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Dyspnea as an Independent Predictor of Mortality

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Abstract

Background—Dyspnea is a common and easily elicited presenting complaint in patients seen by physicians who evaluate and take care of chronic respiratory disorders. Although dyspnea is subjective and tends to increase with age or reduced lung function, it appears to be reproducible as a symptom and often signifies serious underlying disease.

Methods—Systematic review of longitudinal studies with dyspnea as the exposure and mortality as the outcome; age, smoking, and lung function had to be controlled for to be included in the review. In addition, a minimum sample size at baseline of 500 subjects was required for each study.

Results—From over 3,000 potential references **ten** longitudinal studies met all criteria and were included. All ten studies suggested that dyspnea was an independent predictor of mortality with point estimates by odds ratio, rate ratio, or hazard ratios ranging from 1.3 up to 2.9-fold greater than baseline. All ten studies had actual or implied 95% confidence interval bands greater than the null value of one.

Conclusion—Dyspnea, a symptom, predicts mortality and is a proxy for underlying diseases, most often of heart and lung. Therefore, chronic dyspnea needs to be evaluated as to etiology to allow for treatment to minimize morbidity and mortality when possible.

Keywords

Dyspnea; dyspnea predicts mortality; lung function and mortality

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Introduction

Dyspnea has been defined as shortness of breath or perceived difficulty breathing or an uncomfortable breathing sensation (1–5). In general, dyspnea is distressful or unpleasant in nature (1–5). This is in contrast to the athlete who might not perceive dyspnea despite exercising at a very high-intensity since a degree of respiratory difficulty is expected and not distressful or upsetting. Dyspnea, a subjective sensation (3), is primarily experienced due to diseases of the heart and lungs (1,2,5,6), albeit it can also include diseases of the neuromuscular apparatus, and occasionally psychological diseases such as anxiety reactions (1,2,5). These four general causes delineate up to 85% of patients with dyspnea as the primary symptom (5) and heart or lung diseases comprise about two thirds (5). In addition, obesity with or particularly without physical conditioning can be a source of dyspnea. There are also cultural as well as psychological factors at play, stoic individuals may complain of much less dyspnea for a given disease than others who are more sensitive to bodily messages (3,5). Nevertheless, dyspnea, particularly if persistent, is often a marker of significant underlying disease that needs to be diagnosed and treated to minimize significant mortality.

The purpose of this brief review is to evaluate the etiology of the common correlates (smoking and lung function) of chronic dyspnea, their impact on mortality and to determine if persistent dyspnea itself is an independent predictor of mortality, separate from these correlated factors. Although dyspnea is not often specified as acute or chronic, in the context of this review we are interested in chronic dyspnea (as elicited from the patient) ie dyspnea present for greater than one month (1,5,7,8).

Materials and Methods – Data Sources

The study sources used in this review were prospective cohort studies since this study design is the best of all observational studies. The longitudinal studies included in table 1 are some of the main longitudinal studies found since 1969 that evaluate lung function in relation to the outcome of mortality. They all give a similar message. The list of studies is not meant to be all inclusive.

Search Strategy

The search for articles related to the focus of this article, Dyspnea as an Independent Predictor of Mortality, came from a PubMed, ISI Web of Knowledge, and SCOPUS search of any/all articles that were highlighted with the following search strategy through March of 2013. English, human, and had the specifics of: Dyspnea and Mortality –systematic review, Dyspnea and Mortality – Clinical Trial, Dyspnea and Mortality. In addition, the same strategy used: Breathlessness and Mortality, Chronic Dyspnea and Mortality, and Chronic Breathlessness and Mortality. Studies referring to other studies in the bibliographies were also reviewed where appropriate.

Study Selection and Data Abstraction

From these searches only longitudinal or cohort studies were considered that controlled for at least age, lung function, and smoking and included at least 500 subjects at baseline. It was

felt that large studies of at least 500 should only be included so they would be more likely to have some power to detect a difference, if present. All studies had to have Dyspnea as an exposure variable and Mortality as the outcome. Ten longitudinal studies met all criteria and were summarized in Table 2.

Data abstracted from the articles included the sampled population, country of origin, age range and number of participants, length of time followed, determination of death and number who died, and point estimate as odds ratio, risk ratio or hazard ratio given.

