

Resting Heart Rate is a Predictor of Mortality in Chronic Obstructive Pulmonary Disease

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ABSTRACT

The clinical significance of high heart rate in COPD is unexplored.

We investigated the association between resting heart rate (RHR), pulmonary function, and prognosis in subjects with COPD.

16,696 subjects above 40 years from The Copenhagen City Heart Study, a prospective study of the general population, followed for 35.3 years, 10,986 deaths occurring.

Analyses were performed using time-dependent Cox-models and net reclassification index (NRI).

RHR increased with severity of COPD ($p < 0.001$). RHR was associated with both cardiovascular and all-cause mortality across all stages of COPD ($p < 0.001$).

Within each stage of COPD, RHR improved the prediction of median life expectancy; the difference between < 65 bpm and > 85 bpm was 5.5 years in no COPD, 9.8 years in mild, 6.7 years in moderate, and 5.9 years in severe/ very severe, ($p < 0.001$). RHR significantly improved risk prediction when added to GOLD stage, (categorical NRI 4.9%, $p = 0.01$; categoryless NRI 23.0%, $p < 0.0001$), or FEV₁ in percent of predicted (categorical NRI 7.8%, $p = 0.002$; categoryless NRI 24.1%, $p < 0.0001$).

RHR increases with severity of COPD. RHR is a readily available clinical variable that improves risk prediction in patients with COPD above and beyond that of pulmonary function alone. RHR may be a potential target for intervention in COPD.

Key words: Biomarkers, Prevention, Pulmonary Heart Disease, Risk Factors, Tachycardia.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world¹ accounting for more than 3 million deaths annually².

COPD is associated with increased resistance in the pulmonary vasculature, pulmonary hypertension, increased right ventricular workload, and in advanced cases right heart failure (cor pulmonale). Pulmonary and cardiovascular dysfunction is thus intimately connected.

It is a common clinical experience that patients with COPD often have high resting heart rates. High resting heart rate is present and associated with poor outcome in other clinical syndromes such as heart failure, a disease entity that shares many clinical features with COPD, such as decreased stroke volume, dyspnea and fatigue.

Recent studies have suggested that beta-blockers may have a beneficial effect on all-cause mortality in patients with COPD³. One of the main properties of beta-blockers is heart rate reduction. Heart rate may therefore potentially be a prognostic marker and therapeutic target in COPD as in other patient groups such as CHD and heart failure^{4, 5}.

Although elevated resting heart rate has been shown to be associated with increased cardiovascular and all-cause mortality in normal subjects and in subjects with heart disease⁶⁻⁸ the contribution of resting heart rate to mortality in patients with COPD has never been examined in the setting of a large-scale population study.

In the present study, the relationship between COPD, resting heart rate, and prognosis was studied. Firstly, we examined whether COPD severity was associated with increase in resting heart rate; secondly, we examined whether resting heart rate was associated with cardiovascular and all-cause mortality in COPD; thirdly we examined

whether resting heart rate could improve prediction of median life expectancy beyond that of GOLD stage¹; and finally, using net reclassification index (NRI), we examined whether adding resting heart rate to models with GOLD stage alone or FEV₁%p alone could reclassify subjects into clinically meaningful higher or lower risks categories of mortality.

METHODS

Population

The Copenhagen City Heart Study is a prospective study of a random population sample 18,974 men and women aged 20 years or older living in Copenhagen, Denmark. The study was initiated in 1976 and has so far included four examinations, the first survey lasted from 1976-78, the second survey from 1981-83, the third from 1991-94, and the fourth from 2001-03. The first cross-sectional survey included 14,223 individuals. Subjects aged 20-49 years have subsequently been added throughout the following surveys to the current total number. The sampling background and methods have been described in detail in several publications⁹⁻¹¹.

