TITLE: Breathlessness limiting exertion in very old adults: findings from the Newcastle 85+ Study

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KEY POINTS

- In the oldest old (>85 years) little is known about the prevalence, or impact of long-term breathlessness.
- We found breathlessness limiting exertion is common in the oldest old but appears to become less prevalent over time due to death or deterioration of participants with cardio-respiratory illness. We also found it was associated with poorer self-rated health, depression**,** more primary care contacts and number of nights in hospital.
- Holistic breathlessness interventions are effective regarding symptoms, quality of life and health service utilisation but clinical trials include few oldest old. These interventions should be considered for the oldest old, but further research conducted to evaluate whether and how interventions should be tailored for this group.

Key words: breathlessness; dyspnoea; older adult; aged; prevalence

ABSTRACT

Introduction

Long-term breathlessness is more common with age. However, in the oldest old (>85 years) little is known about the prevalence, or impact of breathlessness. We estimated *breathlessness limiting exertion* prevalence and explored i) associated characteristics; and ii) whether *breathlessness limiting exertion* explains clinical and social/functional outcomes.

Methods

Health and socio-demographic characteristics were extracted from the Newcastle 85+ Study cohort. Phase 1 (baseline) and follow-up data (18 months, Phase 2; 36 months, Phase 3; 60 months, Phase 4 after baseline) were examined using descriptive statistics and cross-sectional regression models.

Results

817 participants provided baseline breathlessness data (38.2% men; mean 84.5 years; SD 0.4). The proportions with any limitation of exertion, or severe limitation by breathlessness were 23% (95%CIs 20 to 25) and 9% (95%CIs 7% to 11%) at baseline; 20% (16% to 25%) and 5% (3% to 8%) at Phase 4. Having more co-morbidities (Odds Ratio (OR) 1.34, 1.18 to 1.54; p<0.001), or self-reported respiratory (OR 1.88, 1.25 to 2.82; p=0.003) or cardiovascular disease (OR 2.38, 1.58 to 3.58; p<0.001) were associated with *breathlessness limiting exertion*. *Breathlessness severely limiting exertion* was associated with poorer self-rated health (OR 0.50, 029 to 0.86; p=0.012), depression (beta-coefficient 0.11, p=0.001), increased primary care contacts (beta-co-efficient 0.13, p=0.001) and number of nights in hospital (OR 1.81; 1.02 to 3.20; p=0.042)

Conclusions

Breathlessness limiting exertion appears to become less prevalent over time due to death or withdrawal of participants with cardio-respiratory illness. *Breathlessness severely limiting exertion* had a wide range of service utilisation and wellbeing impacts.

INTRODUCTION

Chronic persistent breathlessness[1]is associated with reduced quality of life,[2,3] social[4] and workplace activity,[5] increased health service utilisation,[6] and a poorer prognosis,[7] including reduced 2- and 10-year survival in those over 70.[8] For older adults, multi-morbidity is the norm;[9] chronic breathlessness may be an added burden to living with multiple long-term conditions with effects on mobility, activities of daily living, social connectedness, and independence in their own homes.

Long-term breathlessness is frequently neglected despite available interventions.[10] Published prevalence estimates in the general population vary between 9% and 59%, depending on the definition used and population studied; the symptom is more prevalent in older people and in women.[7,11-14] Prevalent conditions such as lung disease, heart failure and cancer[15] become more common with age and cause chronic and acute-on-chronic[16] breathlessness.

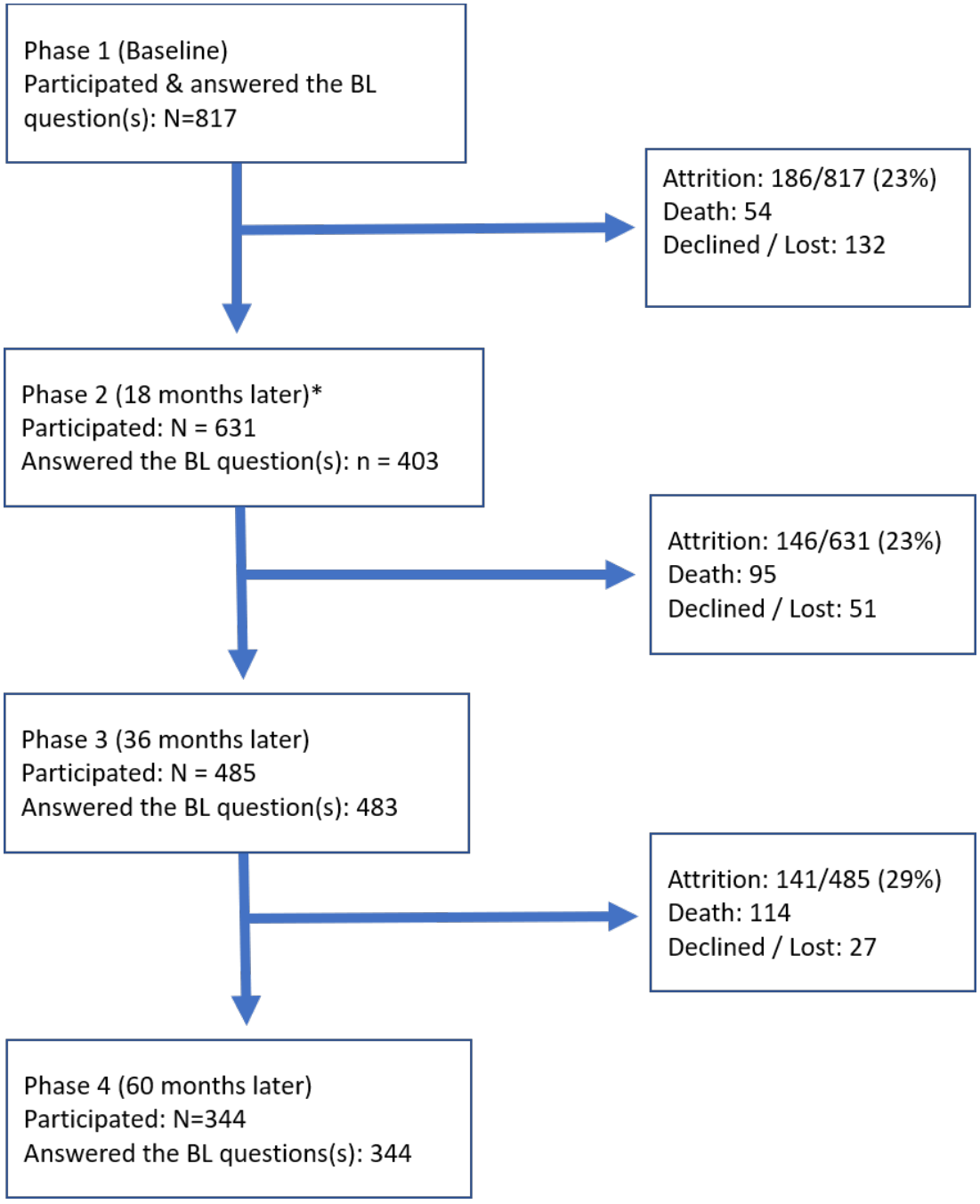
Although the prevalence of chronic breathlessness increases with age, amongst older adults we reported a negative association with the oldest old having a lower prevalence than the youngest old.[17] The Newcastle 85+ Study,[9,18] which aimed to explore the health and service use of a cohort of the oldest old, allows exploration of its impact in this often-neglected group.

