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DYSPNEA: A STRONG INDEPENDENT FACTOR FOR LONG-TERM MORTALITY IN THE ELDERLY

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Abstract: *Objective:* To determine the association between dyspnea at entry into the PAQUID cohort and 13-year mortality, taking into consideration BMI and other mortality-related factors. *Methods: Design:* Longitudinal study. *Setting:* In Dordogne and Gironde, South Western France. *Subjects:* A total of 3646 French community dwellers aged 65 years old and over from the PAQUID study were included. Main outcome measures: dyspnea measured on 5-grades scale, mortality measured over 13 years of follow-up. Adjustment variables: age, gender, BMI (kg/m^2), antecedent of ischemic heart disease, antecedent of stroke, hypertension, smoking history and diabetes. *Results:* The study sample included 3646 subjects out of whom 54.11% died at 13 years of follow-up, 57.3% of participants were women and mean age was 75.3 (SD 6.8) years. Univariate analysis showed that dyspnea was associated with 13-year mortality. Death occurred in 45.6% of non-dyspneic subjects , 51.8% in those with level 1 of dyspnea, 65.6% in level 2 and 80.6% in level 3 and 4 ($P<10^{-4}$). The median survival was at 13.26 (SD 0.20) years for level-0 of dyspnea, 12.33 (SD 0.31) years for level-1 of dyspnea, 9.28 (SD 0.44) years for level-2 and 6.43 (SD 0.45) years for level-3 and 4 ($P=10^{-3}$). In the multivariate analysis, the risk of mortality for level1 compared to level-0 was HR=1.13 (CI95%=[1.01-1.26]); this risk increases to HR=1.42 (CI95%=[1.25-1.63]) for level-2 and to HR=1.90 (CI95%=[1.61-2.25]) for level-3 and 4. *Conclusion:* These findings suggest that the relationship between long-term mortality and dyspnea is strong, consistent and independent of other covariates in the elderly.

Key words: Dyspnea, mortality, elderly, morbidity, ageing, cohort.

Introduction

Dyspnea is a symptom frequently reported by elderly subjects. The prevalence of dyspnea in patients aged 65 years old and over is estimated at 21% (1) and 34% in subjects aged 84 years old and over (2).

Dyspnea can be defined as a feeling of difficult or labored breathing disproportionate to the level of the produced effort 1. Although its etiologies are variable, dyspnea is a common symptom of many acute or chronic disorders, but the most common causes are cardiovascular and respiratory diseases (3), particularly cardiac failure, chronic obstructive pulmonary diseases (COPD) (4) and asthma (5). Whatever its etiology is, dyspnea is recognized as inducing a high degree of disability (6) that may itself lead to mortality (7).

In some studies, dyspnea has been considered as a better marker of respiratory illness than respiratory function (8).

Using an epidemiological program that studies factors of functional and cerebral ageing (PAQUID (Persons Aged QUID)) (9), we have previously shown that dyspnea is a very common symptom in the elderly and depends in particular on previous occupational activity in this cohort (10). It also proved to be a disabling symptom limiting most daily living activities 6. In the elderly, many factors are known to have a strong relationship with mortality; especially age, sex, occupational activity, social class, and morbidity (11). In old age, co-morbidities are more severe, more frequent and may be related to dyspnea and lead to disability. Recent overall studies have also confirmed that smoking at this age, which is one of the main risk factors of chronic respiratory diseases, is also associated with mortality (12).

In addition to the presence of frequent multiple pathologies, old age is characterized by a high prevalence of both underweight and overweight (13). Obesity has become a serious public health issue, especially in developed countries and its prevalence is increasing in elderly subjects (14). A growing body of evidence indicates that obesity is associated with a wide range of health conditions, including respiratory diseases such as COPD and asthma (15). At the other extremity of Body Mass Index (BMI) range, being underweight is also associated with an increased risk of mortality, especially in older adults (16).

Numerous studies have examined the association between body mass index (BMI; in kg/m^2) or weight change and pulmonary function testing variables. These associations vary in different subpopulations (17).

In this paper, we attempt to determine the association between dyspnea at entry into the PAQUID cohort and mortality occurring during the 13-years follow-up, taking into consideration BMI and other mortality-related factors.

Methods

Mortality associated with dyspnea was examined using data from the 13-years mortality follow-up of the PAQUID study, a prospective cohort study of mental and physical ageing in

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south-western France (the Gironde and the Dordogne administrative regions). The general methodology of the PAQUID study has been described elsewhere (9). Sample selection was based on a three-step random procedure stratified for age, sex, and size of the urban area of residence. Among the 5555 eligible subjects, 3777 gave their written consent to participate and were visited at home by a specifically trained psychologist for the baseline interview. The sample was representative of age and sex distribution of elderly community dwellers of the area (9). The main variables of interest in this analysis were mortality and dyspnea. Every death occurring during follow-up was recorded systematically. If a subject could not be reached at the follow-up visit planned every two years, we checked with a proxy and his/her general practitioner if he/she had died. Otherwise, a letter was sent to the city administration asking if they had registered his death certificate. Date of death was also recorded.

