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## **The determinants of dyspnoea evaluated by the mMRC scale: The French Palomb cohort**

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6 **The determinants of dyspnoea evaluated by the mMRC scale: The**  
7 **French Palomb cohort**

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## 37 Abstract

38 **Introduction and Objective:** Dyspnoea is a major symptom in COPD patients, but the determinants that  
39 could be associated with a higher dyspnoea mMRC score in COPD patients remain unclear. Our research aimed  
40 to study the determinants of dyspnoea at the threshold of 1, 2, 3 and 4 mMRC.

41 **Patients and Methods:** Diagnosis of COPD was made using spirometry with post-bronchodilator  $\frac{FEV_1}{FVC} < 70\%$ .  
42 An online questionnaire has been employed by pulmonologists to recruit COPD patients. The following  
43 variables were collected: age, gender, BMI, FEV<sub>1</sub>, RV, IC, TLC, FRC, mMRC, frequency of exacerbations and  
44 comorbidities. The LASSO was used to select the variables associated with the mMRC dyspnoea scale in a  
45 subgroup (who had no missing IC, RV and FRC values) of 421 COPD patients defined by the previously  
46 mentioned variables.

47 **Results:** 1,973 patients (65.3% males, average age= 66±10, 38% current smokers) were included. Dyspnoea  
48 was correlated with a low FEV<sub>1</sub> and with the number of exacerbations in the past 12 months. Multivariate  
49 analysis showed that the determinants of dyspnoea(mMRC≥2) are: FEV<sub>1</sub>: OR=3.71[2.86-4.82]; anxiety:  
50 OR=2.52[1.82-3.47]; cough: OR=1.94[1.57-2.40]; bronchiectasis: OR=1.84[1.03-3.29]; age: OR=1.80[1.45-2.24];  
51 hyperinflation (RV/TLC): OR=1.68[1.34-2.11]; ischemic cardiopathy: OR=1.63[1.22-2.18]; hypertension:  
52 OR=1.52[1.21-1.91]; exacerbations (≥2): OR=1.41[1.10-1.81]; women: OR=1.39[1.10-1.74] and overweight:  
53 OR=1.33[1.06-1.67]. The subgroup analysis showed that: FEV<sub>1</sub>: OR=3.47[1.96-6.12]; exacerbations (≥2)  
54 OR=2.31[1.33- 4.17] and hyperinflation (IC/TLC) OR=0.57[0.35-0.85] were associated with higher dyspnoea  
55 (mMRC≥2).

56 **Conclusion:** Our results showed that dyspnoea is related to the severity of airflow limitation, gender,  
57 exacerbations, comorbidities and hyperinflation.

58

59 **Key Words:** COPD, dyspnoea, mMRC, hyperinflation, sensitivity analysis.

60 **Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; mMRC, Modified Medical Research Council;  
61 FEV<sub>1</sub>, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; BMI, Body Mass index; RV, Residual  
62 Volume; IC, Inspiratory Capacity; TLC, Total Lung Capacity; FRC, Functional Residual Capacity; LASSO, Least  
63 Absolute Shrinkage and Selection Operator;

64

65

66 **1. Introduction**

67 Dyspnoea is the most dominant and defining symptom of COPD [1]. In many cases dyspnoea is linked to a  
68 worsening of COPD and an increased mortality risk [2]. Therefore, dyspnoea is of public health importance and  
69 needs more attention, especially since the degree of dyspnoea is an important and valid factor in the  
70 assessment of COPD severity.

71 It is difficult to design methods capable of capturing the various dimensions of the complex pathophysiological  
72 and psychosocial etiology of dyspnoea. Moreover, there exists a scarcity of consensus on the use of the present  
73 tools for capturing the confused dyspnoea history, in clinical investigation context [3]. Furthermore, despite  
74 therapeutic management (use of long-acting muscarinic antagonists, long-acting beta-2 agonists, short-acting  
75 beta-2 agonists and inhaled corticosteroids), patients with advanced COPD usually suffer from dyspnoea. For  
76 better patient management, clinicians must evaluate patient's dyspnoea history and interactions on a regular  
77 basis. While there are many instruments available for evaluating dyspnoea, no classification system or  
78 instrument is deemed optimal for COPD patients.

79 According to GOLD recommendations, the mMRC scale was used by clinicians to assess dyspnoea. This scale  
80 measures breathing difficulty in two classes (dyspnoea mMRC 0-1 and dyspnoea mMRC  $\geq 2$ ). A basic inquiry  
81 regarding the existence or absence of higher dyspnoea will certainly not serve to drive therapy, as it would lack  
82 clarity on the advanced state of the disease and hence inadequate management of the disease [4]. Existing  
83 knowledge gaps such as medical dyspnoea norm, cognitive disability evaluation and determination of the  
84 quality of dyspnoea treatment in patients warrant a sensitivity analysis using different mMRC scale cut-off  
85 values to define higher dyspnoea [5]. Owing to the total absence of sensitivity analyses in this framework, the  
86 evaluation of the determinants of dyspnoea becomes very complicated. Hence, in our cohort, we successfully  
87 performed a sensitivity analysis for higher dyspnoea with different cut-off values: mMRC scale  $\geq 1$ ; mMRC scale  
88  $\geq 2$ ; mMRC scale  $\geq 3$  and mMRC scale  $\geq 4$ .

89 Our research aimed to assess the determinants that might be associated with dyspnoea in COPD patients with  
90 a focus in the relationship in between mMRC scale and hyperinflation and propose a sensitivity analysis for  
91 higher dyspnoea.

92        **2. Patients and Methods**

93        2.1. Study design and population

94        The Palomb project: A cohort of COPD patients enrolled in pulmonary clinics in south west of France in a  
95        real-life setting as an ongoing, prospective, multicenter and observational study.