We investigated the extent to which, i) medical condition(s) and other characteristics explain the presence of *breathlessness limiting exertion*; and ii) *breathlessness limiting exertion* explains clinical, social and functional outcomes including healthcare utilisation.

METHODS

THE NEWCASTLE 85+ STUDY COHORT

In this secondary data analysis, data relating to breathlessness and health and socio-demographic characteristics were extracted from the population-based Newcastle 85+ Study cohort, the methods of which have been reported elsewhere.[9,18] Eligible participants were consenting very old adults born in 1921, aged 85 in 2006, living in Northeast England registered with participating general practices in Newcastle or North Tyneside and providing written informed consent.[18] For the first multi-dimensional health assessment, data were collected between June 2006 and October 2007. The subsequent phases of the data collection took place 18 months (Phase 2), 36 months (Phase 3) and 60 months (Phase 4) after baseline (Phase 1). More details about retention from Phase 1 to Phase 4 are presented in the flowchart (Figure 1).



Notes. BL = breathlessness. * In Phase 2, the questions on breathlessness were only administered to participants who were randomised into the cardiac sub-study.

Figure 1. Retention from Phase 1 to Phase 4. Only the participants who answered at least one of the breathlessness questions at baseline are included in this flowchart.

The Newcastle 85+ Study was approved by the Newcastle and North Tyneside Local Research Committee One (Ref: 06/Q0905/2).

HYPOTHESES

In people aged 85 and over:

1. Breathlessness limiting exertion becomes less prevalent as the oldest old grow older.
2. Variables such as higher age, higher physical activity levels and more social participation are inversely related to breathlessness limiting exertion. Other variables, such as number and type (e.g., heart and lung diseases) of medical conditions, smoking/ex smoking and inflammation are positively related to breathlessness limiting exertion.
3. Chronic breathlessness is associated with poorer clinical, social and functional outcomes.

DATASET FOR ANALYSIS

Phases 1, 2, 3 and 4 were included in the descriptive analysis of ongoing participation by disease (Fig 1). Phases 1, 3 and 4 were included in the analysis of prevalence of breathlessness at each. Phase 2 data were not included because questions on self-reported breathlessness were administered to less than 50% of participants who provided baseline breathlessness data.

Phase 1 and Phase 3 formed the dataset for the multivariable analyses. Data from Phase 4 were not included due to insufficient sample size.

Phase 3 cross-sectional analyses were not feasible in some models, due to a lower sample size due to death (n=227; 27.8%) or withdrawal (n=105; 12.9%) compared to those who provided breathlessness data at Phase 1.

ANALYSIS

Outcome variables: Hypotheses 1 and 2

Binary breathlessness variables:

We derived two binary variables relating to two levels of breathlessness over the past four weeks; *any breathlessness limiting exertion*, and *breathlessness severely limiting exertion* ("any breathlessness" and "severe breathlessness", see Box 1).

To address hypothesis 1, the prevalence of the two levels was estimated for Phases 1, 3 and 4 and presented within 95% confidence intervals. Using data regarding deaths and withdrawals, the proportions of those with and without severe breathlessness and those with and without cardiovascular, lung disease or cancer still participating in Phases 2, 3 and 4 were calculated.

Box 1. Survey questions for limiting chronic breathlessness and categorisations in our study with study hypotheses

Survey questions relating to breathlessness outcome variable:

1. So in the last 4 weeks, has shortness of breath limited your ability to move around your home (on one level)? [Possible answers: Yes / No / Limited for reason(s) unrelated to shortness of breath]
2. (if so) How much has shortness of breath limited your ability to move around your home (on one level)? [Possible answers: A bit / A lot / Completely unable to move around the home due to shortness of breath]
3. In the last 4 weeks, has shortness of breath limited your ability to walk outdoors on the level, at your own pace? [Possible answers: Yes / No / Limited for reason(s) unrelated to shortness of breath]
4. (if so) How much has shortness of breath limited your ability to walk outdoors, on the level, at your own pace? [Possible answers: A bit / A lot / Completely unable to walk outdoors, on the level, at own pace due to shortness of breath]

Categorisations in our study:

Binary variable (hypotheses 1 and 2)

1. Any breathlessness limiting exertion ("*any breathlessness"*): (Yes to 1 AND/OR Yes to 3) = breathless; rest = not breathless
2. Breathlessness severely limiting exertion ("*severe breathlessness"*): ([Yes to 1 AND ("A lot" or "Completely unable…") to 2] AND/OR [Yes to 3 AND ("A lot" or "Completely unable…") to 4]) = breathless; rest = not breathless

Outcome variables: Hypothesis 3

Self-rated health:

Self-rated health is an overall assessment of physical and psychosocial health and a good indicator of health status and subsequent morbidity and mortality.[19.20]

Depression:

Depression was measured using the Geriatric Depression Scale (GDS) total score.[21] Depression is prevalent in older adults and associated with limiting breathlessness in those over 70.[20] Values less than 5 indicate no depression, whilst values over 10 almost always indicate depression.