Level of dyspnea at baseline was obtained by a direct question using an adaptation of the Fletcher scale (18). It consisted in asking the subject whether he or she felt out of breath in some of the following circumstances: never (level 0), during major effort such as climbing a flight of stairs (level 1), minor effort such as walking with other people of one's own age on the flat at a normal pace (level 2), during everyday activities such as dressing or undressing (level 3), or permanent dyspnea even at rest (level 4). Hence, each subject was scored between 0 and 4. Level 3 and 4 was subsequently grouped into a single category of dyspnea because of the small sample sizes in level 4.

BMI at baseline was calculated as self-reported weight (kg) divided by self-reported height (m) squared, which we further divided into six grades. The thresholds of BMI considered were those recommended by the World Health Organization and the U.S. federal guidelines 19-21. For the current analyses, the normal-weight category (18.5 – 24.9 kg/m^2) was subdivided into two categories: (18.5-22) (grade 1 normal weight) and (22.0-24.9) (grade 2 normal weight). Obesity was subsequently grouped into a single category of BMI of 30.0 kg/m^2 and higher because of the small sample sizes in each obesity class.

Smoking status at baseline was recorded as follows: former smokers who quitted more than 10 years ago, former smokers who have recently quitted smoking (< 10 years); current smokers with consumption under 20 pack per year, current smokers with a consumption of 20 pack a year or more and non-smokers.

Co-morbidity included antecedent of ischemic heart disease, antecedent of stroke, hypertension and diabetes. A subject was considered as diabetic if he had 2 out of the 3 following criteria: presence of diabetes, presence of a diabetic regime or utilization of diabetes medications.

Statistical analysis

First, we described the distribution of dyspnea at entry into the cohort. By univariate analysis, we compared 13-years mortality rates according to dyspnea grade and 13-years survival curves were obtained using the Kaplan-Meier methods. In order to adjust potential confounding factors, we performed a multivariate analysis with the Cox proportional hazards model. The dependent variable was time to death over 13-years of follow-up. Dyspnea was introduced as the principal explanatory variable. Hazard ratios for mortality were estimated for each dyspnea grade with absence of dyspnea as reference category.

Table 1

Characteristics of study population according to dyspnea status. PAQUID baseline, 1988-89 (N=3646)

	Dyspnea level					
	Level 0 n=1373	**Level 1 n=1367**	**Level 2 n=610**	**Levels 3 and 4 n=268**	**P**	**Total**
Women, %	54.8	56.9	62.8	58.6	$<10^{-2}$	57.3
Mean age (SD)	74.3 (6.7)	74.9 (6.46)	76.6 (6.9)	78.5 (7.0)	$<10^{-3}$	75.3 (6.8)
Mean BMI	23.9 (3.4)	24.8 (3.9)	25.3 (4.4)	24.9 (4.8)	$<10^{-3}$	24.6 (3.9)
BMI class, %					$<10^{-3}$	
< 18.5	4.3	4.0	4.4	6.0		4.3
[18.5-21.9]	23.2	18.5	18.2	22.8		20.5
[22-24.9]	38.2	33.0	28.4	25.4		33.6
[25-29.9]	29.8	34.8	36.4	33.2		33.1
≥ 30	4.5	9.7	12.6	12.6		8.4
Diabetes, %	6.8	7.6	14.3	16.0	$<10^{-3}$	9.0
Smoking status, %					0.04	
Current smokers (≥20 pack year)	6.7	5.5	3.9	3.0		5.5
Current smokers (< 20 pack year)	3.9	5.2	2.5	4.1		4.2
Former smokers (<10 years)	10.4	10.0	10.3	12.7		10.4
Former smokers (≥10years)	17.1	17.8	17.0	19.8		17.6
Never-smokers	61.8	61.4	66.2	60.4		62.3
Hypertension, %	73.8	79.2	79.7	77.4	$<10^{-2}$	77.1
Ischemic heart disease antecedent, %	8.7	21.4	38.2	49.4	$<10^{-3}$	21.4
Stroke antecedent, %	5.1	5.3	9.2	10.8	$<10^{-3}$	6.4

In the first model, we studied the association between dyspnea and mortality taking into account age and sex. In the second model, and to address potential confounding factors, relative risks and 95 percent confidence intervals were adjusted for BMI, age, sex, smoking status and co-morbidity.