96        The research duration began on January 2014 and ended on January 2018. 1,973 patients were enrolled in  
97        the study by pulmonologists: The data was obtained using a web-site questionnaire fulfilled by the  
98        pulmonologist on a secure platform and with specific agreement obtained for the storage of health data. The  
99        inclusion criterion was a diagnosis of COPD on the basis of a lung function test according to the ATS/ ERS  
100        recommendations [6] and made using spirometry with post-bronchodilator (forced expiratory volume in one  
101        second / forced vital capacity < 70%) FEV1/FVC<70%. Patients were excluded if they didn't have the lung  
102        function criteria of COPD.

103        A pulmonary function test (PFT) was performed for COPD patients by pulmonologists at a clinic visit; the  
104        pulmonologists/study coordinators enter patient information, lung function values and patient's mMRC  
105        (modified medical research council) scale at the same clinic visit. The first reported mMRC dyspnoea grade at  
106        inclusion was used to measure dyspnoea.

107        Measurements

108        The online questionnaire (**additional file 1**) included the subsequent sections: demographic and tobacco  
109        smoke information's, clinical symptoms, lung volumes, comorbidities and treatments.

110        2.1.1. Dyspnoea scale

111        We used a simple, 5-point grading system (**Table 1**) called the mMRC scale, that tests breathing problems  
112        through everyday tasks [7]. The final value determines the extent of disability caused by dyspnoea. A  
113        pulmonologists coaching was provided to help patients to select a score on the mMRC scale. We used four cut-  
114        off values for a higher/lower dyspnoea group (**Table 1**).

115        2.1.2. COPD severity and Static hyperinflation

116 The 2017 GOLD [2] classification had changed, taking into account the GOLD grade [8] (I:  $FEV_1 > 80\%$ ; II:  
117  $80\% \geq FEV_1 \geq 50\%$ ; III:  $50\% > FEV_1 \geq 30\%$  and IV:  $30\% > FEV_1$ ), the mMRC dyspnoea grade ( $<2$  or  $\geq 2$ ) and the  
118 number of exacerbations ( $<2$  or  $\geq 2$ ) per year risk (refined ABCD tool) without comorbidities.

119 Recently, the ratio of residual volume to total lung capacity (RV/TLC) has been described as a distinct  
120 factor of poor prognosis in COPD patients [9, 10]. In our study, RV, IC (inspiratory capacity), FRC (functional  
121 residual capacity) and TLC were measured. The RV/TLC ratio was used to set three cut-off values for static  
122 hyperinflation: patients without hyperinflation ( $RV/TLC < 130\%$ ); patients with moderate hyperinflation ( $130\% \leq$   
123  $RV/TLC < 220\%$ ); and patients with severe hyperinflation ( $220\% \leq RV/TLC$ ). A variety of measures of  
124 hyperinflation have been used, but they all do not have the same meaning. [11] So, we decided to investigate  
125 the effects of other measures of hyperinflation [12] (FRC/TLC and IC/TLC ratio) by mMRC scale in the subgroups  
126 (who had no missing IC, RV and FRC values) of 421 patients defined by the previously mentioned variables.

### 127 2.1.3. Comorbidities

128 Twenty-three comorbidities were systematically recorded by the pulmonologist (see annex). Comorbidity  
129 diagnosis was first confirmed by patient care report, and then by the analysis of the patient's medication  
130 history (data not shown). Patients with presence of cardiovascular comorbidities are patients who had at least  
131 one of the following comorbidities: hypertension, ischemic cardiopathy, arrhythmia, left heart failure,  
132 atheroma, stroke, pulmonary hypertension or lower extremity artery disease.

### 133 2.1.4. Medications used for COPD

134 At the inclusion clinical visit, use of long-acting muscarinic antagonists (LAMAs), long-acting beta-2 agonists  
135 (LABAs), short-acting beta-2 agonists (SABAs) and inhaled corticosteroids (ICS) was collected.

### 136 2.2. Statistical analysis

137 Categorical variables are presented as proportions and continuous variables are presented as mean and  
138 SD. We performed a univariate logistic regression analysis between mMRC dyspnoea scale and  $FEV_1$ , number of  
139 exacerbations, gender, static hyperinflation and comorbidities. Statistically significant differences between  
140 groups were tested by Wilcoxon test, chi-square test, or fisher's exact tests, as appropriate. We performed an  
141 in-depth cross-analysis of different factors, to describe the similarities/differences existing between dyspnoea  
142 groups. Relationships between mMRC dyspnoea grade and clinical variables were examined by both Pearson

143 and spearman correlation coefficients. A logistic regression multivariate model with a backward elimination  
144 procedure was computed to identify factors associated with higher dyspnoea group. This model included the  
145 studied comorbidities, age, gender, hyperinflation, cough, sputum, the number of exacerbations and other  
146 parameters. Independent variables included in the model were also those showing a  $P < 0.05$  in bivariate  
147 analysis. We also performed a sensitivity analysis for higher dyspnoea with different cut-off values: mMRC scale  
148  $\geq 1$ ; mMRC scale  $\geq 2$ ; mMRC scale  $\geq 3$  and mMRC scale  $\geq 4$ . The least absolute shrinkage and selection operator  
149 (LASSO [13]: a machine learning regression analysis method that performs both variable selection and  
150 regularization in order to enhance the prediction accuracy and interpretability of the statistical model it  
151 produces) was used to select the variables associated with the mMRC dyspnoea scale in a subgroup of patients  
152 who had no missing RV, IC and FRC values. All analyses were performed with R version 3.3.2 and SAS software  
153 version 9.4.

### 154 **3. Results**

#### 155 3.1. Characteristics of the Patients.

156 1,973 patients with COPD were included in the PALOMB cohort and their characteristics are summarized  
157 in **Table 2**. They were mostly men (65.33%), with a mean age (SD) of 66.11 (10.98) years, mean post-  
158 bronchodilator FEV<sub>1</sub> was 58.11% (19.5%). They were symptomatic COPD patients with mild to very severe  
159 airflow obstruction associated with frequent comorbidities. 59.35% of patients reported one or more  
160 exacerbations in the previous 12 months. 33.63% women had more than two exacerbations compared to  
161 24.52% of men ( $P < 0.0001$ ). 1,158 patients were considered to have higher dyspnoea (mMRC grade  $\geq 2$ ) and  
162 59.14 % of patients suffer from the static hyperinflation ( $RV/TLC \geq 120\%$ ).