Health service utilisation:

Health service utilisation was measured by number of primary care team attendances, and the number of nights spent in hospital over the previous 12 months. Chronic breathlessness

in the general adult population is associated with increased attendance in primary and secondary care.[6]

Explanatory variables: hypothesis 2 and 3

Bivariate analyses were conducted to explore the relationship between explanatory and outcome variables for the relevant hypotheses. The candidate variables primarily encompassed sociodemographic, health status and health service utilisation (for detail see Appendices Tables 1, 3 and 4). Of particular note, the Timed Up and Go (TUG) test [22] was included as, although no direct association has been published between the TUG and breathlessness in older adults, population studies show reduced mobility in those with severe breathlessness.[3] In addition, an association between chronic breathlessness and changes in the hypothalamic-pituitary-adrenal axis has been observed,[23,24] therefore the biomarkers cortisol and HS CRP were included.

For hypothesis 2, the breathlessness variable was included as a binary outcome variable (see Box 1). For hypothesis 3, the breathlessness variable was included as a three-category explanatory variable: 1. Breathlessness severely limiting exertion (see above, "*severe breathlessness"*); 2. Breathlessness limiting exertion, but not severely (see above, *"mild-moderate breathlessness"*); 3. Those who answered "no" or had diminished mobility due to reasons unrelated to breathlessness, were classified as not having limiting breathlessness (*"no breathlessness").*

Statistical methods

As many variables passed a threshold signifying a statistically significant relationship of $p<0.2$, the number was reduced to avoid overfitting given the small sample size in Phase 3. Candidate variables were prioritised according to plausible explanations supported by the literature. Sex and age were included into each model, despite lack of association with breathlessness in the bivariate analyses.

Apart from descriptive statistics, the analyses concerning Hypotheses 2 and 3 were performed using multiple regression models. Concerning Hypothesis 2, logistic regression was used due to the binary nature of the outcome variables. Concerning Hypotheses 3, ordinal and linear regression models were applied due to the categorical and continuous nature of the outcome variables.

RESULTS

Breathlessness data were provided by 817 participants at baseline (38.2% men; average age 84.5 years; SD 0.4 years). Most (78% in both Phases) self-reported good to excellent health. Phase 1 mean (3.6, SD 2.6) and median (3, IQR 2 to 5) values for the GDS were below the threshold for possible depression. The average number of self-reported illnesses was greater than 1 (Phase 1: mean 1.7, SD 1.4; Phase 3: mean 2.1, SD 1.5). Timed-Up-and-Go (TUG) times indicated a population with limited mobility, at risk of falls and frailty (Phase 1: mean 19s, SD 15s, median 14s, IQR 11s to 20s; Phase 3: mean 22s, SD 18.8s, median 17s, IQR 12s to 24s). Consistent with TUG times, self-reported physical activity indicated that although most reported mildly energetic physical activity at least once a week (74%), this dropped to 35% for moderate and 5% for very energetic physical activity. Most (83%) were not current drivers at Phase 1, rising to 88% by Phase 3.

Participants had contacted primary care on average 10 times in the previous year (Phase 1), increasing to 11.4 times in the previous year in Phase 3. Mean cortisol levels were higher than mean values in middle- and advanced age community-dwelling adults,[25] although within the range. Mean High Specificity C-Reactive Protein (Hs-CRP) levels were moderately raised consistent with systemic inflammation.[26]
For detailed descriptive statistics of all included variables see Appendices Tables 2-4.

HYPOTHESIS 1. PREVALENCE

The proportion of participants with *any breathlessness* at baseline was 23% (95% confidence intervals 20 to 25). At Phase 4, it was 20% (16 to 25) (Appendices Table 2). The numerical decrease was more marked for those with *severe breathlessness* (9%; 95% CIs 7% to 11% at baseline: 5%; 3% to 8% at Phase 4) (Appendices Table 1).

Of ongoing participants, the proportion with cancer, cardio-respiratory disease or *severe breathlessness* numerically decreased over time, e.g., of those with a history of cancer at baseline, 42% participated in Phase 4 compared with 52% of those without a history of cancer. This pattern was most marked for *severe breathlessness* (29.5% with the condition *vs*. 52.2% without it in Phase 4) (Figure 2).