P=0.05 was the level of statistical significance. Statistical analyses were performed with SAS® software 9.1.

Results

Of the 3777 PAQUID cohort subjects 131 (3.4%) with missing BMI at baseline were eliminated. No significant difference was found between these subjects (n=131) and those included in the analysis (n=3646) according to demographic data (age, sex and level of education). 57.3% of the participants were women. Mean age was 75.3 years (SD 6.8 years).

As in inclusion in the study, 7.4% of the subjects were classified in dyspnea level 3 or 4; 16.9% in level 2; 37.5% in level 1 and 37.6% in level 0 i.e. without dyspnea. The general description of the sample according to dyspnea status at baseline is presented in Table 1. Participants in each dyspnea class differed significantly for all the characteristics examined here (Table 1). In particular, severely dyspneic subjects (level 3 or 4) were often underweight (BMI < 18.5) or obese (BMI ≥ 30). Also, severely dyspneic subjects were often diabetics (16.0%). Subjects with severe dyspnea have more ischemic heart disease or stroke antecedent. There were more former smokers among the subjects with severe dyspnea.

Of the 3646 individuals, 1973 (54.1%) died over the 13 years of follow-up. Univariate analysis showed that dyspnea was associated with mortality in 13-years of follow-up. Death occurred in 45.6% of the subjects in level 0 of dyspnea, 51.8% in level 1, 65.6% in level 2 and 80.6% in level 3 and 4 ($P<10^{-4}$).

Figure 1 shows unadjusted Kaplan Meier survival curves by dyspnea status. The mortality increased with the level of dyspnea. The survival median was 13.26 (standard deviation, SD 0.20) years for level 0 of dyspnea, 12.33 (SD 0.31) years for level 1 of dyspnea, 9.28 (SD 0.44) years for level 2 and 6.43 (SD 0.45) years for level 3 and 4 combined ($P=10^{-3}$).

Results of the multivariate Cox proportional hazards model are presented in Table 2.

After adjustment for age and sex, the mortality risk increase with dyspnea level. The relative risk of mortality for level 1 compared to level 0 was HR=1.16 (CI95%=[1.04-1.29]); this risk increased to HR=1.55 (CI95%=[1.37-1.76]) for level 2 and to HR=2.14 (CI95%=[1.83-2.50]) for level 3 and 4. The addition of BMI, smoking status and co-morbidities (diabetes, hypertension, ischemic heart disease antecedent, stroke antecedent), did not substantially change this association. The relative risk of mortality for level 1 compared to level 0 was HR=1.13 (CI95%=[1.01-1.26]); this risk increases to HR=1.42 (CI95%=[1.25-1.63]) for level 2 and to HR=1.90

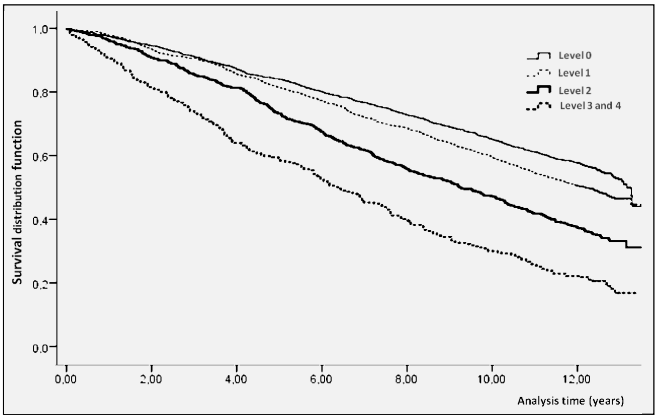
Table 2
A Cox proportional hazards model: Association between dyspnea and mortality over 13 years of follow-up of the PAQUID study ($P<10^{-4}$)