Subjects

All subjects were of Caucasian descent. In the present study, only subject aged 40 or above were included. Subjects with atrial fibrillation or flutter were excluded from the analyses; also cases with missing data on resting heart rate or pulmonary function were excluded (N = 375). Information on vital status and causes of death was obtained from national registers. Cardiovascular death was defined as ICD-8 codes 390–458 and ICD-10 codes I00-I99. A total of 106 subjects were lost to follow-up due to emigration; follow-up was therefore 99.4 % complete.

The study was approved by The Regional Ethical Committee approved the study (H-KF-01-144/01). All participants gave written informed consent.

Measurements

All subjects underwent physical examinations as well as a self-administered questionnaire providing medical history, smoking (*never, former, current*) and drinking habits (*never, monthly, weekly, and everyday drinker*), leisure time physical activity (*sedentary*, referring to “light activity less than 2 hours per week”, *moderate*, referring to “light activity 2-4 hours per week”, and *high*, referring to “light activity >4 hours per week” or “high activity >2 hours per week”), medication, and history of contacts with the health-care system. Blood pressure was measured with the London School of Hygiene Sphygmomanometer. Plasma cholesterol, high-sensitivity CRP, fibrinogen, and blood glucose values were measured on non-fasting venous blood samples¹². A 12-lead ECG was recorded at rest in a supine position and coded according to the Minnesota code. Resting heart rate was read from the ECG.

In survey 1 and 2, forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC) were measured with an electronic spirometer (Monaghan N 403; Littleton, CO, USA), which was calibrated daily. In survey 3 and 4, a dry wedge spirometer (Vitalograph, Maidenhead, UK), which was calibrated weekly, was used. The best FEV₁ and FVC of three were used in the analyses. Lung function data are reported as a percentage of predicted value according to age, sex and height (FEV₁%p)¹³.

Severity of COPD was classified according to the GOLD classification¹:

Mild COPD : FEV₁/FVC<70% and FEV₁%p≥80 (GOLD 1)

Moderate COPD : FEV₁/FVC<70% and 50≤FEV₁%p<80 (GOLD 2)

Severe COPD : FEV₁/FVC<70% and 30≤FEV₁%p<50 (GOLD 3)

Very severe COPD : FEV₁/FVC<70% and FEV₁%p<30% (GOLD 4)

Statistics

All statistical analyses were carried out using the statistical software R, version 2.13.1. For demographics, Kruskal-Wallis test was used for continuous variables and Fischer's exact test for categorical variables.

First, we studied the association between resting heart rate and severity of COPD (GOLD stage). For each subject, only observations from the first study visit were used. The robustness of the association was examined by performing two analyses, **a)** univariate; and **b)** adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol drinking habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischemic heart disease, electrocardiographic evidence of ischemic heart disease (Minnesota Codes 1-1 and 1-2), previous stroke, previous diagnosis of any cancer (information from the Danish Cancer Registry), self-reported diabetes or fasting glucose higher than 11.1 mmol/L. Additional subanalyses were performed in the fully adjusted model also including covariates available only in survey 3 and 4. These covariates were high-sensitivity CRP, fibrinogen, use of statins, use of medication for asthma or bronchitis, and dyspnea (MRC).

Secondly, the association between resting heart rate and cardiovascular and all-cause mortality was studied using both uni- and multivariate models (**a)** and **b)**, see above) in a Cox proportional hazards model with time-dependent covariates. The assumption of proportionality in the Cox regression models was tested with the score process test.

Thirdly, to assess if resting heart rate in addition to GOLD stage predicts mortality better than GOLD stage alone Kaplan-Meier survival curves for all-cause mortality were fitted and median life expectancy calculated for GOLD stage alone, and for GOLD stage stratified by resting heart rate.