Dyspnea Reproducibility

In order to consider chronic dyspnea as an independent predictor, its determination should be reliable. In other words, those who say they have dyspnea (or no dyspnea) on a questionnaire should also say the same thing on follow-up questionnaire. If the repeat questionnaire is too far in the future, it is possible that dyspnea reported in follow-up questionnaire is due to acquisition of new disease.

Dyspnea reliability has been evaluated in two studies (9,10). In both, the presence or absence of dyspnea was determined by questionnaire and documented as a dichotomous outcome variable (yes or no) (9,10). When the baseline questionnaire noted that dyspnea was present, the reproducibility of this response determined from one week to one month later was between 68.6 to 72.5% of the time (9) in one study and 91% in a second study (10). The latter study determined reproducibility after 2 weeks but less than 9 months later (10). When the baseline questionnaire noted that dyspnea was absent, the reproducibility was 90% (9) and 96% (10) on follow-up in these two studies. Based on this data it appears that determining the presence or absence of dyspnea by questionnaire is fairly reliable.

Dyspnea Mortality Associations: Smoking and Lung Function

Smoking and Mortality

Mortality from smoking has been well documented in prospective studies in men (11–14) and women (14,15). Smoking is the number one cause of preventable mortality world-wide with estimates of 5 million deaths annually among 1.1 billion smokers. Smoking is strongly associated with both heart and lung diseases, which often manifest as dyspnea (16). Therefore, mortality studies using dyspnea as a predictor variable need to control for smoking, a confounding variable.

Lung Function and Mortality

Table 1 summarizes data on lung function and mortality from seventeen longitudinal studies published since 1969 (17–33). None of these studies controlled for dyspnea. All studies except number 6 (22) use all cause mortality as a primary outcome variable and all studies come to the same general conclusion; people with better lung function have less overall mortality than those with reduced lung function over time. This is true for both women and men. Many but not all studies controlled for smoking, and the results were the same. Furthermore, studies number 7, 11, 13, 16, 17 (23,27,29,32,33) had at least subgroups with nonsmokers and the results did not change. In fact, studies 11 and 17 were in nonsmokers

only (27,33). Study number 13 (29) in particular had 5,013 male and female never smokers with a 1.95-fold (1.62 – 2.35) greater mortality in the lowest versus highest quintile of predicted FEV1% (after adjustment for age, gender, blood pressure, cholesterol, BMI, and social class). When looking at restrictive lung disease in nonsmokers, study number 16 found a 1.6 (1.2 – 2.1)-fold greater risk of mortality in those with restrictive disease compared to those with normal lung function (32). Reduced lung function of any type appears to be associated with greater overall mortality, independent of smoking.

A potential bias in all these studies in table 1 is inadvertently including subjects with serious disease at baseline. The underlying disease may have secondarily resulted in a reduction in lung function. This would result in spurious findings suggesting reduced lung function resulted in mortality, instead of serious disease itself determining mortality ie reverse causation. To eliminate this potential bias, three studies (29,31,33) excluded subjects who died before the 5 year or 10 year mark and re-analyzed the data. Again, results clearly demonstrated that subjects with low lung function had greater all cause mortality relative to those with normal lung function (29,31,33).

The largest of the studies in table 1 called study 13 (29) found an inverse dose-response relationship between lung function and all-cause mortality; this data further solidifies the Exposure (reduced lung function)-Outcome (all-cause mortality) relationship. In addition, when percentage population attributable risk for mortality was calculated, lung function (FEV1) was second in importance to cigarette smoking as a mortality risk factor (29). This suggests that in middle aged nonsmokers without comorbidities, reduced lung function is the number one risk factor for death over time.

The mechanism underlying the effect of reduced lung function is not known. Many theories have been postulated. First, it is known that the lungs are a primary line of defense and an important means of eliminating metabolic waste. Impairment in lung function thus could result in many diseases if toxic oxygen radicals and metabolic waste are handled less efficiently (31,34). Second, other extraneous factors may result in both impaired lung function and other non-lung diseases which cause mortality such as heart disease. In this latter case, reduced lung function may or may not contribute to increased mortality or be related to the primary cause of death (21,23). Third, second hand smoke exposure in utero, in the early years before adulthood or while a young adult may result in a reduction in lung function that in turn impacts on long-term survival (35–37). Maximally attained lung function occurs between ages 18 and 24 and plateaus until about age 35 (38). After age 35, there is a normal slow decline in lung function due to age. Subjects who do not attain their maximal lung function and/or have accelerated lung function loss in early adulthood may be more prone to increased mortality over the life-span (39). Finally, a number of studies suggest that systemic inflammation may accelerate lung function loss even in nonsmokers. Different markers of inflammation have been postulated including: 1) fibrinogen (40,41), 2) the more sensitive C-reactive protein assay as tested in young adults (42), 3) fibrinogen and C reactive protein (43), or 4) other direct lung markers such as intercellular adhesion molecule (ICAM)-1 and soluble P-selectin (44). All these studies (40, 42–44) show stronger effects in smokers than nonsmokers but the effect persists after controlling for smoking. This implies that those with suboptimal maximally attained lung function would be at higher

