years)			
<70	Ref	Ref	Ref
70-74	0.82 (0.64–1.06)	0.86 (0.68–1.08)	0.77 (0.55–1.07)
75-79	0.86 (0.68–1.07)	0.87 (0.71–1.07)	0.83 (0.62–1.12)
≥80	0.87 (0.67–1.14)	0.87 (0.68–1.10)	0.90 (0.64–1.27)
Smoking			
Never	0.88 (0.53–1.46)	0.96 (0.60–1.51)	0.75 (0.40–1.40)
Former	0.98 (0.73–1.31)	1.03 (0.80–1.33)	0.88 (0.61–1.27)
Occasional	0.86 (0.53–1.40)	0.93 (0.60–1.44)	0.74 (0.40–1.34)
Current	Ref	Ref	Ref
BMI (kg/m^2)			
>22.0	1.03 (0.80–1.31)	1.00 (0.81–1.25)	1.07 (0.78–1.45)
22.0–29.9	Ref	Ref	Ref
≥ 30.0	**1.28 (1.05 to 1.56)**	**1.28 (1.07 to 1.52)**	1.26 (0.97–1.63)
Exacerbations	**2.04 (1.73 to 2.41)**	**1.88 (1.62 to 2.19)**	**2.37 (1.92 to 2.94)**
GOLD stages			
I	Ref	Ref	Ref
II	**1.42 (1.08 to 1.86)**	**1.39 (1.09 to 1.78)**	1.43 (1.00–2.03)
III-IV	**2.00 (1.50 to 2.65)**	**1.85 (1.43 to 2.39)**	**2.26 (1.56 to 3.27)**

Results from negative binomial regression, adjusted for sex, age (four groups), BMI (three groups), smoking status (four groups), exacerbations or not previous year and GOLD spirometric stages (three groups). *Abbreviations: BMI = body mass index, CI = confidence interval, D-12 = Dyspnoea-12, GOLD = Global initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, IRR = incidence rate ratio.*

32]. We believe that descriptors of breathlessness may be a more sensitive way of capturing the symptom burden in patients with COPD and comorbidity, as the two important studied comorbid conditions both influence breathlessness but in different ways. MCID of D-12 may be a suitable measure to assess the clinically significant effect of pharmacological and non-pharmacological interventions in COPD with comorbid heart disease and depression/anxiety.

Our secondary findings that moderate-severe lung function impairment and a history of exacerbations are associated with persistent breathlessness confirm previously well-known associations [2,32], although the knowledge was extended to include D-12 and its domains. We also confirmed the previously reported association of female sex with increased mMRC [33]. It has previously been reported that healthy women, due to lower lung volume, have a higher prevalence of activity related breathlessness [34], which may explain our finding of increased mMRC in the female patients. Interestingly female sex was not associated with increased D12 scores.

We found that obesity was associated with the activity-related and physical dimension of breathlessness, but not with the affective dimension. This is consistent with previous findings of factors influencing breathlessness in the general population [35]. The finding that higher age was associated with lower risk of total and physical D-12 scores may potentially be explained by the previously shown association between high age and reduced intensity of activity in elderly with COPD [36].

A major strength and a novelty of this study is the high generalizability due to real-world data for patients from both primary and secondary care. Limitations include attrition due to missing lung function data in some patients. Further, as we do not have measurements at a standardized level of exertion, breathlessness may be underestimated in the studied population. It is known that patients with impaired exercise capacity reduce their physical activity level to avoid symptoms and it has been recommended that breathlessness is measured at a standardised level of exertion [37,38]. It is also known that the mMRC scale may misclassify exertional breathlessness [39].

The clinical implication of the study is that it seems appropriate to assess interventions for breathlessness in patients with COPD and heart disease or depression/anxiety with D-12 in daily practice. Subsequently, future use of D-12 in both randomized controlled studies and in clinical praxis is warranted.

5. Conclusion

In patients with COPD, comorbid heart disease is associated with more prevalent and worse breathlessness and with both activity-related and physical and affective domains of breathlessness while depression/anxiety is associated with the affective domain of breathlessness. As the influence of different dimensions of breathlessness may differ according to comorbidity the D-12 instrument with both physical and affective dimensions adds more information when assessing breathlessness in patients with COPD.