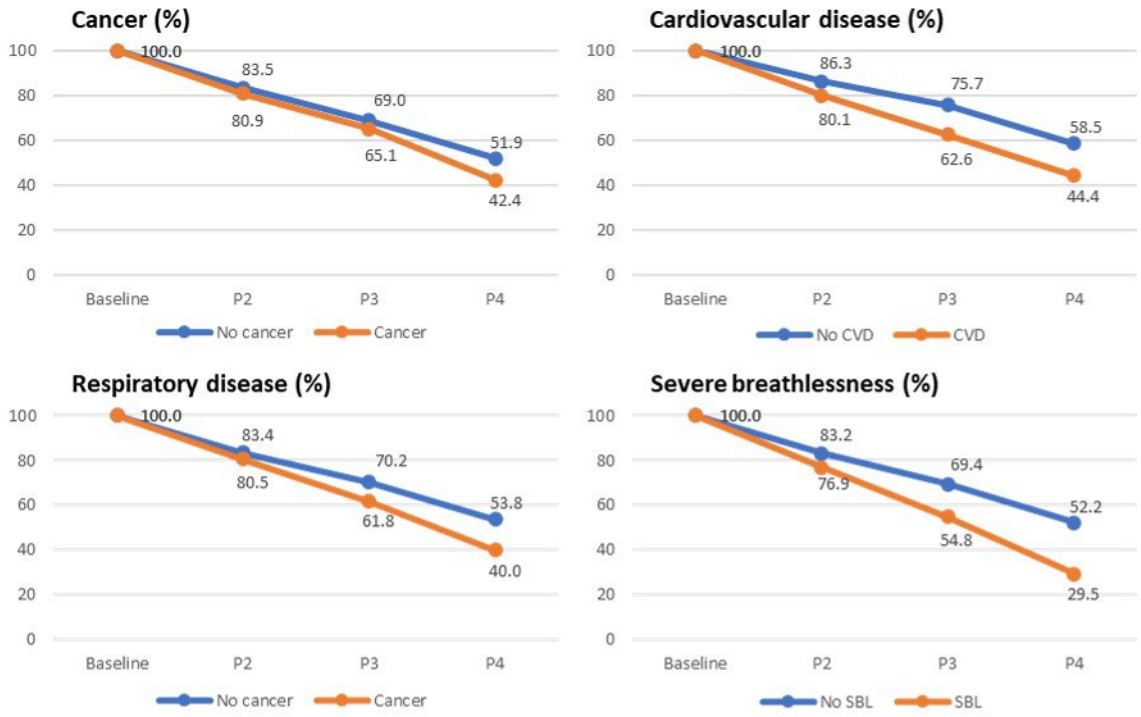


Figure 2. Survival percentages by phase, disease status and severe breathlessness (n=810 to 817 at baseline). Participants who withdrew their consent at any stage count as missing from that point on.

HYPOTHESIS 2. VARIABLES ASSOCIATED WITH *BREATHLESSNESS LIMITING EXERTION*

In the multivariable analysis, (Table 1) having more illnesses (OR 1.34, 95% CIs 1.18 to 1.54; p<0.001), self-reported respiratory (1.88, 1.25 to 2.82; p=0.003) or cardiovascular disease (2.38, 1.58 to 3.58; p<0.001) were significantly associated with *any breathlessness*. Associated variables of *severe breathlessness* only were the same but with higher likelihood (more illnesses: 1.51, 95% CIs 1.26 to 1.82; p=0.001; respiratory: 3.07, 1.73 to 5.45; p<0.001; cardiovascular: 2.74, 1.39 to 5.40; p=0.004), and cortisol levels (0.998; 0.996 to 0.995; p=0.015). In Phase 3, the strongest association was seen for respiratory disease. For all models, the percentage of variation explained was at most 24%, indicating other factors at play.

Table 1. Associations with breathlessness limiting and severely limiting exertion: logistic regression models[1]

	Model 1: Phase 1 (n=712) Outcome: Any breathlessness				Model 2: Phase 1 (n=712) Outcome: Severe breathlessness				Model 3: Phase 3 (n=378) Outcome: Any breathlessness			
	n	**OR**	**95% Cis**	**p**	**n**	**OR**	**95% CIs**	**p**	**n**	**OR**	**95% CIs**	**p**
Age	712	1.17	0.76, 1.79	0.472	378	1.42	0.74, 2.72	0.286	378	1.09	0.59, 2.03	0.777
Sex												
Male	283	1			283	1			142	1		
Female	429	1.24	0.83, 1.85	0.297	429	1.48	0.80, 2.75	0.210	236	1.10	0.61, 1.97	0.754
Smoking status[1]												
Never	260	1		0.881	260	1		0.881				
Ex-smokers	405	1.41	0.93, 2.14	0.107	405	1.01	0.54, 1.89	0.966				
Smokers	47	1.42	0.64, 3.13	0.389	47	1.32	0.43, 4.10	0.627				
Higher education												
No	628	1			628	1			316	1		
Yes	84	0.85	0.46, 1.57	0.606	84	0.38	0.11, 1.33	0.129	62	0.98	0.46, 2.08	0.957
No. self-reported illnesses (excl. breathlessness)	712	**1.35**	**1.18, 1.54**	**<0.001**	712	**1.51**	**1.26, 1.82**	**<0.001**	378	**1.27**	**1.06, 1.52**	**0.010**
Cancer												
No	611	1			611	1			305			
Yes	101	0.76	0.44, 1.32	0.333	101	0.90	0.40, 1.99	0.790	73	0.85	0.43, 1.70	0.652
Respiratory disease												
No	534	1			534	1			274			
Yes	178	**1.88**	**1.25, 2.82**	**0.003**	178	**3.07**	**1.73, 5.45**	**<0.01**	104	**2.49**	**1.43, 4.34**	**0.001**
Cardiovascular disease												
No	317	1			317	1			153	1		
Yes	395	**2.38**	**1.58, 3.58**	**<0.01**	395	**2.74**	**1.39, 5.40**	**0.004**	225	**2.15**	**1.19, 3.88**	**0.011**
TUG (seconds)	712	1.00	0.99, 1.01	0.965	712	1.01	0.99, 1.02	0.311	378	1.01	0.99, 1.02	0.357
HS CRP	712	1.01	1.00, 1.02	0.156	712	1.01	1.00, 1.03	0.093	378	1.01	1.00, 1.03	0.133
Cortisol	712	1.00	1.00, 1.00	0.833	712	**1.00**	**0.99, 1.00**	**0.015**	378	1.00	0.99, 1.00	0.053

Notes. [1] Models for breathlessness severely limiting exertion were not included due to an insufficient number of events per variable. R^2 (Nagelkerke): 0.148 for Model 1; 0.244 for Model 2; 0.157 for Model 3. CI= confidence interval; BL= breathlessness; CV = cardiovascular disease; TUG = Timed up and go test; HS CRP = high specificity C-reactive Protein

Table 2. Associations with loneliness and self-rated health – ordinal regression models at Phase 1. Higher values indicate more frequent loneliness and better health, respectively.