163 Stratification of the population according to the dyspnoea scale showed that was more frequent in  
164 women and overweight patients, and also correlated with the number of exacerbations. Dyspnoea was higher  
165 in patients with presence of cardiovascular comorbidities (60.45% Vs 39.55%), and more precisely in  
166 hypertensive patients (41.28%) and patients with ischemic cardiopathy (20.81%). Dyspnoea was also frequent  
167 in patients with presence of anxiety (21.85%), with 10 out of the 23 comorbidities being related to dyspnoea  
168 **(Table 3)**.

#### 169 3.2. Relationship between mMRC grade and morphometric, clinical and functional data.

170 According to **Fig. 1**, the GOLD grade (I, II, III and IV) was related to mMRC scale ( $P < 0.0001$ ). However, the  
171 correlation (**Fig. 2**) between mMRC and FEV<sub>1</sub> (% predicted) was low ( $r = 0.36$ ;  $P < 0.0001$ ). A Spearman non-  
172 parametric analysis (**Fig. 2**) found no correlations between mMRC grade and considered comorbidities. The  
173 correlation between depression and anxiety was low ( $r = 0.37$ ;  $p < 0.0001$ ). The presence of a chronic cough and  
174 sputum maintained a high correlation ( $r = 0.65$ ;  $p < 0.0001$ ). Furthermore, no significant correlation was found  
175 between mMRC grade and age, gender or BMI.

176 Univariate analysis was used to evaluate relationships between mMRC scale and hyperinflation. RV/TLC  
177 ratio was significantly different between mMRC scale 0 - 4 ( $p < 0.0001$ ). Dyspnoea was more frequent in patients  
178 with presence of hyperinflation (68.65%) than in patients with absence of hyperinflation (31.35%). more  
179 precisely, dyspnoea was more frequent (67.76%) in patients with presence of mild hyperinflation (**Table S1**).

### 180 3.3. Independent factors associated with the mMRC dyspnoea scale.

181 Multiple logistic regression analysis indicated that the presence of comorbidities such as Dyslipidemia,  
182 depression, asthma and left heart failure was not significantly different between the lower and the higher  
183 mMRC dyspnoea groups (0 - 1 Vs.  $\geq 2$ ).

184 Regardless of the cut-off values set to distinguish higher dyspnoea clusters, the severity of FEV<sub>1</sub> and  
185 anxiety remained linked with dyspnoea (**Table 4**). This data is also presented as a multiple forest plot diagram  
186 (**Fig. S1**) to make it easier to understand and interpret. The increase in the mMRC threshold (1; 2; 3 and 4)  
187 implies a substantial rise in the odds ratio of the severity of FEV<sub>1</sub> ( $\leq 50\%$ ): 2.93[1.92-4.49] vs. 3.71[2.86-4.82];  
188 and vs. 4.30[3.30-5.60]; and vs. 4.66[2.96-7.31]. The results do not change substantially with added adjustment  
189 for factors such as: age, gender and FEV<sub>1</sub> (**Table S2**).

190 The information on medications used to treat COPD is important as they affect dyspnoea and could affect  
191 relationships among patient characteristics and mMRC scores. In our cohort, patients with mMRC  $\geq 2$ , compared  
192 with those with mild dyspnoea (mMRC = 1) or those with absence of dyspnoea (mMRC = 0) were more  
193 intensively treated with COPD inhaled treatments (**Table 5**).

### 194 3.4. Subgroup analysis

195 Box plot of the relationships between RV, IC, FRC, RV/TLC, IC/TLC and FRC/TLC ratio (% predicted), as  
196 indicators of static hyperinflation, and mMRC dyspnoea scale, as measure of dyspnoea, were assessed (**Fig. 3**).  
197 Increasing values of RV/TLC and FRC/TLC ratio (and decreasing value of IC/TLC ratio) were observed across

198 increasing values of mMRC dyspnoea scale from 0 to 4. The LASSO was used to select the variables associated  
199 with the mMRC dyspnoea scale in a subgroup (n=421) of COPD patients who had no missing RV, IC and FRC  
200 values (A descriptive analysis was done to show the differences in between this subsample and the rest of the  
201 sample: **Table S3**). 32 variables were subjected to lasso regression, and only 7 variables were selected: age,  
202 cough, the number of exacerbations, BMI, FEV<sub>1</sub>, IC/TLC ratio and depression. Multiple logistic regression  
203 analysis was employed to examine the contribution of the variables selected by lasso to mMRC scale: FEV<sub>1</sub>:  
204 OR=3.47[1.96-6.12]; exacerbations (≥2): OR=2.31[1.33- 4.17] and hyperinflation (IC/TLC): OR=0.57[0.35-0.85]  
205 were associated with higher dyspnoea (mMRC≥2) in this subgroup of patients.

#### 206 **4. Discussion**

207 The most interesting result in the current study of COPD patients is the specific relationship between the  
208 static hyperinflation (defined by the IC / TLC ratio) and the mMRC dyspnoea scale. With a comparable degree of  
209 COPD severity the majority of hyperinflated patients had higher dyspnoea than those with lower  
210 hyperinflation. Dyspnoea is described as a physical perception with different degrees of severity of uneasy  
211 breathing [14] and a widely used parameter for assessment of COPD severity [15]. GOLD has recognized a need  
212 for a more rigorous evaluation of symptoms, rather than a quick and easy breathlessness calculation [16].  
213 However, many studies have highlighted the importance of dyspnoea in COPD patients such as the Spanish  
214 COPD study [17]. There is considerable disagreement about the appropriate methodology for measuring  
215 dyspnoea. We opted for the mMRC scale since it is a unidimensional quantitative measurement of severity of  
216 dyspnoea, and is used by pulmonologists worldwide.