risk of mortality over time even though they do not smoke, if systemic inflammation is not prevented.

Dyspnea as an Independent Predictor of Mortality

Dyspnea, a subjective symptom (3), has been examined less often as a primary exposure variable in longitudinal studies looking at mortality. Most likely, this has been due to its presumed subjective, and therefore, less reliable nature. Nevertheless, since most people do not complain of dyspnea, its presence is not normal and may signify severe disease. The prevalence of dyspnea in random populations varies with age. It was as low as 2.4% in a population with ages 18 and over (10) to 32% in a random sample of a population aged 70 and older who lived at home (45).

There are two well-known hospital-based longitudinal studies that have used dyspnea as a complaint and followed patients over time looking at all cause mortality. An emergency department (ED) study found that dyspnea as a presenting complaint (with no history of asthma and no wheezing on exam) in the ED was associated with 1.37-fold greater mortality over 10 years compared with the general population (46). A second study evaluated patients with known COPD and found that dyspnea was as good a predictor of all cause mortality as FEV_1 (47).

There are at least three longitudinal studies done in the elderly that have used dyspnea as the exposure variable with mortality as the outcome, none of which controlled for lung function (48,49,50). The largest was a study of 2,762 subjects age 65 or older followed for 8 years (48). Dyspnea was by medical research council (MRC) grades 1–5 determined by questionnaire (51). After adjustment for age, smoking, and former occupation dyspnea was found to be a significant independent predictor of mortality at dyspnea grades 3, 4, and 5 compared to dyspnea grade 1 with hazard ratios of 1.4 (95% C.I., 1.2–1.7), 2.0 (1.6–2.5), and 6.0 (3.7–9.7), respectively. A second study enrolled 1,169 elderly subjects age 75 or older by postal questionnaire and defined dyspnea by the MRC grades 1–5 at baseline (49). The participants were followed for 10 years and it was found that dyspnea grades 3–5 combined versus grades 1–2 as referent had a 1.94 (1.11–3.38) greater odds of mortality after adjustment for age, gender (males had a higher mortality), and medical comorbidities (49). The third study in only 114 subjects followed for 8 years again using the MRC dyspnea scale found a hazard ratio of 1.2 (0.94–1.5) per one point increase in MRC score after adjusting for age and gender (50). Since lung function was not adjusted for in these three studies it is always possible that the increased mortality was at least partly related to poor lung function. This would mean that dyspnea may not actually be independently associated with mortality.

Ten occupational or population-based cohort studies summarized in Table 2 have found dyspnea at baseline (as determined by questionnaire) to be an independent predictor of all cause (6 studies) and cardiovascular disease (4 studies) mortality after controlling for age, smoking, and lung function (52–58). Mortality over time varied from 5% up to 39% of the population followed with higher percentages generally seen with longer follow-ups (Table 2). The point estimate ratios varied showing a 1.3 to 2.9-fold greater mortality over time

with dyspnea at baseline relative to no dyspnea. In the three studies that included both females and males, the results were the same (54,56,58). In the one study that evaluated whether dyspnea remitted after the baseline questionnaire, it was found that the risk of mortality was no different from the general population (58). This emphasizes the importance of persistent or chronic dyspnea as being the predictor of mortality (58). These studies in table 2 included four occupational groups, two random samples, and four general community samples. This varied mixture of study populations all with different investigators coming to the same general conclusion strengthens the argument that dyspnea as a symptom can be an independent risk factor for mortality. It should be noted that these ten studies are the only prospective ones available using dyspnea as an exposure, mortality as the outcome with control for age, smoking, and lung function.