	Model 1: Loneliness* (n=724)					Model 2: Self-rated health** (n=721)			
	n	**OR**	**95% CIs**	**p**		**n**	**OR**	**95% CIs**	**P**
DEPENDENT VARIABLE: Feeling lonely					**DEPENDENT VARIABLE: Self-rated health**				
Never	412				Poor or Fair	153			
Sometimes	245				Good	269			
Often or Always	67				Very good	215			
					Excellent	84			
INDEPENDENT VARIABLES:									
Age	724	0.78	0.53, 1.13	0.181		721	0.95	0.69, 1.31	0.759
Number of self-reported illnesses^	724	1.05	0.93, 1.18	0.445		721	**0.66**	**0.59, 0.74**	**<0.001**
GDS score (depression)	724	**1.42**	**1.32, 1.53**	**<0.001**		721	**0.84**	**0.79, 0.90**	**<0.001**
Timed Up and Go (seconds)	724	**0.98**	**0.97, 0.99**	**0.010**		721	**0.98**	**0.97, 0.99**	**0.002**
Breathlessness									
No breathlessness	553	1				550	1		
Mild-moderate breathlessness	105	0.70	0.44, 1.11	0.125		105	0.85	0.57, 1.27	0.424
Severe breathlessness	66	0.97	0.55, 1.71	0.922		66	**0.50**	**0.29, 0.86**	**0.012**
Sex									
Male	285	1				282	1		
Female	439	**1.92**	**1.31, 2.82**	**0.001**		439	0.94	0.67, 1.32	0.732
Smoking status									
Never						261	1		
Ex-smokers						412	1.20	0.88, 1.63	0.248
Smokers						48	0.78	0.43, 1.41	0.408
Higher education									
No	638	1				635	1		
Yes	86	0.76	0.46, 1.27	0.300		86	1.38	0.90, 2.13	0.143
Living alone									
No	279	1				277	1		
Yes	422	**4.83**	**3.32, 7.04**	**0.000**		421	1.34	0.99, 1.82	0.060
Not applicable (care home, etc.)	23	**3.89**	**1.51, 10.01**	**0.005**		23	**3.33**	**1.41, 7.88**	**0.006**

Driving									
No	587	1				586	1		
Yes	137	1.20	0.74, 1.93	0.462		135	1.00	0.67, 1.49	0.995
Very energetic physical activity									
No	682	1				679	1		
Yes	42	1.56	0.76, 3.22	0.225		42	1.35	0.72, 2.50	0.350
Moderately energetic physical activity									
No	446	1				445	1		
Yes	278	1.34	0.90, 1.97	0.146		276	1.37	0.98, 1.93	0.067
Mildly energetic physical activity									
No	139	1				138	1		
Yes	585	0.70	0.44, 1.09	0.117		583	1.44	0.95, 2.19	0.086

Notes. Test of parallel lines: p=0.090 for Model 1; p=0.514 for Model 2. Pseudo R^2: 0.300 for Model 1; 0.298 for Model 2. CIs= confidence intervals.

HYPOTHESIS 3. THE RELATIONSHIP BETWEEN *BREATHLESSNESS LIMITING EXERTION* AND LONELINESS, SELF-RATED HEALTH, DEPRESSION, HEALTH SERVICE UTILISATION.

Severe breathlessness was associated with poorer self-rated health (OR 0.50, 029 to 0.86; p=0.012), but not loneliness. The association with *mild-moderate breathlessness* with self-rated health was not significant (OR 0.85, 0.57 to 1.27; p = 0.424; Table 2). Due to the high number of variables in the models presented in Table 1, the model with severe breathlessness as outcome had to be restricted only to the baseline, given the lower sample size and the particularly low prevalence rates of severe breathlessness in Phase 3.

The association with *mild-moderate breathlessness* with self-rated health was not significant (OR 0.85, 0.57 to 1.27; p = 0.424; Table 2). *Mild-moderate breathlessness* was associated with depression, and *severe breathlessness* was associated with more primary care contacts (Table 3) and number of hospital nights (Table 4). In the repeated cross-sectional analyses, *any breathlessness* was associated with depression. At Phase 3, breathlessness was not significantly associated with the number of primary care contacts or hospital nights although the point estimate for *severe breathlessness* showed higher odds ratios (Tables 3 and 4).

Table 3. Associations with Geriatric Depression Scale score and Contacts with primary care team members in the last 12 months – linear regression models, Phases 1 and 3