Finally, we studied whether the addition of resting heart rate to pulmonary function (GOLD stage, or FEV₁%p) would improve the predictive accuracy for mortality. Firstly, we calculated Harrell's C-statistic with and without resting heart rate. C-statistics assess the prognostic ability of a variable using a binary outcome. Since C-statistics are not developed for risk prediction models¹⁴, we also assessed the net reclassification index (NRI)^{15, 16}. The dataset was split in half – one half for developing the models and the other half for validating the models¹⁶. For the NRI, risk categories for mortality during a 10-year follow-up period based on GOLD stages in the development dataset were determined as <25%; 25%-35%; 35%-50%; and ≥50%; only subjects with GOLD stage 2 or higher were included. The categorical NRI provides information about how adding resting heart rate to GOLD stage or FEV₁%p correctly reclassifies subjects who do not have an event into a lower risk category and subjects who do get an event into a higher risk category. The categoryless NRI provides information on improved reclassification into higher or lower risk without predefined risk categories; i.e., a subject whose risk estimation is improved from 26% to 33% would in the categorical analysis not be considered reclassified due to the limits of the categories whereas in the categoryless analysis this person would be registered as correctly reclassified. Statistical significance was assumed at a value of $p < 0.05$.

RESULTS

A total of 16,696 subjects were included. During the 35.3 years of follow-up (mean 20.1 years), 5,394 cardiovascular deaths and 10,986 all-cause deaths occurred.

Clinical characteristics are shown in Table 1.

COPD SEVERITY AND LEVELS OF RESTING HEART RATE

Resting heart rate increased with severity of COPD (figure 1a and 1b).

Compared to subjects with no COPD mean (95% CI) resting heart rate was 0.5 (-1.2 to 0.2) bpm higher in subjects with mild COPD, 1.4 (1.0 to 1.9) bpm higher in subjects with moderate COPD, 4.5 (3.7 to 5.2) bpm higher in subjects with severe COPD, and 10.4 (8.9 to 11.9) bpm higher in subjects with very severe COPD (figure 1a). In the multivariate model including age, sex, smoking, blood pressure, cholesterol, BMI, physical activity, alcohol, medication, diabetes, and previous cardiovascular disease and cancer (see statistics) the difference in resting heart rates was -0.3 (-1.0 to 0.3) bpm, 0.9 (0.4 to 1.3) bpm, 3.9 (3.1 to 4.6) bpm, and 9.9 (8.4 to 11.4) bpm, respectively (figure 1b). P for trend was less than 0.001 in both analyses.

In a subanalysis also including use of asthma or bronchitis medication, MRC class, high-sensitivity CRP, fibrinogen, and use of statins in the full multivariate model the positive relationship between resting heart rate and COPD severity remained highly significant ($p < 0.001$).

RESTING HEART RATE AND MORTALITY

Resting heart rate was highly significantly associated with both cardiovascular and all-cause mortality in both uni- and multivariate models, see table 2. There was no interaction between COPD severity and heart rate with regard to mortality. However, there was a significant interaction with smoking; elevated heart rate was associated with greater risk in current and former smokers. This has previously been discussed in detail.⁷

GOLD STAGE, RESTING HEART RATE, AND MEDIAN LIFE EXPECTANCY

Pulmonary function according to the GOLD staging was highly predictive of mortality. Median life expectancy was 78.8 (78.4; 79.2) years in the no COPD group, 77.9 (75.6; 79.5) years in the mild COPD, 73.4 (72.2; 74.4) years in moderate COPD, and 67.2 (65.2; 68.9) years in severe/ very severe COPD.

Figure 2 shows median life expectancy by GOLD class and resting heart rate. As shown, median life expectancy decreased with increase in resting heart rate across all GOLD stages. Median life expectancies (95% CI) in no COPD were 80.9 (80.2; 81.6) years in subjects with resting heart rate <65 BPM, 79.7 (79.1; 80.2) years in resting heart rates 65-74 BPM, 78.2 (77.6; 79.0) years in resting heart rates 75-84 BPM, and 75.4 (74.5; 76.3) years in resting heart rate ≥85 BPM. In subjects with mild COPD median life expectancies were 80.5 (77.9; 84.2) years, 79.5 (74.4; 82.8) years, 78.9 (74.7; 81.4) years, and 70.7 (67.0; 75.6) years. In moderate COPD median life expectancies were 76.2 (73.3; 78.7), 74.1 (72.4; 75.8), 73.1 (70.8; 74.9), and 69.5 (67.2; 71.6); and in severe/ very severe COPD median life expectancies were 70.4 (65.3; 74.0), 68.2 (61.9; 73.1), 68.0 (63.9; 69.4), and 64.5 (62.7; 67.7), respectively. Thus, the difference in median life expectancy