217 A recent study showed that the number of comorbidities can predict dyspnoea [18]. Moreover, mMRC scores  
218 were significantly higher in patients with psychiatric co-morbidity, particularly anxiety and depression [19].  
219 Dyspnoea is a potential predictor of depression in COPD [17, 20]. This association however, has not been  
220 reflected in a few studies [21] possibly due to a catastrophic misinterpretation of the sensation of dyspnoea.  
221 The cause and effect relationship between anxiety and dyspnoea is, however, unclear. There are indications  
222 that dyspnoea is major cause of anxiety [22, 23] while other studies indicate that anxiety intensify the  
223 subjective sensation of dyspnoea [24, 25].

224 In our study 59.38% patients were considered to have higher dyspnoea (mMRC≥2) and hypertension was  
225 the most frequent comorbidity in all dyspnoea grades. The observed association between dyspnoea and

226 cardiovascular comorbidities can be explained partly by shared risk factors such as smoking, age, and inactivity.  
227 However, it is also thought that a systemic inflammatory process related to COPD may independently increase  
228 the risk of cardiovascular disease.

229 Despite difficulties in accurate quantification of dyspnoea symptoms due to self-reporting [14], we  
230 observed that dyspnoea was more frequent in women - a finding supported by several other studies [26]. We  
231 found a significant increase between dyspnoea and the mean age of our study. Previous studies show a  
232 consistent association between age and the mMRC dyspnoea score [26], also reflected in middle-aged  
233 participants in COPDGene study [27]. In our study, dyspnoea was more frequent in overweight patients aligning  
234 with previous studies linking obesity to dyspnoea [28]. Contrastingly, in one study the level of dyspnoea  
235 increased as the BMI categories moved from underweight to overweight [29]. Exacerbations partly characterize  
236 a worsening of dyspnoea. Studies showed that the number of exacerbations correlates with mMRC grade and  
237 that the “frequent exacerbations” phenotype surpasses dyspnoea on the quality of life [30]. However, these  
238 differences are attributable to the COPD patients’ perceptions of dyspnoea [31].

239 The CHAIN cohort established mMRC grade  $\geq 2$  as a good threshold through survival analysis [32]. The cut-  
240 off value of the dyspnoea mMRC scale suggested by the GOLD classification is the most commonly used. Lower  
241 mMRC scores indicate low dyspnoea. Hence, in our study, post dichotomization of mMRC, a response with  
242 mMRC more than 1, 2, 3 and 4 was employed to separate lower Vs. higher dyspnoea [2].

243 Static hyperinflation was also associated with dyspnoea [33] and may also be a predictor of mortality when  
244 expressed as either IC/TLC ratio [33], an increased RV [33]. RV increases owing to an extreme expiratory flow  
245 limitation at lung volume. As COPD progresses, the rise in RV is larger than the rise in TLC (higher RV / TLC  
246 ratio), resulting in a decrease in VC (vital capacity) and a consequent decline in FEV<sub>1</sub>. However, static  
247 hyperinflation cut-off values have never been standardized. Two studies [34, 35] have suggested that  
248 hyperinflation should be defined as FRC (functional residual capacity) instead of increased RV or RV/TLC ratio  
249 [36] but these studies [34, 35], use RV to analyse different treatments for emphysema. Many research [37, 38],  
250 have centred on the usage of IC during clinical practice for assessment of static hyperinflation. Unfortunately,  
251 we could not analyse the FRC, the IC or the IC/TLC ratio because of their limitations in clinical practice and their  
252 missing values in our data. That is why we opted for a subgroup (n=421) of COPD patients who had no missing  
253 IC and FRC values, to investigate the correlations between mMRC scale and FRC, FRC/TLC or IC/TLC ratio, to

254 evaluate the effects of other measures of hyperinflation by mMRC scale in the subgroups of 421 patients  
255 defined by the previously mentioned variables. FEV<sub>1</sub> OR=3.47[1.96-6.12]; exacerbations (≥2) OR=2.31[1.33-  
256 4.17] and hyperinflation (IC/TLC) OR=0.57[0.35-0.85] were associated with higher dyspnoea (mMRC≥2) in the  
257 subgroup of patients.

258 In the French "Initiatives BPCO" cohort of COPD patients [39] with a wide range of air-flow limitation,  
259 mMRC dyspnoea grades and baseline dyspnea index (BDI) scores were correlated at the group level. These two  
260 measurements shared most, but not all, of their determinants, which explained a moderate proportion of their  
261 variations. This study [39] suggested that mMRC and BDI scores explore quite differently the dyspnoea  
262 intensity in COPD patients and thus should ideally be used in combination. Consistent with our result, Thierry  
263 Perez et al. [39] found that FEV<sub>1</sub>, hyperinflation, depression, and comorbidities are all major determinants of  
264 mMRC and BDI dyspnea scores.

265 Our analysis has a range of advantages and disadvantages. Firstly, pulmonologists reported the patient  
266 comorbidities, although comorbidities were underdiagnosed in previous research – representing real life. The  
267 apnea syndrome was diagnosed by a polysomnography performed by the same pulmonologist who diagnosed  
268 COPD. We find a strong association between the comorbidities recorded and their care adherence. Secondly,  
269 we cannot generalize the findings in COPD patients to the general population, as our COPD patients have been  
270 managed by a general practitioner and a pulmonologist. Thirdly, the GOLD classification would differ according  
271 to the symptom scale, CAT (COPD Assessment Test) vs mMRC, but in our cohort, we focused on the mMRC  
272 grade by developing more sensitivity analysis. It's well founded that multiple considerations, such as the choice  
273 of the variables, the association between the factors chosen and the scientific judgement of the investigators  
274 can influence the analysis and therefore the results. To limit the impact of the specific correlation between  
275 variables, we first performed an in-depth cross-analysis of different factors; independent variables included in  
276 the model were also those showing a P<0.05 in bivariate analysis. Lastly, most of PALOMB patients are covered  
277 by health insurance, meaning that there exists an unrecognized population of uninsured patients who probably  
278 have a higher prevalence of frequent dyspnoea.

279 Despite its limitations, this is one of the few studies that have investigated the association of higher  
280 dyspnoea and several determinants in COPD patients.

