

**Breathlessness, anxiety, depression and function - the BAD-F study: a cross-sectional, population prevalence study in adults.**

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Word count (excluding abstract, references, tables and figures): 2896

Abstract word count: 247

## **ABSTRACT**

### **Introduction**

Chronic breathlessness is associated with depression, but its relationship to anxiety is less clear.

### **Objectives**

This study evaluated associations between chronic breathlessness and: anxiety; depression; functional status in the general population.

### **Methods**

This cross sectional cohort of consenting adults ( $\geq 18$  years) used an online survey. Quota sampling ( $n=3,000$ ) was employed reflecting the 2016 national census for sex, age and place of residence. Other data included: Patient Health Questionnaire for Depression and Anxiety (PHQ-4); the modified Medical Research Council (mMRC) breathlessness scale and the Australia-modified Karnofsky Performance Scale (AKPS). Multinomial logistic regression assessed predictors.

### **Results**

2977 respondents had all relevant scores; female- 51.2%; median age 45.0 (range 18-92). Prevalence of breathlessness ( $mMRC \geq 2$ ) was 2.4%; anxiety 6.0%; depression 2.7%; co-existing anxiety/depression 6.1% and poorer functional status ( $AKPS \leq 60$ ) 1.6%.

Poorest function was in the co-existing anxiety/depression group with 11.6%. The highest proportions of people with breathlessness were found in the co-existing anxiety/depression group (10.6%) and depression only (8.8%).

In multinomial regression, depression only and co-existing anxiety/depression were predicted by older age, longer duration of breathlessness, and poorer functional status ( $AKPS \leq 60$ ). The relationship between poorer functional status and co-existing anxiety/depression was striking (OR 16.1; 95% 8.3, 31.4).

Adjusted odds ratios for breathlessness and: depression only was 5.5 (95% CI 2.3,12.9); and 5.1 for co-existing anxiety/depression group (95% CI 2.7,9.7).

### **Conclusion**

Clinically important breathlessness ( $mMRC \geq 2$ ) was associated with depression only and co-existing anxiety/depression. Poorer function associated with psychological morbidity in the general population requires further research.

Key words: chronic breathlessness, anxiety, depression, population survey, prevalence study

Running Title: Anxiety and chronic breathlessness

## INTRODUCTION

Chronic breathlessness is a distinct clinical syndrome.[1] It is highly prevalent across high income countries, with the likelihood of even higher rates in low and middle income countries.[2-4] Disabling breathlessness in daily life due to chronic breathlessness (measured on the modified Medical Research Council breathlessness scale (mMRC)[5]) is experienced by 2.6% of the population.[5,6] Chronic breathlessness is clinically under-recognised [7] and, even when recognised, under-treated.[8] Chronic breathlessness is associated with poorer physical and mental quality of life, [9] increased health service utilisation, [10,11] and is strongly correlated with depressive symptoms and poorer survival. [12] The picture for anxiety and its impact on chronic breathlessness at the general adult population level is less clear although an association has been noted in older adults.[13] It is likely that researchers and clinicians may have simply extrapolated the effects of acute breathlessness and anxiety into the context of chronic breathlessness.

Anxiety and depression are also highly prevalent across the community; they often coexist, [10] are under-recognised and under-treated. [10-14] Lifetime prevalence rates for anxiety are 16.6% in people aged 18-64 years. [14] Using measurement tools from those on which this study relies (Patient Health Questionnaire Depression Scale (PHQ-9) and the Generalized Anxiety Disorder Scale (GAD-7)), Swedish population lifetime prevalence estimates for one or both conditions demonstrate significant overlap of the two conditions: depression 17.2% (95% confidence intervals (CI) 15.1, 19.4); anxiety 14.7% (95% CI 12.7, 16.6); and both 28.2%. [15]

The relationship between anxiety, depression and *chronic breathlessness* in the general population is poorly delineated. Many chronic conditions are associated with psychological comorbidity, limiting care options and self-management, [16] and worsening clinical outcomes. [17] However, most of these studies have been done in relation to diagnostic groups, such as people with chronic obstructive pulmonary disease (COPD) or heart failure, rather than in relation to the symptom itself. In addition, study cohorts are mostly of people who have had contact with health services. Given two phase III trials of anxiolytics in chronic breathlessness were strongly negative, [18,19] a better understanding of the relationship between anxiety and chronic breathlessness at a population level, independent of health service utilisation, is timely. The current study specifically targets the general population to gain a view about any potential relationship, independently of health service contact. The aim of the present study was to evaluate the associations between chronic breathlessness anxiety, depression and levels of function across a general population.