It should be noted that eight of the ten studies in table 2 had hazard ratios, rate ratios, or one with an odds ratio that had 95% confidence intervals all above one. The two exceptions had p values in the articles less than 0.025 or smaller consistent with a 95% confidence interval greater than the null value of one if it had been calculated (53,54). Therefore, all ten large studies that can be found have been definitive in finding that dyspnea is an independent predictor of mortality when controlling for age, smoking, and lung function.

What Does Chronic Dyspnea Represent?

The two most common causes of death in the world now and for the foreseeable future are ischemic heart disease and cerebrovascular disease (59,60). The former is associated with dyspnea and subjects with dyspnea are more likely to have known or occult heart disease. In addition, deconditioning and obesity are associated with dyspnea (61,62). Both are also associated with an increased mortality (63–65). Finally, most chronic lung diseases are well-known causes of dyspnea with the two most common general categories being obstructive or restrictive (66,67). Therefore, the majority of patients with chronic dyspnea have diseases or conditions that result in increased mortality, albeit they may or may not have been clinically diagnosed. Two thirds of the time these diseases are related to diseases of the heart or lung (1,2,5,6), with anxiety and diseases of the neuromuscular apparatus rounding out dyspnea etiologies to about 85% (5).

As a specific example, it was recently found that dyspnea is associated with excess arsenic exposure from drinking water (68). However, well water arsenic exposure is known to cause heart and lung disease, the two most common causes of dyspnea (69–72). It is felt that the arsenic-dyspnea relationship is secondary to the heart and lung diseases that chronic well water exposure to arsenic causes (68).

Therefore, chronic dyspnea represents (73) an underlying disease process most commonly originating from the heart or lungs that predicts an increased cardiovascular and all-cause mortality. This increased mortality has been shown to be independent of smoking, lung function and age (Table 2). As more advanced diagnostic testing becomes available, dyspnea will probably cease to be an independent predictor when all relevant diseases and conditions are detected and controlled for. Until that time, the symptom of dyspnea should

result in a work-up looking for the etiology so that it can be treated to minimize morbidity and mortality.

Conclusions

Dyspnea when measured by questionnaire as a chronic symptom has been found to be an independent predictor of mortality in longitudinal studies when controlling for the three strongest predictors of mortality; age, smoking, and lung function (table 2). All studies where dyspnea was determined were observational in nature and it is always possible that unknown confounding produced the results. However, dyspnea as a marker of disease that results in mortality is biologically plausible since most diseases that manifest with dyspnea result in greater mortality than the general population.

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Table 1

Pulmonary Function and Association with Mortality –**17** Longitudinal Studies.

Characteristic	**Study 1**	**Study 2**	**Study 3**	**Study 4**	**Study 5**	**Study 6**
Number	200	2652	226	129	2539	2718
Gender	22 female 178 male	1525 female 1127 male	109 female 117 male	25 female 124 male	1244 female 1295 male	2718 men
Age Range	59 ± 8 years	35 – 79	20 – 69	20 – 77	20 – 83	25 – 64
Group Surveyed	COPD patients.	Framingham volunteers.	Random sample	COPD patients.	Nonpatient adults.	Random sample
Years of Survey	1960–1964	Framingham 5 to 10 exam.	1967	1964–1968	1971–1976	1954 – 1961
Follow-up Time	4 – 8 years	18 years	6 – 7 years	10 years	4.7 years, mean	20 – 25 years
Lung Function Type	All with FEV1 < 60% predicted.	FVC	FEV1/FVC ratio	FEV1 (all less than 1 liter)	FEV1/FVC ratio	FEV1/Height^3 or FEV1/Ht^3
Deaths	94	325	19	77	108	104
Comparison	Hi vs Low Unequal Tertiles of FEV1	Logistic Risk Function	Normal vs FEV1/FVC ≤ 60% predicted.	Survival vs Died	Normal vs FEV1/FVC < 68% Predicted.	Highest vs lowest lung function.
Age Adjusted	Yes	Yes	No	No	Yes	No
Smok. Adjusted	Yes.	Yes	No	No	Yes	No
Effect Measure	Crude OR = 16.57.	None	Crude OR = 2.7	None	Risk Ratio = 1.81	Crude Risk ratio = 10.9
Conclusion	Low Tertile FEV1 with highest mortality.	Lower FVC have higher risk of dying.	Lower FEV1/FVC with 2.7-fold greater odds of dying than normal FEV1/FVC.	Low B.D. response or greater ↓ FEV1 over time predicted death	Lower FEV1/FVC with 1.8-fold greater risk of dying than normal FEV1/FVC	Lower FEV1/Ht^3 with 11-fold greater risk of dying of COPD than higher
Year, Reference	1969, 17	1975, 18	1976, 19	1979, 20	1982, 21	1983, 22