## 281 5. Conclusions

282 Regardless of the cut-off values set to identify higher dyspnoea, our results suggested that dyspnoea is  
283 related to the severity of airflow limitation, gender, exacerbations, comorbidities and hyperinflation. Revealing  
284 that the hyperinflation defined by an IC/TLC ratio was a better determinant of the mMRC dyspnoea scale in  
285 comparison to both RV/TLC and FRC/TLC ratios. These cohort results illustrate in real-life the multifactorial  
286 aspect of dyspnoea in COPD patients. The development of a predictive score by assigning a weight to each  
287 determinant category would provide interesting information. Risk factors associated with higher dyspnoea  
288 should be used to develop and externally validate a new higher dyspnoea risk score in other cohorts. Future  
289 studies are needed for validation of this prediction rule and its value in clinical practice.

### 290 **Authorship statement**

291 All authors contributed to the acquisition of the data. CR and E-HO had full access to all of the data in the study and takes responsibility for  
292 the integrity of the data and accuracy of the data analysis. CR, E-HO, AB, CN, LF, FLG, LN, JMD, MM and AO contributed to the conception  
293 and design of the study. All authors read and approved the final manuscript.

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297 interpretation of the data, or in the preparation, review or approval of the manuscript.

### 298 **Disclosure of interest**

299 Mr. Ouaalaya has nothing to disclose; Dr. Falque has nothing to disclose; Dr. Dupis has nothing to disclose; Dr. Sabatini has nothing to  
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### 314 **Availability of data and materials**

315 The data that support the findings of this study are available from INSERM U1219 Epicene Team but restrictions apply to the availability of  
316 these data, which were used under license for the current study, and so are not publicly available. Data are however available from the  
317 authors upon reasonable request and with permission of INSERM U1219 Epicene Team.

### 318 **Ethics approval and consent to participate**

319 The CNIL (National Data Protection and Privacy Commission) and the CCTIRS (Advisory Committee for Data Processing in Health Research)  
320 approved the study, and informed consent was taken before enrolment. The authors had asked the local ethics committee for feedback  
321 regarding the need for ethical clearance for such a retrospective analysis, and were advised that this was not warranted.

### 322 **Consent for publication**

323 Consent for publication statement is not applicable as no personal information is provided in this manuscript.

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448 **Table 1** The dyspnoea mMRC scale utilized in GOLD guidelines.

GOLD classification	mMRC wording	Analysis groups: Different cut off for a higher/lower dyspnoea group			
Less symptoms	0: I only get breathless with strenuous exercise.	Lower dyspnoea (mMRC <1)			
	1: I get short of breath when hurrying on level ground or walking up a slight hill.		Lower dyspnoea (mMRC <2)		
More symptoms	2: On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.	Higher dyspnoea (mMRC ≥ 1)		Lower dyspnoea (mMRC <3)	Lower dyspnoea (mMRC <4)
	3: I stop for breath after walking about 100 yards or after a few minutes on level ground.		Higher dyspnoea (mMRC ≥ 2)		
	4: I am too breathless to leave the house or I am breathless when dressing.			Higher dyspnoea (mMRC ≥ 3)	Higher dyspnoea (mMRC ≥ 4)

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450 **Table 2** Summary of the characteristics of COPD patients (1,973) according to Dyspnoea grade mMRC.

Subjects characteristics, n (%)		Dyspnoea mMRC « 0 » n=221	Dyspnoea mMRC « 1 » n=571	Dyspnoea mMRC « 2 » n=627	Dyspnoea mMRC « 3 » n=425	Dyspnoea mMRC « 4 » n=106	P Value
Variable names	Data in all patients						
Males, n (%)	1,289(65.33)	166(75.11)	369(64.62)	401(63.96)	265(62.35)	71(66.98)	0.0193
Age, yrs. mean(SD)	66.11 (10.98)	62.9 (10.20)	63.3 (10.40)	66.2 (10.80)	69.4 (10.61)	73.1 (10.71)	<0.0001
BMI, (kg/m <sup>2</sup> ), mean(SD)	26.69 (10.80)	26.05 (5.08)	26.3 (5.48)	27.2 (17.11)	26.55 (6.27)	27.59 (7.57)	0.4502
<21 (underweight), n (%)	331(16.78)	32 (14.47)	93 (16.31)	107 (17.07)	76 (17.83)	20 (18.87)	0.3322
[21-26](normal), n (%)	683(34.62)	86 (38.90)	196 (34.37)	216 (34.45)	147 (34.61)	28 (26.42)	
[26-29](overweight), n (%)	396(20.07)	49 (22.17)	129 (22.63)	117 (18.66)	77 (18.12)	19 (17.92)	

≥29 (obese), n (%)	563(28.54)	54 (24.43)	153 (26.80)	187 (29.82)	125 (29.41)	39 (36.79)	
FEV <sub>1</sub> , % pred, Mean (SD)	58.11 (19.50)	71.7 (16.70)	65.5 (15.90)	56.11 (17.71)	48.2 (18.70)	40.5 (20.11)	0.4504
Chronic cough, n (%)	1,124(56.97)	97(43.90)	273(47.80)	383(61.08)	288(67.73)	74(69.81)	<0.0001
Chronic sputum, n (%)	795(40.30)	71 (32.13)	174 (30.47)	270 (43.06)	216 (50.82)	57 (53.77)	<0.0001
Current smokers, n (%)	793(40.2)	107 (48.42)	238 (41.68)	253 (40.35)	159 (37.41)	30 (28.30)	0.0064
0-1 exacerbation, n (%)	1,427(72.33)	183(82.80)	465(81.40)	464(74)	243(57.12)	56(52.80)	<0.0001
≥ 2 exacerbations, n (%)	546(27.67)	38(17.20)	106(18.61)	163(26)	182(42.91)	50(47.22)	<0.0001
Pulmonary rehabilitation, n (%)	157(8)	4(1.80)	18(3.15)	50(7.93)	62(14.63)	23(21.71)	<0.0001
Smoking cessation, n (%)	155(7.81)	15(6.82)	52(9.10)	44(7.02)	37(8.74)	6(5.63)	0.5087
Hyperinflation (RV/TLC≥120%), n (%)	1,167(59.14)	79(35.75)	277(48.51)	402(64.11)	313(73.65)	80(75.47)	<0.0001