	Model 1 (N=3618)			Model 2 (N=3594)		
	HR_{aj}[1]	95%CI[2]	P	HR_{aj}[1]	95%CI[2]	P
Sex (Women vs Men)	0.55	[0.50-0.60]	$<10^{-3}$	0.65	[0.58-0.73]	$<10^{-3}$
Age	1.11	[1.11-1.12]	$<10^{-3}$	1.12	[1.11-1.12]	$<10^{-3}$
Dyspnea level			$<10^{-3}$			$<10^{-3}$
Level 0	1	--		1	--	
Level 1	1.16	[1.04-1.29]		1.13	[1.01-1.26]	
Level 2	1.55	[1.37-1.76]		1.42	[1.25-1.63]	
Level 3 and 4	2.14	[1.83-2.50]		1.90	[1.61-2.25]	
BMI Classes						$<10^{-3}$
< 18.5				1.40	[1.14-1.73]	
[18.5-21.9]				1.26	[1.11-1.43]	
[22-24.9]	--	--		1	--	
[25-29.9]				0.99	[0.88-1.11]	
≥ 30				1.08	[0.90-1.29]	
Diabetes	--	--		1.49	[1.29-1.73]	$<10^{-3}$
Smoking status						$<10^{-3}$
Current smokers (≥20 pack year)	--	--		1.67	[1.34-2.08]	
Current smokers (< 20 pack year)	--	--		1.33	[1.08-1.65]	
Former smokers (<10 years)	--	--		1.42	[1.21-1.67]	
Former smokers (≥10years)	--	--		1.22	[1.06-1.41]	
Never-smokers	--	--		1	--	
Hypertension	--	--		1.03	[0.92-1.16]	0.60
Ischemic heart disease antecedent	--	--		1.14	[1.02-1.27]	0.02
Stroke antecedent	--	--		1.24	[1.05-1.46]	0.01

1. Adjusted hazard ratio; 2. 95% confidence intervals for adjusted hazard ratio; Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, BMI, diabetes, smoking status, hypertension, ischemic heart disease antecedent and stroke antecedent.

(CI95%=[1.61-2.25]) for level 3 and 4. Smoking status and each co-morbidity except hypertension were also independent predictors of mortality. Notably, being underweight but not obesity was also associated with an increased risk of mortality.

Figure 1
Kaplan Meier survival estimated by dyspnea level



Discussion

Based on a representative sample of people aged 65 and over followed-up for 13 years, the results of this study show that dyspnea at this age is closely associated to long-term mortality, even when BMI, age, sex, smoking status and co-morbidity are taken into account. These findings in the elderly suggest that the relationship between mortality and dyspnea is consistent, stable and independent of other covariates.

All the previous studies found out a significant association between dyspnea and mortality in elderly subjects (22, 23). But these studies focused only on short-term mortality and follow-up did not exceed 8 years. Moreover, they have not taken into consideration the known covariates related to mortality in the elderly, such as co-morbidities and BMI. The study conducted by B. Huijnen et al. (23) took into account, as an adjustment variable, only two variables (age and sex) and J.F. Tessier et al. (22) studied the relationship between dyspnea at entry into the PAQUID cohort and mortality which have occurred during the 8-years follow-up, taking into consideration only four variables (age, sex, smoking status and occupation).

Our findings are consistent with those of recent studies. Dyspnea that occurs frequently in the elderly, is associated with poor health and represents a risk factor for mortality (22-24).

Dyspnea is not a specific symptom although its etiologies are variable (3, 25). Indeed, dyspnea is a common symptom of many acute or chronic disorders, but the most common causes are cardiovascular and respiratory diseases (3), particularly cardiac failure, COPD (3) and asthma (5). In our study, we evidenced an association between dyspnea and both underweight and obesity, which could have been confounders in the relationship of dyspnea to mortality. Our results show that this relationship was independent of BMI.

Cardiovascular diseases, known as a source of dyspnea, are the main cause of death in Europe, accounting for 49% of all deaths and 30% of all premature deaths before the age of 65 (26).

In a recent study, dyspnea is associated with respiratory and all-cause mortality (22, 27). It was the second most important factor independently related to respiratory mortality and was the most important factor associated with all-cause mortality (27).

COPD is associated with chronic dyspnea. Worldwide, COPD is the only leading cause of death that still have a rising mortality rate. It represents an increasing burden worldwide, reported to be the sixth leading cause of death in 1990 (28) and the fourth in 2000 (24). By the year 2020, COPD is foreseen that it will have been the third leading cause of death in the world (29).

The main point of strength in our study is the long period of follow-up of all the study subjects and the included set of clinical control variables. On the other hand, several limitations should be noted, the number of subjects and deaths was reasonably large, but it did not allow us to perform detailed analysis according to the cause of death.

Another limitation is the lack of objective-measure of respiratory function such as FEV1 (forced expiratory volume), even though respiratory function is difficult to be measured in the elderly. Lung function is well known to be a predictor of mortality (30); however, Knuiman et al. (30) and Vestbo et al. 8 found out that dyspnea is related to mortality from all causes independently of lung function. On the other hand, a practical problem in assessing results of spirometry in older subjects is that the reference value is often derived by linear extrapolation of rates of decline in studies of subjects aged more than 70 years old (31). Thus, clinical assessment of dyspnea provides a simple and valid indicator of prognosis in terms of mortality.

In conclusion, the association between dyspnea and mortality remains strong, consistent and stable regardless of BMI and other mortality factors in this elderly population. Dyspnea appears to be a good global independent predictive index of health status in the elderly.

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