	Dependent variable: Geriatric Depression Scale score									
	Model 1: Phase 1 (n=724)					**Model 2: Phase 3 (n=388)**				
	B	**SE B**	**B**	**P**	**R^2**	**B**	**SE B**	**β**	**p**	**R^2**
Mild-moderate breathlessness	**0.81**	**0.24**	**0.11**	**0.001**		**0.68**	**0.32**	**0.10**	**0.038**	
Severe breathlessness	**0.80**	**0.30**	**0.09**	**0.009**		0.71	0.48	0.07	0.144	
Female sex	0.10	0.20	0.02	0.626		-0.14	0.27	-0.03	0.610	
Higher education	0.17	0.26	0.02	0.524		-0.03	0.31	0.00	0.927	
Driving	-0.15	0.24	-0.02	0.532		**-0.99**	**0.34**	**-0.15**	**0.004**	
Very energetic physical activities	-0.38	0.37	-0.04	0.313		-0.20	0.74	-0.01	0.786	
Moderately energetic physical activities	**-1.22**	**0.20**	**-0.24**	**<0.001**		**-1.17**	**0.29**	**-0.21**	**<0.001**	
Mildly energetic physical activities	**-0.72**	**0.24**	**-0.11**	**0.003**		**-1.12**	**0.30**	**-0.21**	**<0.001**	
Living alone	0.03	0.18	0.01	0.887		0.46	0.26	0.09	0.080	
Living in a care home, etc.	-0.88	0.52	-0.06	0.089		0.12	0.64	0.01	0.852	
Age	0.12	0.19	0.02	0.529		-0.21	0.26	-0.04	0.418	
Nr. of self-reported illnesses (excl. breathlessness)	**0.30**	**0.06**	**0.18**	**<0.001**		0.08	0.08	0.05	0.323	
TUG (seconds)	0.01	0.01	0.05	0.159		0.00	0.01	0.03	0.584	
R^2 unadjusted					0.224					0.207
R^2 adjusted					0.210					0.179
	Dependent variable: Contacts with primary care team members in the last 12 months									
	Model 3: Phase 1 (n=725)					**Model 4: Phase 3 (n=387)**				
	B	**SE B**	**B**	**P**	**R^2**	**B**	**SE B**	**β**	**p**	**R^2**
Mild-moderate breathlessness	-0.38	0.82	-0.02	0.641		0.08	1.17	0.00	0.943	
Severe breathlessness	**3.54**	**1.04**	**0.13**	**0.001**		2.11	1.71	0.06	0.219	
Female	-0.37	0.63	-0.02	0.564		-0.57	0.91	-0.03	0.535	
Higher education	-0.90	0.88	-0.04	0.307		0.04	1.11	0.00	0.968	
Living alone	-0.07	0.62	0.00	0.906		-0.89	0.92	-0.05	0.337	
Living in a care home, etc.	-3.02	1.71	-0.07	0.077		0.09	2.23	0.00	0.968	
Ex-smokers	-0.39	0.62	-0.03	0.527						
Smokers	**-2.99**	**1.19**	**-0.10**	**0.012**						
Age	0.06	0.65	0.00	0.926		-1.55	0.93	-0.08	0.096	
Nr. of self-reported illnesses (excl. breathlessness)	**0.69**	**0.21**	**0.13**	**0.001**		**1.09**	**0.29**	**0.19**	**0.000**	
TUG (seconds)	0.00	0.02	0.00	0.911		0.05	0.03	0.09	0.074	
GDS score	0.20	0.12	0.06	0.105		0.22	0.17	0.07	0.209	
R^2 unadjusted					0.071					0.078
R^2 adjusted					0.055					0.053

TUG= Timed up and go; GDS = Geriatric Depression Scale

Table 4. Predictors of number of hospital nights in the last 12 months – ordinal regression models, Phases 1 and 3

	Model 1: Phase 1 (n=724)				Model 2: Phase 3 (n=390)			
	n	**OR**	**95% CIs**	**p**	**n**	**OR**	**95% CIs**	**p**
DEPENDENT VARIABLE: Nr. of nights in hospital last 12 mths.								
0 nights	571				302			
1-6 nights	68				34			
7+ nights	85				54			
INDEPENDENT VARIABLES:								
Age	724	1.03	0.67, 1.57	0.898	390	1.50	0.86, 2.63	0.157
Nr. of self-reported illnesses (excl. breathlessness)	724	1.10	0.96, 1.25	0.158	390	1.09	0.92, 1.30	0.293
GDS score	724	**1.12**	**1.04, 1.20**	**0.003**	390	1.09	0.99, 1.21	0.069
TUG (seconds)	724	**1.02**	**1.01, 1.03**	**0.003**	390	**1.02**	**1.00, 1.04**	**0.014**
Breathlessness								
Mild-moderate breathlessness	105	1.08	0.64, 1.80	0.781	57	0.85	0.42, 1.73	0.657
Severe breathlessness	65	**1.81**	**1.02, 3.20**	**0.042**	24	1.28	0.51, 3.16	0.600
No breathlessness	554	1.00			309	1.00		
Sex								
Male	285	1.00			148	1.00		
Female	439	0.67	0.45, 1.00	0.051	242	0.89	0.51, 1.54	0.680
Higher education								
No	638	1.00			328	1.00		
Yes	86	1.12	0.63, 1.97	0.698	62	0.85	0.42, 1.72	0.647
Living alone								
No	278	1.00			132	1.00		
Yes	423	1.33	0.89, 2.00	0.168	243	1.57	0.88, 2.80	0.127
Not applicable (care home, etc.)	23	0.97	0.30, 3.17	0.959	15	1.52	0.42, 5.43	0.521
Smoking status								
Never	263	1.00						
Ex-smokers	412	1.31	0.87, 1.98	0.198				
Smokers	49	0.75	0.32, 1.74	0.504				

Notes. Test of parallel lines: P1 p=0.330; P3 p=0.091. Notes: Test of parallel lines: p=0.330 for Model 1; p=0.091 for Model 2. Pseudo R^2: 0.087 for Model 1; 0.069 for Model 2.

TUG = Timed up and go; GDS = Geriatric Depression Scale

DISCUSSION

This is the first study of the prevalence and impact of breathlessness limiting exertion in the oldest old, the fastest growing sub-group in the population by percentage change. [27] The cohort study underlying the data provides a valuable source of insights into this burgeoning population. [28,29] Data demonstrate that the proportion of people experiencing breathlessness reduces over time. Most likely, this is due to mortality or deterioration in people with more severe breathlessness. In this setting, breathlessness is a harbinger of

death given the aetiologies that underlie it, consistent with other large population studies that span a wider age range. [17,45] Those *without* long-term breathlessness are more likely to outlive their contemporaries *with* breathlessness. Breathlessness limiting exertion is associated with having more long-term illnesses. Any breathlessness limiting exertion was also associated with depression and, if exertion was severely limited by breathlessness, with poorer self-rated health, more primary care visits and more nights in hospital. Levels of physical activity were inversely associated with depression in a dose-related pattern. Self-rated health was inversely associated with breathlessness, depression and the timed up and go (TUG).