## METHODS

### *Study design and population*

This was a population-based, cross sectional cohort study conducted in November 2018, using an online data collection survey of people 18 or older who had provided consent to be contacted for such surveys and reconfirmed consent at the time of participation. A quota

sampling survey was performed, aligned to industry standards and best practices; up to 30,000 potential respondents for each sex were invited from a market research data collection company's database of double opt in - registered respondents to ensure 3,000 eligible responses. Quotas were created so the final sample frame was representative of the characteristics of the Australian population reflecting the 2016 national census by sex, age (18-34; 35-44; 45-54; 55-64;  $\geq 65$ ), state or territory of residence, and metropolitan/non-metropolitan. This was a quota-governed survey where 'cells' were created to match the national demographic combining each of these four parameters. Working towards the nationally representative cell targets where everyone who accepted the invitation to complete a survey (topic unspecified) initially qualified, as each demographic 'cell' was filled with the required number of representative respondents, subsequent respondents who met those demographic criteria did not proceed to the full questionnaire. The study can therefore be replicated in a different population by setting these identical parameters. The proportion of 'over-subscription' for each demographic cell is unknown.

#### *Data collection and key measures*

Anxiety and depression were assessed using the Patient Health Questionnaire for Depression and Anxiety (PHQ-4); a validated ultra-brief screening tool to detect clinically important anxiety, depression or both. [20] The two questions on anxiety were derived from the Generalized Anxiety Disorder-7 item scale (GAD-7) into the GAD-2, and the two questions on depression were derived from the PHQ-9 into the PHQ-2. GAD-2 and PHQ-2 scores can be analysed separately or, using the PHQ-4, together. Scores for each question range from 0-3 giving a potential total of 0-12 for the PHQ-4. Higher scores reflect higher levels of depression or anxiety. Clinically important differences were dichotomised according to the recommended threshold of  $>3$  for each subscale creating four mutually exclusive groups: 'No Anxiety or Depression'; 'Anxiety only'; 'Depression only'; and 'Co-existing Anxiety/Depression'.

Chronic breathlessness was assessed using the five point (0-4) ordinal modified mMRC breathlessness scale; a widely used scale designed for large-scale epidemiological studies. [5,21] Higher scores reflect worse disability and impact on function related to breathlessness. The scale reflects the level of exertion that induces breathlessness sufficient to have an impact on the respondent. Higher scores reflect increasing functional impairment by breathlessness. A score of  $\geq 2$  is likely to represent breathlessness-related disability experienced on a daily basis, so the population was dichotomised at that point for all analyses. Respondents who reported breathlessness (score  $>0$ ) were asked about its duration in months and years to build on previous estimates. [22]

Functional status was assessed using the AKPS, an 11-point ordinal scale (0-100 in 10 point increments). [23] Higher scores indicate better functional status. Scores below 70 indicate an increasing need for help from other people in activities of daily living, so data in this study were dichotomised at this point (100-70;  $\leq 60$ ).

See Appendix 1 for the complete survey questions across all four domains (anxiety, depression, breathlessness, and function) and demographics.

### *Statistical analyses*

Respondents' characteristics were compared between anxiety/depression status using a chi-square test for categorical variables and analysis of variance (ANOVA) or Kruskal-Wallis for continuous variables depending on the nature of the data. Multinomial logistic regression was carried out to assess the predictors of group membership for the anxiety/depression status. Odds ratios (OR), adjusted odds ratio (AOR) and 95% confidence interval (CI) for the likelihood of being breathless were examined using multiple logistic regression. Adjustments were made for age, sex and functionality of the respondents.