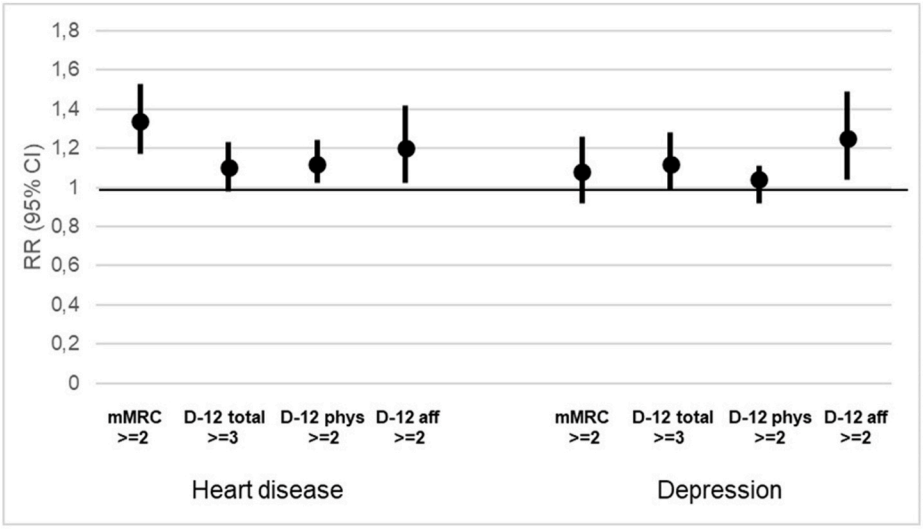

Fig. 4. Associations with having clinically significant breathlessness scores
Results from multivariable logistic regression with clinically significant breathlessness in activity and daily life, in patients with COPD and comorbid heart disease and depression/anxiety. Adjustment was made for sex, age, body mass index, smoking status, exacerbations previous 12 months and lung function. The horizontal solid line indicates no difference (RR = 1) Abbreviations: D-12 = Dyspnoea-12, mMRC = modified Medical Research Council, RR=Relative Risk ratio, CI = confidence interval.

CRediT authorship contribution statement

Gabriella Eliason: Writing – original draft, Formal analysis, Conceptualization. **Magnus Ekström:** Writing – original draft, Conceptualization. **Scott Montgomery:** Writing – original draft, Formal analysis, Conceptualization. **Maaike Giezeman:** Writing – original draft, Conceptualization. **Mikael Hasselgren:** Writing – original draft, Conceptualization. **Christer Janson:** Writing – original draft, Conceptualization. **Marta A. Kisiel:** Writing – original draft, Conceptualization. **Karin Lisspers:** Writing – original draft, Conceptualization. **Anna Nager:** Writing – original draft, Conceptualization. **Hanna Sandelowsky:** Writing – original draft, Conceptualization. **Björn Ställberg:** Writing – original draft, Conceptualization. **Josefin Sundh:** Writing – original draft, Supervision, Methodology, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships unrelated to this work which may be considered as potential competing interests: ME, MG, KL, HS, BS, JS reports a relationship with Astra Zeneca that includes: consulting or advisory and speaking and lecture fees. ME, MS, MG, KL, HS, BS, JS reports a relationship with Boehringer Ingelheim that includes: consulting or advisory and speaking and lecture fees. ME, KS, HS, BS, JS reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. ME reports a relationship with Roche that includes: speaking and lecture fees. MG, HS reports a relationship with Orion Pharma that includes: speaking and lecture fees. HS, JS reports a relationship with Cheisi that includes: consulting or advisory and speaking and lecture fees. KL, HS, BS reports a relationship with GlaxoSmithKline that includes: consulting or advisory and speaking and lecture fees. HS reports a relationship with ALK that includes: consulting or advisory and speaking and lecture fees. HS reports a relationship with TEVA that includes: speaking and lecture fees. JS reports a relationship witTakedah that includes: speaking and lecture fees. HS reports a relationship with Sanofi that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108053.

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