Previous work amongst older adults have been in younger groups and show a higher prevalence of breathlessness.[13] Our data suggest that the findings of decreasing prevalence very late in life is likely due to deterioration, withdrawal, or death of those with breathlessness-causing illnesses.[17] Age-related physical changes affecting lung capacity may also contribute to breathlessness in the very old (reduced peri-airway supportive tissue,[30] chest wall compliance[31] and diaphragmatic strength[32]) but the net effect appears to be disease related.

Variables associated with breathlessness.
Consistent with other studies, having more illnesses, and specifically lung and heart disease,[15] was associated with breathlessness limiting exertion. We found no association with sex, Sex differences in one study of breathlessness disappear when adjusted for absolute lung volumes.[33] If lung volume sex differences become smaller in the very old,[34] our sample size may have been insufficient to detect breathlessness differences. Likewise, although point estimates showed increased odds of breathlessness with smoking and education, this was not significant, reflecting a smaller contribution in the oldest old. Previous work demonstrated that once adjusted for other social determinants, education is not associated with health outcome in older adults.[35,36]

Impact of breathlessness.
The “dose-dependent” association between breathlessness and primary and secondary health service utilisation is documented in a general adult population.[6] Breathlessness severely limiting exertion is associated with both increased primary care contacts and more nights in hospital. The increased use of GPs has been previously noted in this age-group, but the relationship with breathlessness was not explored.[37]

The relationship between breathlessness in the general adult population and mobility has been described. [3] However, although the central importance of maintaining mobility for the physical and mental well-being of older adults is established,[38,39] the link with breathlessness as a possible important contributing factor has had little or no attention. There appears to be a complex interplay between physical exertion and ensuing

breathlessness which leads to a vicious cycle of avoidance of activity to avoid breathlessness, deconditioning, accelerated muscle loss, itself then leading to worse breathlessness triggered by less and less exertion.[40]

The wider consequences of depression,[41] anxiety,[41] social withdrawal,[42] and loss of role form another vicious cycle which can aggravate breathlessness through emotional triggers. These connected cycles are well-described in the Breathing-Thinking-Functioning clinical framework for holistic breathlessness management.[40] Holistic breathlessness management, including psychosocial and physical exercise interventions targeting these vicious cycles, reduces hospital nights and depression in clinical trials.[43]

Strengths and limitations

This was a secondary analysis that was conceived after the data were collected. These data provide missing information about a complex interplay between disease, ageing and breathlessness in the oldest old. Given the pseudo R^2 values, other factors are at play that will need to be explored. Although in the multivariate regression models all the dependent variables were mutually adjusted, we did not calculate interactions between cardiovascular and respiratory diseases on the prevalence over time.

Implications for clinical practice and research

Breathlessness services improve breathlessness, psychosocial wellbeing and help to facilitate more judicious use of health service utilisation by addressing the vicious downward cycle of reduced mobility, deconditioning, social interaction and mental health.[43] To date, clinical trial populations and health services research rarely focuses on the oldest old. Community-based long-term illness care should include routine enquiry about breathlessness-related limitations, currently often invisible due to lack of enquiry,[10] with appropriate breathlessness management. Equally, when breathlessness is identified, clinicians should inquire about other potential long-term health problems. Current knowledge about limiting breathlessness, its impact and benefits from interventions is based on data from younger populations; further study in the oldest old would help develop tailored interventions for this group.

CONCLUSIONS

Breathlessness limiting exertion affects between one in four and five oldest adults, becoming less prevalent over time. Breathlessness severely limiting exertion was associated with more primary care contacts and hospital nights, depression, and worse self-reported health. Holistic breathlessness interventions may improve service utilisation and wellbeing; further study in the oldest old would help develop such interventions tailored for this group.

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Appendices

Table 1 Variables included in the multivariable models, with rationale.

Age, sex and weight	The prevalence of breathlessness increases i) with older age,[13] except in the very old, when it declines with increasing age,[17] and ii) in women[11] The interplay between age-related changes and sex is complex, and increased breathlessness intensity ratings in older women disappear when differences in maximal respiratory capacity are adjusted for.[33] Body-mass index (BMI) is associated with breathlessness in the adult population[44] and older adults (≥50 years)[45] in a ”U-shaped” manner, with breathlessness greater in those under- and overweight compared with those of normal weight.
Socio-economic factors	Markers of deprivation (e.g., education, household income) are directly associated with rates of breathlessness at a population level.[46]
Medical condition and smoking status	Breathlessness is a common symptom in people with long-term medical conditions of the heart and lungs, and cancer, increasing in prevalence in late-stage disease.[15] We therefore included the following variables from this dataset: number of self-reported illnesses; respiratory disease; cardiovascular disease; cancer. Although many of these diseases are smoking related, smoking is also associated with breathlessness in a dose-dependent manner even in the absence of demonstrable respiratory disease; smoking status was therefore included.[47]
Living status, physical activity, disability and depression	Loneliness and depression in older adults are associated,[48] as are breathlessness and depression.[17] Driving has been associated with benefits regarding quality of life and loneliness in older adults.[49]
Blood markers of inflammation (CRP, cortisol)	An association between chronic breathlessness and changes in the hypothalamic-pituitary-adrenal axis has been observed.[23] A small observational study of salivary cortisol measures in people with advanced diseases and moderate-to-severe chronic breathlessness showed evidence of hypothalamo-pituitary-adrenal axis dysregulation.[24]
Measures of physical function (timed up and go)	The Timed Up and Go (TUG) test was developed in 1991 as a test of mobility and physical function in older adults.[22] More recently, it is used as a screening tool for the risk of falls in community dwelling older adults with a cut point of ≥13.5 seconds predicting higher risk,[50] although the predictive value

	has been questioned.[51] It also appears to predict frailty, where a cut off of >16 seconds achieves a positive prediction value of more than 50% (specificity 98%).[52] Although no direct association has been published between the TUG and breathlessness in older adults, population studies show reduced mobility in those with severe breathlessness.[3]