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software Version 24.0 (Armonk, NY: IBM Corporation, 2016). A  $p$ -value  $< 0.05$  or CI not including one was considered statistically significant.

To confirm the representative nature of the sample, the data were weighted by the same key characteristics of the 2016 Australian Census [24,25] with no change in weighted data, reflecting closely the current national population. As such, no weightings were applied to the dataset for analyses.

### *Data imputation*

Given the nature of the survey, no data were imputed.

### *Ethics approval and consent*

This was a community survey governed under the Australian Market and Social Research Society code of conduct that aligns with best global practice for social online research survey and quantitative data collection. No identifying information was collected for individual respondents. Consent was provided at two separate points: at the time of joining the database and at the time of accepting to participate in this particular survey.

## **RESULTS**

In November 2018, once 3000 eligible adults had responded, the cohort for the study was formed. There were missing scores for both anxiety and depression for 24 respondents, leaving 2977 people for the final analysis. Demographic characteristics of the study sample closely matched those of the Australian population aged 18 and above on sex (female: 51.2% and 50.2% respectively), median age (45.0 vs. 45.0 years), the state or territory of residence and whether they lived in metropolitan or non-metropolitan locales (Table 1).

The prevalence of clinically important breathlessness (mMRC  $\geq 2$ ) was 2.4% in the population (n=72). Anxiety alone was present in 6.0% (n=179) of the population and depression in 2.7% (n=80). Coexisting anxiety/depression was present in 6.1% of the cohort (n=181). Decreased functional status (AKPS  $\leq 60$ ) was found in 1.6% (n=49) of respondents (Table 2).

Characteristics for each of the psychological morbidities are presented in Table 2. Age, experiencing breathlessness, duration of breathlessness and functionality were significantly associated with psychological morbidity. From an age perspective, the highest median age was recorded for those in the group with no anxiety or depression. From a gender perspective a higher proportion of females was noted within the anxiety-only group. The highest proportion of those with decreased functionality was in the co-existing anxiety/depression group with 11.6% (n=21). The highest proportions of people with breathlessness were found in the co-existing anxiety/depression group and depression only group with 10.6% and 8.8% respectively.

Anxiety, co-existing anxiety/depression and, particularly, depression alone, were associated with higher prevalence of chronic breathlessness. (Table 2; Figure 1a). Similarly, co-existing anxiety/depression was associated with a longer duration of breathlessness (Figure 2).

In multinomial regression analyses with psychological morbidity as the dependent outcome, older age, longer duration of breathlessness, and worse functional status (AKPS  $\leq 60$ ) predicted depression only and co-existing anxiety/depression (Table 3). The relationship between poor functional status and psychological morbidity was striking (Figure 1b), especially in relation to the presence of co-existing anxiety/depression (OR 16.1; 95% 8.3, 31.4). The factors associated with anxiety only were sex, where men were less likely than women to be anxious, older age and duration of breathlessness.

From multivariate analysis, results relating to experiencing breathlessness are presented in Table 4. In comparison to those with no anxiety or depression, those in the depression only group and the co-existing anxiety/depression groups showed a significant increase in the prevalence of breathlessness. The odds of breathlessness were estimated to be 5.5 times higher among the depression only group (AOR=5.5, 95% CI 2.3,12.9) and 5.1 times higher among those in the co-existing anxiety/depression group (AOR=5.1, 95% CI 2.7,9.7) (Table 4).

## **DISCUSSION**

The presence of clinically important breathlessness (mMRC  $\geq 2$ ) was strongly associated with the presence of clinically relevant levels of psychological morbidity in a cross-sectional community cohort of adults with prevalence of chronic breathlessness similar to previous studies in the Australian population. [6] Although the relationship between COPD and depression is well documented, this current study defines the relationship between breathlessness, anxiety and depression, in a representative community population, and not

contacted because of their use of health services. The association extends to all adult age groups, with findings from a study in the elderly showing the same strong associations. [13] The very strong association between poorer functional status and psychological morbidity has not previously been described at the population level. Similarly, the association between duration of breathlessness and psychological morbidity is a new finding that has not been described in population-based studies.