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452 **Table 3** Comorbidities associated with COPD according to dyspnoea grade (mMRC)

Comorbidities, n (%)	Dyspnoea mMRC « 0 » n=221	Dyspnoea mMRC « 1 » n=571	Dyspnoea mMRC « 2 » n=627	Dyspnoea mMRC « 3 » n=425	Dyspnoea mMRC « 4 » n=106	P Value
Hypertension, 734(37.21)	75(33.92)	167(29.25)	248(39.56)	171(40.23)	59(55.69)	<0.0001
Dyslipidemia, 446(22.61)	47(21.26)	106(18.56)	123(19.61)	128(30.11)	34(32.07)	<0.0001
Ischemic cardiopathy, 353(17.97)	30(13.57)	76(13.34)	100(15.94)	105(24.78)	36(33.96)	<0.0001
Apnea Syndrome, 340(17.23)	59(26.69)	112(19.61)	80(12.75)	67(15.76)	19(17.92)	<0.0001
Anxiety, 318(16.13)	10(4.52)	55(9.63)	92(14.67)	114(26.82)	47(44.33)	<0.0001
Depression, 282(14.34)	22(9.95)	58(10.15)	78(12.44)	89(20.94)	33(31.13)	<0.0001
Diabetes, 250(12.67)	32(14.47)	51(8.93)	76(12.12)	69(16.23)	19(17.92)	0.0037
Arrhythmia, 241(12.24)	20(9.04)	52(9.13)	81(12.91)	61(14.35)	25(23.58)	0.0002
Left heart failure, 100(5.07)	3(1.35)	17(2.97)	26(4.14)	32(7.52)	20(18.86)	<0.0001
Bronchiectasis, 92(4.66)	6(2.71)	12(2.12)	42(6.69)	27(6.35)	5(4.71)	0.0009
Cardiovascular comorbidities, 1,087(55.17)	109(49.32)	262(45.88)	353(56.37)	269(63.29)	78(73.58)	<0.0001

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455 **Table 4** Multivariate analysis (in 1,973 COPD patients) indicating variables associated with higher dyspnoea,

456 considering mMRC more than 1, 2, 3 and 4.

	OR [95% CI]			
	Higher dyspnoea (mMRC grade ≥1)	Higher dyspnoea (mMRC grade ≥2)	Higher dyspnoea (mMRC grade ≥3)	Higher dyspnoea (mMRC grade ≥4)
FEV <sub>1</sub> (% pred.)	2.93[1.92 - 4.49]	3.71[2.86 - 4.82]	4.30[3.30 - 5.60]	4.66[2.96 - 7.31]
Anxiety	4.09[2.12 - 7.89]	2.52[1.82 - 3.47]	2.47[1.82 - 3.37]	3.65[2.26 - 5.89]
Age	1.63[1.22 - 2.17]	1.80[1.45 - 2.24]	2.27[1.78 - 2.88]	2.85[1.75 - 4.64]
Cough	1.71[1.29 - 2.27]	1.94[1.57 - 2.40]	1.60[1.25 - 2.05]	-----
Hyperinflation	1.71[1.26 - 2.33]	1.68[1.34 - 2.11]	1.34[1.01 - 1.76]	-----
Gender (Women vs. Men)	1.76[1.26 - 2.46]	1.39[1.10 - 1.74]	1.30[1.00 - 1.68]	-----
BMI	1.76[1.28 - 2.41]	1.33[1.06 - 1.67]	-----	-----
Ischemic cardiopathy	-----	1.63[1.22 - 2.18]	1.90[1.41 - 2.54]	-----

Number of exacerbations during the past year	-----	1.41[1.10 - 1.81]	1.84[1.43 - 2.36]	-----
Depression	-----	-----	1.67[1.19 - 2.34]	2.01[1.19 - 3.40]
Hypertension	-----	1.52[1.21 - 1.91]	-----	1.62[1.04 - 2.50]
Bronchiectasis	-----	1.84[1.03 - 3.29]	-----	-----
Dyslipidemia	-----	-----	1.81[1.38 - 2.38]	-----
Asthma	-----	-----	1.44[1.00 - 2.08]	-----
Left heart failure	-----	-----	-----	3.35[1.84 - 6.11]

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460 **Table 5** COPD inhaled treatments according to dyspnoea grade (mMRC)

Medication, n (%)	Dyspnoea mMRC « 0 » n=221	Dyspnoea mMRC « 1 » n=571	Dyspnoea mMRC « 2 » n=627	Dyspnoea mMRC « 3 » n=425	Dyspnoea mMRC « 4 » n=106	P Value
SABA, 749(37.96)	41 (18.55)	185 (32.47)	243 (38.76)	214 (50.35)	60 (56.65)	<0.0001
LABA, 628(31.83)	46 (20.81)	185 (32.46)	208 (33.17)	150 (35.29)	34 (32.08)	0.0042
LAMA, 936(47.44)	53 (23.98)	234 (40.98)	327 (52.15)	255 (60)	57 (53.77)	<0.0001
LABA or LAMA, 1252(63.46)	84 (38.01)	339 (59.37)	436 (69.54)	311 (73.18)	68 (64.15)	<0.0001
LABA and LAMA, 312(15.81)	15 (6.79)	80 (14.01)	99 (15.79)	94 (22.12)	23 (21.74)	<0.0001
Inhaled corticosteroids, 101(5.12)	2 (0.91)	15 (2.63)	30 (4.78)	40 (9.41)	13 (12.26)	<0.0001
Fixed combination (ICS + LABA), 532(26.96)	28 (12.67)	110 (19.26)	184 (29.35)	161 (37.88)	42 (39.62)	<0.0001