Appendices

Table 2. Prevalence of breathlessness by Phase

		Phase 1			Phase 3			Phase 4		
		n	%	95%CIs	n	%	95%CIs	n	%	95%CIs
Any breathlessness										
	No	633	78	75 to 80	385	80	76 to 83	274	80	75 to 84
	Yes	184	23	20 to 25	98	20	17 to 24	70	20	16 to 25
	Total	817	100		483	100		344	100	
Severe breathlessness										
	No	746	91	89 to 93	452	94	91 to 96	326	95	92 to 97
	Yes	71	9	7 to 11	31	6	4 to 9	18	5	3 to 8
	Total	817	100		483	100		344	100	

CIs= confidence intervals

Appendices Table 3. Descriptives of the study variables which were included in the final multivariate models – binary and categorical variables

		Phase 1		Phase 3	
		n	%	n	%
Any breathlessness (BL)					
	No BL[1]	633	77.5	385	79.7
	BL	184	22.5	98	20.3
	Total	817		483	
Severe breathlessness (SBL)					
	No SBL[1]	746	91.3	452	93.6
	SBL	71	8.7	31	6.4
	Total	817		483	
Sex					
	Male	312	38.2	176	36.4
	Female	505	61.8	307	63.6
	Total	817		483	
Full time higher education[2]					
	No	718	88.4	413	85.7
	Yes	94	11.6	69	14.3
	Total	812		482	
Living alone					
	Yes	447	54.8	273	56.5
	No	288	35.3	150	31.1
	Not applicable[3]	81	9.9	60	12.4
	Total	816		483	
Currently driving					
	No	679	83.1	425	88.0
	Yes	138	16.9	58	12.0
	Total	817		483	
Smoking status					
	Never smokers	311	38.1	NA	NA
	Ex-smokers	451	55.2	NA	NA
	Smokers	55	6.7	NA	NA
	Total	817		NA	
Cancer					
	Never diagnosed	692	85.4	382	81.3
	Ever diagnosed	118	14.6	88	18.7
	Total	810		470	
Any respiratory disease					
	Never diagnosed	609	74.7	344	73.2
	Ever diagnosed	206	25.3	126	26.8
	Total	815		470	
Any CV disease					
	Never diagnosed	353	43.4	184	39.2

	Ever diagnosed	461	56.6	285	60.8
	Total	814		469	
Very energetic physical activity					
	Less than once a week	773	94.7	472	97.7
	At least once a week	43	5.3	11	2.3
	Total	816		483	
Moderately energetic physical activity					
	Less than once a week	532	65.2	381	78.9
	at least once a week	284	34.8	102	21.1
	Total	816		483	
Mildly energetic physical activity					
	Less than once a week	210	25.7	181	37.5
	At least once a week	606	74.3	302	62.5
	Total	816		483	
Loneliness					
	Never	448	55.7	282	61.0
	Sometimes	277	34.5	142	30.7
	Often	62	7.7	32	6.9
	Always	17	2.1	6	1.3
	Total	804		462	
Self-rated health					
	Poor	24	3.0	10	2.1
	Fair	148	18.7	92	19.7
	Good	296	37.4	177	37.9
	Very good	238	30.1	149	31.9
	Excellent	85	10.7	39	8.4
	Total	791		467	
Nights spent in hospital (last 12 mths.)					
	0	635	77.9	357	74.8
	1-6	75	9.2	45	9.4
	7+	105	12.9	75	15.7
	Total	815		477	

Notes. [1]Includes movement limited for other reasons as well as the answer "don't know". [2] Data collected only at Phase 1; the Phase 3 column describes the participants at Phase 3 with their education levels as measured at Phase 1. [3] Included residential homes, nursing homes, etc.
NA= not applicable

Appendices Table 4. Descriptives of the study variables which were included in the final multivariate models – continuous variables

	Phase 1				Phase 3			
	N	**Mean**	**SD**	**Median (Q1, Q3)[1]**	**N**	**Mean**	**SD**	**Median(Q1, Q3)[1]**
Age[2]	815	85	0.44	85, 85 to 86	480	88	0.43	88, 88 to 89
Geriatric Depression Scale - total score[3]	762	3.6	2.6	3, 2 to 5	442	3.4	2.5	3, 2 to 5
Number of self-reported illnesses, excl. breathlessness	812	1.7	1.4	1, 1 to 3	483	2.1	1.5	2, 1 to 3
Timed up and go test in seconds[4]	749	19	15	14, 11 to 20	401	22	18.8	17, 12 to 24
High sensitivity C-reactive protein (mg/l)*	773	6.8	14.3	2.6, 1.2 to 6.0	434	5.6	13.1	2.4, 1.1 to 4.8
Cortisol in nmol/l	774	507	137	506, 427 to 580	434	513.99	137	516, 423 to 607
Primary care team contacts (last 12 mths.)	815	10	7.7	9, 5 to 14	477	11.4	8.2	10, 6 to 15.5

Notes. [1] Weighted averages; [2] Age at Phase 3 only approximate: about three years after age at Phase 1; The exact dates of the multiple interviews may vary; [3] Answers "don't know" counted as not depressed (score = 0); [4] If attempted and completed; Q1 = first quartile; Q2 = third quartile; PCTM = primary care team members

*the distribution of High sensitivity C-reactive protein is very skewed: most participants had very low values, and a few had high values. Therefore, the mean is higher than the median, or even the 3rd quartile.