Although the findings of a strong association between breathlessness, depression and co-existent depression/anxiety may not be surprising, this is the first time that the relationship has been documented in this way and a lack of association with anxiety alone demonstrated.

This study reflects similar results to randomly selected households where one member was interviewed face-to-face across a representative sample of one Australian state using the same question for chronic breathlessness that combined the mMRC and a time frame. [6] The overall rate of mMRC  $\geq 2$  was the same (2.4% in this study versus 2.6% in the previous study). [6]

The association between longer duration of breathlessness and psychological morbidity was an important finding. One possible explanation is that longer duration of breathlessness is correlated with more advanced disease and worse function, factors that may contribute to anxiety and/or depression. However, people who experience breathlessness for long periods also undergo structural brain changes affecting limbic and peri-limbic regions, which regulate emotions and were shown to be associated with fear of breathlessness in people with chronic breathlessness. [26,27] Thus, such changes may contribute to anxiety, depression or both in this population.

Causes of chronic breathlessness include advanced respiratory disease and chronic heart failure. The relationship between disease severity, symptom severity and functional abilities is complex and even in clinical cohorts, not well defined. [28] From a large meta-analysis in clinical studies, more severe heart failure was associated with worsening functional status and higher likelihood of depression. [28] Likewise, in COPD, the relationship between disease, symptom and functional decline has been defined in large prospective and cross sectional studies. [29] However, this is the first population-based study to explore the relationship between chronic breathlessness and functional status at a population level.

Two large evaluation-phase placebo controlled trials of medications that may address anxiety (buspirone, sertraline) or depression (sertraline) in the presence of chronic breathlessness have been strongly negative. [18,19] Given the strong association of anxiety and depression with chronic breathlessness, this may seem surprising. However, the trial populations were not those with breathlessness *and* psychological comorbidity and thus not powered to identify benefit in a sub-group with clinically significant anxiety/depression.

Functional decline is a final common pathway through many chronic complex conditions as they become chronic, progressive conditions. The relationship between depression and

functional decline has been well defined in the elderly and, as seen in this study there is a close relationship between co-existing anxiety/depression and functional decline although not necessarily between anxiety alone and functional decline. [30] Rate of change in functional status is strongly correlated with and predictive of prognosis in cancer and AIDS. [31,32] The relationship at a population level of the strong relationship between functional change and depression and anxiety is striking and has not been reported before. Functional decline leads to decreasing autonomy, loss of independence, increasing social isolation, [33] deconditioning which can further worsen breathlessness all of which may contribute to aggravating anxious and depressive symptoms. [34] Whether psychological comorbidity is a consequence of breathlessness itself or of the functional / social losses imposed by breathlessness is still to be determined.

### *Strengths*

This study is based on a purposive population sample using a web-based panel that reaches into the community, independent of prior health service contact for the formation of the cohort. This therefore more likely reflects the real prevalence of chronic breathlessness, functional status, psychological morbidity and their relationship with each other in the general population. Australia has very high rates of home internet usage making such web-based panels highly relevant. The topic of the survey was not revealed before respondents engaged. Response rates with internet surveys are now higher than postal or telephone surveys, or face-to-face interviews.

### *Limitations*

This study could only reach people who were members of a web-based panel and therefore technologically adept. As such, despite the respondents reflecting the demographics of the Australian population from the most recent national census, there may be unquantifiable biases in the tech-savvy, internet using respondents, potentially limiting the generalisability to the population as a whole. No causality can be assigned, only associations between the factors studied. This is especially a concern given the socio-economic gradient for smoking tobacco and its causal effect in COPD in the community, potentially underestimating the prevalence. The sample engaged were, however, representative of the community for key demographic factors of age, sex, state or territory of residence and metropolitan/non-metropolitan.