Characteristic	**Study 7**	**Study 8**	**Study 9**	**Study 10**	**Study 11**	**Study 12**
Number	874	387	1061	2,887	2710	1956
Gender	male	male	male	1624 female 1263 male	2048 female 652 male	1956 male
Age Range	17 – 97	55 – 64	30 – 59	19 – 70	20 – 69	21 – 80
Group Surveyed	Healthy volunteers	Random sample	Factory Workers	Random sample	Random age stratified	Volunteers, veterans
Years of Survey	1958 – 1979	1957	1960 – 1961	1968	1976 – 1978	1961 – 1969
Follow-up Time	Up to 24 years	20 years	22 years	13 years	8 years	Up to 30 years
Lung Function Type	FEV1% predicted	FEV(0.75)	FEV1/Ht^3	FEV1% predicted	FEV1% predicted	FEV1

Characteristic	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12
Deaths	214	267	369	355	195	170
Comparison	High vs low percent predicted FEV1	Percent deaths by lung volume at baseline.	Higher vs lower $FEV1/Ht^3$	FEV1 ≥ 65% predicted vs less than this value.	High vs low FEV1% predicted.	FEV1, dichotomous
Age Adjusted	Yes	Yes	Yes	Yes	Yes	Yes
Smok. Adjusted	Yes	No	Yes	Yes	Yes	Yes
Effect Measure	HR = 1.25 for 20% ↓ in FEV1 percent predicted.	100% died if volume < 1 liter. 39.3% died if volume ≥ 3 liters.	HR = 1.22	OR = 1.43, female OR = 2.49, male	HR = 1.65 for a 50% ↓ in FEV1	HR = 1.67 (1.25 – 2.22)
Conclusion	The risk of dying is 1.25-fold greater with a 20% ↓ in FEV1 % predicted.	As baseline lung volume decreases risk of dying increases over time.	Risk of dying is 1.22-fold greater with 50 ml ↓ in FEV1 in normal size male.	Odds of dying greater with reduced lung function over time.	Risk of dying was 1.65-fold greater if FEV1% predicted ↓ by 50%.	Risk of dying was 1.7-fold greater in low vs high FEV1 groups.
Year, Reference	1985, 23	1986, 24	1986, 25	1986, 26	1990, 27	1995, 28

Characteristic	Study 13	Study 14	Study 15	Study 16	Study 17
Number	15,411	1691	1195	5542	3083
Gender	8353 female 7058 male	940 female 751 male	641 female 554 male	3034 female 2508 male	3083 male
Age Range	45 – 64	25 – 79	20 – 89	25 – 74	40 – 64
Group Surveyed	Population-based	Electoral Roll	Random sample	Probability sample	Civil Servants
Years of Survey	1972 – 1976	1969 – 1975	1960 – 1961	1971 – 1975	1967 – 1970
Follow-up Time	15 years	20 – 26 years	29 years	17.9 years, median	35 years
Lung Function Type	FEV1% predicted	FEV1 average-3 measurements	FEV1% predicted	FEV1, FVC. & FEV1/FVC ratio	FEV1
Deaths	4,439	438	580	1301	1545
Comparison	By quintiles of FEV1% predicted.	↓ in FEV1 of 1 liter comparison.	Highest vs lowest quintile.	Obstructive (OLD) or restrictive(RLD) vs no lung disease	HR per one SD decrease in FEV1
Age Adjusted	Yes	Yes	Yes	Yes	Yes
Smok. Adjusted	Yes	Yes	Yes	Yes	Yes
Effect Measure	HR = 1.89, female (1.63 – 2.20) HR = 1.92, male (1.68 – 2.20)	HR = 1.77, female (1.09 – 2.86) HR = 1.42, male (1.08 – 1.87)	HR = 1.81, female (1.24 – 2.63) HR = 2.24, male (1.60 – 3.13)	HR = 1.6, RLD (1.2 – 2.1) HR = 1.3, OLD (0.8 – 2.1)	HR = 1.12 (1.05 – 1.19)
Conclusion	Risk of dying was 1.9-fold greater in lowest vs highest quintile of FEV1% predicted.	Reduced lung function is a predictor of mortality over time.	Reduced pulmonary function is a long-term predictor of mortality.	RLD in nonsmokers & OLD in smokers only is a predictor of mortality.	Risk of dying was 1.12-fold greater with 1 SD decrease in FEV1 over time.
Year, Reference	1996, 29	1999, 30	2000, 31	2003, 32	2006, 33

FEV1 = forced vital capacity in one second, FVC = forced vital capacity, COPD = chronic obstructive pulmonary disease, OR = odds ratio, HR = Hazard Ratio. % = percent. Smok. = smoking. Type of death was all-cause mortality in all studies except study 6 which was COPD deaths.