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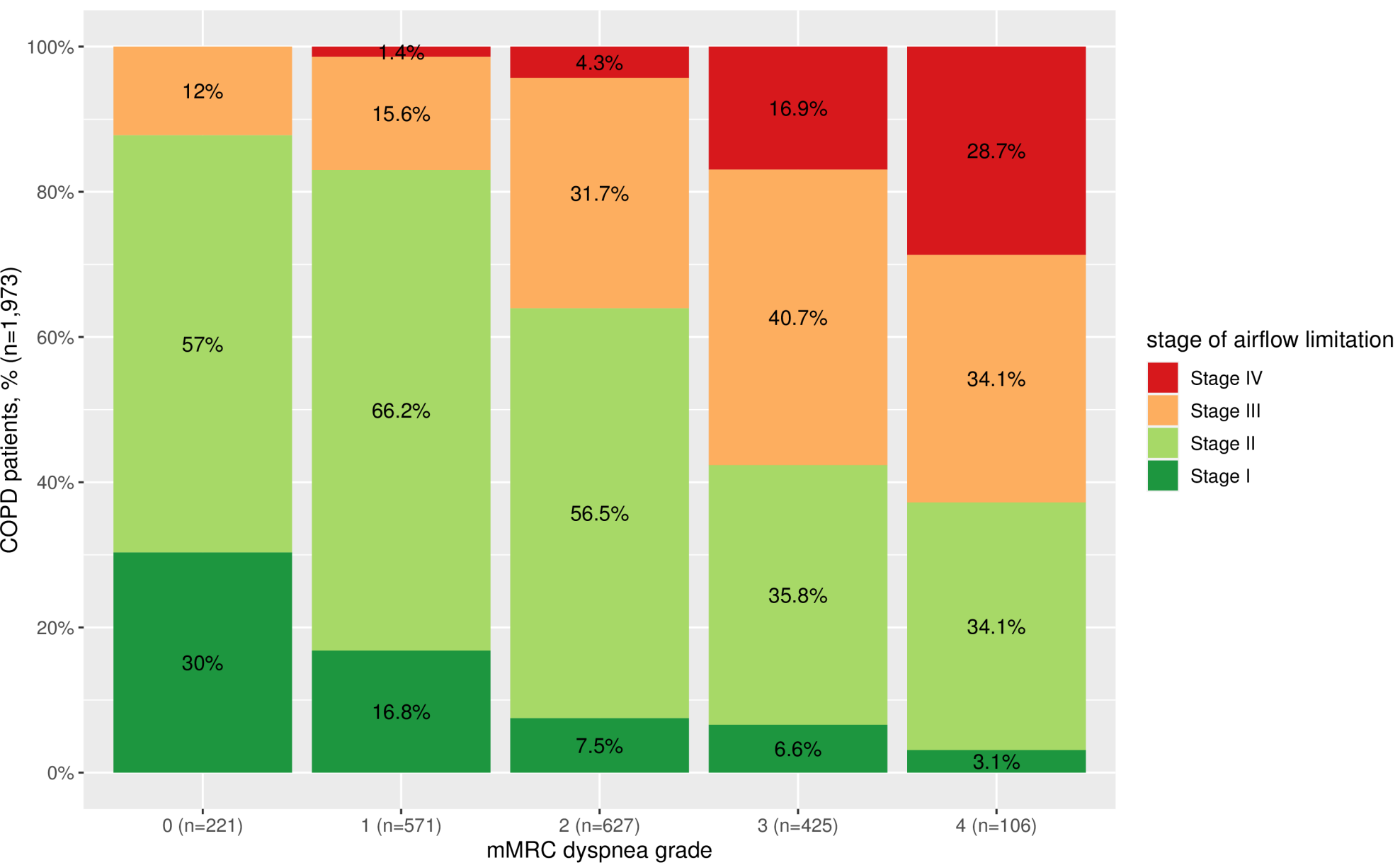
## 465 **Figure Legends**

466 **Fig. 1** mMRC dyspnoea grade distribution by stage of airflow limitation.

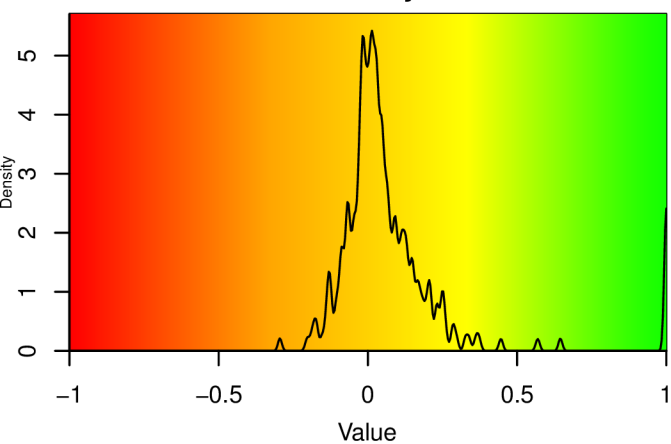
467 **Fig. 2** Spearman correlations heat map for variables in dyspnoea model in the PALOMB cohort.

468 Colours in each cell indicate the strength of the relationship.

469 **Fig. 3** Box plot for RV, IC, FRC, RV/TLC, IC/TLC and FRC/TLC ratio by dyspnoea mMRC scale in the subgroup of  
470 421 COPD patients.