The absence of significance for the association between chronic breathlessness and anxiety alone in the multivariable model may represent a type II error that may disappear with a larger study cohort of people with mMRC breathlessness level 2-4. Data on potential confounders of known associations with chronic breathlessness including smoking history, heart and lung function, objective measures of daily activities and socioeconomic status were unavailable. The study did not seek the respondents' perceptions of their causes of breathlessness because this has been defined previously in cross-sectional population studies in Australia. [22]



### *Implications for clinical practice*

This study highlights the need to screen for anxiety and depression in people with deteriorating function and in moderate to severe chronic breathlessness. As the population becomes more likely to die from chronic progressive conditions, the life-time likelihood of functional decline is increasing and screening for anxiety and depression needs to be built into clinical care pathways, which should be adequately resourced. In chronic breathlessness, such an approach is supported with data showing pre-study and post-study scores of people with COPD who engaged with pulmonary rehabilitation where scores for people with either anxiety or depression or both raised at baseline fell by a clinically meaningful level for all three groups. [35]

### *Implications for future research*

Given the rates of co-existent anxiety/depression found in people with moderate to severe chronic breathlessness, a key question will be whether or not the successful symptomatic treatment of the person's chronic breathlessness could predictably reduce anxiety, depression or both. Clinical trials into non-pharmacological and pharmacological symptomatic treatments for chronic breathlessness need to consider the PHQ4 as a secondary outcome and, potentially, even a primary outcome. Conversely, as previous trials have not addressed the impact of treating mental health morbidity (for example, a trial population of people with anxiety and/or depression and chronic breathlessness), a further key question is whether or not successful treatment of anxiety states or clinical depression in those with chronic breathlessness improves the symptom of breathlessness.

Data sharing. Data are available on request from bona fide researchers

### **Conflict of Interests:**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### **Acknowledgements:**

The research team are indebted to Research Profile for their excellent assistance, especially Spike Games and Lavindi Wickramasooriya. Thank you to all of the respondents who gave their time. Thank you, as always, to Debbie Marriott and Linda Brown for their skilful help and support in bringing this project to fruition.

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**Table 1.** Internet-based quota-based national survey study sample compared with the Australian population from the 2016 census

	Study Sample (n=2,977)	Australian Population (N=18,190,239)
	n (%)	n (%)
<b>Age Category</b>		
18 – 34	895 (30.1)	5,512,542 (30.3)
35 – 44	560 (18.8)	3,144,297 (17.3)
45 – 54	538 (18.1)	3,104,299 (17.1)
55 – 64	446 (15.0)	2,753,037 (15.1)
≥ 65	538 (18.1)	3,676,064 (20.2)
<b>Sex</b>		
Male	1,485(49.9)	8,871,622 (48.8)
Female	1,492 (50.1)	9,318,617 (51.2)
<b>State or territory</b>		
NSW	914 (30.7)	5,827,179 (32.0)
VIC	763 (25.6)	4,638,884 (25.5)
QLD	604 (20.3)	3,611,968 (19.9)
SA	228 (7.7)	1,323,884 (7.3)
WA	313 (10.5)	1,907,253 (10.5)
TAS	69 (2.3)	400,777 (2.2)
NT	30 (1.0)	170,694 (0.9)
ACT	56 (1.9)	309,600 (1.7)

**Table 2:** Relationships between psychological morbidity and key factors from a community internet survey of the general population. n=2,977