Table 2

Dyspnea and its Association with Mortality – Ten Cohort Studies.

Characteristic	**Study 1**	**Study 2**	**Study 3**	**Study 4**	**Study 5**
Study	Tecumseh	Whitehall	WHO	Sweden	West Scotland
Dyspnea Definition	SOB walking on the level	SOB walking on the level.	SOB walking on the level.	SOB walking on the level.	SOB walking on the level.
Number	844	17717	4903	607	6,859
Gender	male	male	male	male	male
Age Range	40–64	40–64	40–64	50–60	45–64
Group Surveyed	General Community	Civil Servant	Occupational Groups	Random Sample	General Community
Year of Initial Survey	1962–65	1967–69	1970–71	1973	1972, 74–75
Follow-up	16 years	10 years	15 years	11 years	6–8 years
Death Number.	103	889	416	107	367
Type of Death	CVD only	CVD only	CVD only	All cause	CVD only
Dyspnea & Death RR	Rate Ratio 1.69 (1.03–2.77)	Rate Ratio 2.39 (2.03–2.81)	Rate Ratio 2.32 (1.82–2.96)	Odds Ratio 2.92	Rate Ratio 2.01 (1.62–2.49)
Conclusion	Dyspnea is a Predictor of CVD Mortality	Dyspnea is a Predictor of CVD Mortality	Dyspnea is a Predictor of CVD Mortality	Dyspnea is a Predictor of all cause Mortality	Dyspnea is a Predictor of CVD Mortality
Year, Reference	1989, 52	1989, 52	1989, 52	1987, 53	1989, 52

Characteristic	**Study 6**	**Study 7**	**Study 8**	**Study 9**	**Study 10**
Study	Framingham	Denmark	Australia	Norway	Netherlands
Dyspnea Definition	SOB walking on the level or SOB climbing stairs.	MRC level 3 or higher SOB. Reference 51	SOB walking with others on level ground.	SOB hurrying on the level or walking uphill.	SOB walking with others on level ground.
Number	3133	1030	4277	1623	7360
Gender	female and male	male	2177 female 2100 male	male	3547 female 3813 male
Age Range	53 – 85	46 – 69	25 – 79	40 – 59	14 – 79
Group Surveyed	Random sample	Occupational Groups	General Population	Healthy Occupational Sub Groups	General Population
Year of Initial Survey	1972–1976	1974–75	1969	1972–75	1965
Follow-up	20 – 25 years	10 years	20–26 years	26 years	43 years
Death Number.	840	219	840 men 637 women	615	2883

Characteristic	Study 6	Study 7	Study 8	Study 9	Study 10
Type of Death	All cause	All cause	All cause	All cause	All cause
Dyspnea & Death RR	HR = 1.67 male, age: 70–86 HR – 1.79 female, age: 53–69	HR = 1.57 (1.13 – 2.20)	Male = 2.33 (1.25 – 4.35) Female = 1.56 (1.07 – 2.29)	HR = 1.43 (1.11 – 1.83)	Overall HR = 1.3 (1.2 – 1.5) male = 1.3 (1.1 – 1.7) female = 1.4 (1.1 –1.6)
Conclusion	Dyspnea is a Predictor of all cause Mortality	Dyspnea a Predictor of all cause Mortality	Dyspnea is a Predictor of all cause Mortality	Dyspnea is Predictor of all cause Mortality	Dyspnea is a Predictor of all cause Mortality
Year, Reference	1989, 54	1988, 55	1999, 56	2006, 57	2012, 58

SOB = shortness of breath, CVD = cardiovascular disease, RR = rate ratio, odds ratio, or hazard ratio, HR = hazard ratio, MRC = Medical Research Council. Scale of 1 to 5 on Breathlessness. See reference 51.