Color Key and Density Plot



-0.02	0.05	0.01	0.01	0.02	0.03	0.02	0.05	0.02	0.02	0.05	0.02	0.11	0.15	0.13	-0.03	0.02	0.13	0.02	0.05	0.07	0.26	0.65	1	Chronic Sputum
-0.09	0.11	-0.03	0	-0.04	0.03	-0.04	-0.01	-0.02	0.01	0.06	0.05	0.07	0.16	0.18	0.03	0.02	0.09	0.01	0.1	0.1	0.29	1	0.65	Chronic Cough
-0.09	0.06	0	0.03	-0.01	0.05	0	0.01	0.03	0.06	0.16	0.15	0.21	0.25	0.03	0.11	0.05	0.11	-0.03	0.13	0.21	1	0.29	0.26	Exacerbations
-0.02	0.05	0.02	0.01	0.04	0.05	-0.02	0.08	0.05	0.03	0.09	0.08	0.06	0.24	0.02	0.15	0.04	0.12	0.07	0.37	1	0.21	0.1	0.07	Anxiety
0.01	-0.03	-0.01	0	0.05	0.02	-0.07	-0.02	-0.02	-0.02	0.04	0.03	0.01	0.14	0.11	0.21	0	-0.04	-0.01	1	0.37	0.13	0.1	0.05	Depression
-0.07	0.05	0.04	-0.04	0	0	0.03	0	0.01	-0.05	-0.07	-0.05	-0.01	0.01	-0.04	-0.02	-0.06	-0.02	1	-0.01	0.07	-0.03	0.01	0.02	Cancer, all causes
-0.01	0	-0.02	-0.01	-0.02	0.03	0.04	0.01	0.03	0.01	0	0.01	0.08	0.06	-0.1	-0.01	0.03	1	-0.02	-0.04	0.12	0.11	0.09	0.13	Bronchiectasis
0.03	-0.02	-0.05	-0.03	-0.02	0	-0.02	-0.03	0.02	0.02	-0.01	0	-0.03	0.05	0	0.06	1	0.03	-0.06	0	0.04	0.05	0.02	0.02	Asthma
-0.19	-0.2	-0.13	-0.12	-0.13	-0.07	-0.13	-0.17	-0.09	-0.06	0.14	0.06	-0.07	0.04	0.15	1	0.06	-0.01	-0.02	0.21	0.15	0.11	0.03	-0.03	Gender
0	-0.13	-0.12	-0.07	-0.09	0.01	-0.29	-0.13	-0.15	-0.09	0.05	0.03	-0.07	-0.08	1	0.15	0	-0.1	-0.04	0.11	0.02	0.03	0.18	0.13	Current smokers
-0.08	0.01	0.12	0.06	0.1	0.09	0.18	0.14	0.09	0.15	0.16	0.25	0.36	1	-0.08	0.04	0.05	0.06	0.01	0.14	0.24	0.25	0.16	0.15	Dyspnea
-0.14	-0.11	0.02	-0.01	-0.03	0.03	0.07	0	0.01	0.09	0.34	0.45	1	0.36	-0.07	-0.07	-0.03	0.08	-0.01	0.01	0.06	0.21	0.07	0.11	FEV1
-0.14	-0.1	-0.02	0	-0.06	-0.01	-0.05	-0.02	-0.06	0.05	0.57	1	0.45	0.25	0.03	0.06	0	0.01	-0.05	0.03	0.08	0.15	0.05	0.02	Hyperinflation
-0.18	-0.18	-0.06	-0.09	-0.09	-0.02	-0.08	-0.07	-0.07	-0.03	1	0.57	0.34	0.16	0.05	0.14	-0.01	0	-0.07	0.04	0.09	0.16	0.06	0.05	Residual volume
0.09	0.07	0.09	0.11	0.12	0.09	0.13	0.23	0.25	1	-0.03	0.05	0.09	0.15	-0.09	-0.06	0.02	0.01	-0.05	-0.02	0.03	0.06	0.01	0.02	Left Heart Failure
0.07	0.08	0.13	0.04	0.06	0.03	0.25	0.23	1	0.25	-0.07	-0.06	0.01	0.09	-0.15	-0.09	0.02	0.03	0.01	-0.02	0.05	0.03	-0.02	0.02	Arrhythmia
0.13	0.11	0.12	0.19	0.2	0.2	0.17	1	0.23	0.23	-0.07	-0.02	0	0.14	-0.13	-0.17	-0.03	0.01	0	-0.02	0.08	0.01	-0.01	0.05	Ischemic cardiopathy
-0.01	0.06	0.23	0.08	0.15	0.11	1	0.17	0.25	0.13	-0.08	-0.05	0.07	0.18	-0.29	-0.13	-0.02	0.04	0.03	-0.07	-0.02	0	-0.04	0.02	Age
0.08	0.03	0.1	0.05	0.17	1	0.11	0.2	0.03	0.09	-0.02	-0.01	0.03	0.09	0.01	-0.07	0	0.03	0	0.02	0.05	0.05	0.03	0.03	Atheroma
0.17	0.2	0.28	0.3	1	0.17	0.15	0.2	0.06	0.12	-0.09	-0.06	-0.03	0.1	-0.09	-0.13	-0.02	-0.02	0	0.05	0.04	-0.01	-0.04	0.02	Dyslipidemia
0.19	0.25	0.21	1	0.3	0.05	0.08	0.19	0.04	0.11	-0.09	0	-0.01	0.06	-0.07	-0.12	-0.03	-0.01	-0.04	0	0.01	0.03	0	0.01	Diabetes
0.15	0.2	1	0.21	0.28	0.1	0.23	0.12	0.13	0.09	-0.06	-0.02	0.02	0.12	-0.12	-0.13	-0.05	-0.02	0.04	-0.01	0.02	0	-0.03	0.01	Hypertension
0.33	1	0.2	0.25	0.2	0.03	0.06	0.11	0.08	0.07	-0.18	-0.1	-0.11	0.01	-0.13	-0.2	-0.02	0	-0.05	-0.03	-0.05	-0.06	-0.11	-0.05	BMI
1	0.33	0.15	0.19	0.17	0.08	-0.01	0.13	0.07	0.09	-0.18	-0.14	-0.14	0.08	0	-0.19	0.03	-0.01	-0.07	0.01	-0.02	-0.09	-0.09	-0.02	Apnea Syndrome

Apnea Syndrome BMI Hypertension Diabetes Dyslipidemia Atheroma Age Ischemic cardiopathy Arrhythmia Left Heart Failure Residual volume Hyperinflation FEV1 Dyspnea Current smokers Gender Asthma Bronchiectasis Cancer, all causes Depression Anxiety Exacerbations Chronic Cough Chronic Sputum