		Total	Psychological Morbidity <sup>#</sup>				p-value
			No anxiety or depression n=2,537	Depression <i>only</i> n=80	Anxiety <i>only</i> n=179	Anxiety/ depression n=181	
Domain measured	Sex n (%)	Female n=1,492 (50.1)	1,244 (49.0)	38 (47.5)	114 (63.7)	96 (53.0)	0.002
		Male n=1,485 (49.9)	1,293 (51.0)	42 (42.5)	65 (36.3)	85 (47.0)	
	Age Mean (SD);median (min,max)		47.8 (15.3) 46.0 (19,87)	40.9 (15.1) 35.5 (20,73)	41.0 (13.7) 38.0 (19,75)	39.4 (12.6) 37.0 (19,73)	<0.001*
	Duration of breathlessness (only in those with self-rated mMRC $\geq$ 2; <i>in months</i> ) Mean (SD)		11.1 (42.0)	17.8 (53.4)	20.6 (68.9)	32.4 (82.0)	<0.001*
	Functionality** n (%)	100-70 n=2,928 (98.3)	2,514 (99.1)	77 (96.2)	177 (98.9)	160 (88.4)	<0.001
		$\leq$ 60 n=49 (1.7)	23 (0.9)	3 (3.8)	2 (1.1)	21 (11.6)	
	Clinically important	No (mMRC <sup>##</sup>	2,497 (98.4)	73 (91.2)	173 (96.6)	160 (89.4)	<0.001

	breathlessness	0-1)					
	n (%)	n=2,905 (97.6)					
	Yes (mMRC## 2-4) n=72 (2.4)	40 (1.6)	7 (8.8)	6 (3.4)	19 (1.6)		

#PHQ4 scores >3/6 for anxiety; >3/6 for depression as clinically relevant cut points defined each symptom; ##mMRC: modified Medical Research Council breathlessness scale; \*both ANOVA and Kruskal-Wallis test were performed and results were comparable, \*\*AKPS: Australia-modified Karnofsky Performance functional status.

**Table 3.** Result of multinomial logistic regression analysis, using age, sex, functionality and duration chronic breathlessness to predict anxiety, depression or both.

	Depression <sup>#</sup> <i>only</i> vs. Neither	Anxious <sup>##</sup> <i>only</i> vs. Neither	Depressed <sup>#</sup> <i>AND</i> anxious <sup>##</sup> vs. Neither
	OR (95% CI)		
Age* (per year)	0.97 (0.95, 0.98)	0.97 (0.96, 0.98)	0.96 (0.94, 0.97)
Sex (Male versus female)	1.07 (0.69, 1.68)	0.56 (0.41, 0.77)	0.86 (0.63, 1.18)
Duration of chronic breathlessness (in months))	1.003 (1.00, 1.007)	1.004 (1.002, 1.006)	1.006 (1.004, 1.008)
Functionality (AKPS <sup>**</sup> : ≤60 versus 100-70)	4.84 (1.39, 16.77)	1.42 (0.33, 6.17)	16.07 (8.23, 31.39)

\*as a continuous variable; \*\*AKPS: Australia-modified Karnofsky Performance functional status; mMRC: modified Medical Research Council breathlessness scale; #Patient Health Questionnaire-2 question (PHQ-2); Generalised Anxiety Disorder-2 question (GAD-2). (Together PHQ-2 and GAD-2 are the PHQ-4).



**Table 4.** Odds ratio and adjusted odds ratio of chronic breathlessness (n=2977)

	Chronic Breathlessness	
	OR (95% CI)	AOR <sup>(a)</sup> (95% CI)
<b>Psychological morbidity</b>		
No anxiety <sup>+</sup> or depression <sup>++</sup>	<i>Ref</i>	<i>Ref</i>
Depression <sup>++</sup> only	6.0 (2.6,13.8)	5.5 (2.3,12.9)
Anxiety <sup>+</sup> only	2.2 (0.9,5.2)	2.1 (0.9,5.2)
Co-existing anxiety <sup>+</sup> /depression <sup>++</sup>	7.3 (4.1,12.9)	5.1 (2.7,9.7)

<sup>(a)</sup>odds ratio adjusted for age, sex and functionality; <sup>++</sup>Patient Health Questionnaire-2 question (PHQ-2);

<sup>+</sup>Generalised Anxiety Disorder-2 question (GAD-2). (Together PHQ-2 and GAD-2 are the PHQ-4).

<sup>#</sup>modified Medical Research Council (mMRC) breathlessness scale 2-4; <sup>##</sup> mMRC 0,1; <sup>\*</sup> Australia-modified Karnofsky Performance Status scale