between a subject with a resting heart rate <65 BPM compared to a subject with resting heart rate ≥85 was 5.5 years in no COPD, 9.8 years in mild COPD, 6.7 years in subjects with moderate COPD, and 5.9 years in subjects with severe/ very severe COPD.

RISK RECLASSIFICATION, ADDING RESTING HEART RATE TO PULMONARY FUNCTION

The addition of resting heart rate to models with pulmonary function alone significantly improved risk prediction.

In a model where pulmonary function was determined as GOLD stage, C-statistics for GOLD stage alone was 0.54 (0.53-0.56) versus 0.57 (0.55-0.60) ($p<0.001$) with GOLD stage and resting heart rate. The categorical NRI was 4.9% ($p=0.01$) (table 3) and the categoryless NRI was 23.0% ($p<0.0001$). In a model where pulmonary function was determined as FEV₁%p, C-statistics was 0.57 (0.54-0.59) versus 0.59 (0.56-0.61) with both FEV₁%p and resting heart rate ($p<0.001$). The categorical NRI was 7.8% ($p=0.002$) (table 4) and the categoryless NRI was 24.1% ($p<0.0001$).

Resting heart rate correctly reclassified subjects across all COPD stages, 76.4% were GOLD 2, 19.7% GOLD 3 and 3.9% GOLD 4 which was similar to the general distribution of COPD (77.9% GOLD 2, 18.3% GOLD 3 and 3.8% GOLD 4). Resting heart rate especially improved the prediction of non-events indicating that subjects with lower resting heart rates had a better survival than expected on the basis of their level of FEV₁.

DISCUSSION

Resting heart rate increases with severity of pulmonary dysfunction in COPD, and improves prediction of mortality above and beyond knowledge of pulmonary function alone. These findings raise the question whether heart rate could be a target for intervention in COPD.

For example, in subjects with moderate COPD, resting heart rate predicts up to 10 years difference in median life expectancy between subjects with resting heart rate <65 and ≥ 85 bpm; in fact, the difference between high and low resting heart rate *within* the same GOLD stage is of a greater magnitude than the differences in life expectancy *between* adjacent GOLD stages – thus, the difference in median life expectancies between mild COPD and moderate COPD was 4.5 years. Hence, resting heart rate improves the identification of subjects with COPD at risk. Monitoring resting heart rate can readily be implemented into clinical practice and the day-to-day patient care.

Also, in terms of differences in absolute risk two important points can be inferred from our findings; firstly, in subjects within same GOLD class but with different resting heart rates elevated resting heart rates is associated with poor prognosis, and in relation to absolute risk, the greater the severity of pulmonary dysfunction the greater is the differences in absolute risk between high and low heart rate categories. For example; in individuals without COPD, the absolute mortality risk in a 10-year period is 17% in the low heart rate groups and 25% in the high heart rate groups and the absolute risk difference is therefore 8%. In comparison, participants with very severe COPD have a poor prognosis and the corresponding absolute mortality risk during a 10-year period is 49% in the low resting heart rate group and 72% in the high resting heart rate group; this means an increased absolute risk of mortality of 23%. Secondly; the proportion of subjects with high heart rate

is far greater in the severe GOLD categories and this implies that a far greater proportion of subjects with severe COPD are under risk compared to subjects with no or less pulmonary dysfunction.

The relationship between elevated heart rate and severity of COPD has never previously been established in a large-scale study. The most important issue is, whether high resting heart rate is a feature of the pulmonary disease, and therefore not a focus for a specific intervention, or whether increased heart rate plays an independent pathophysiological role and therefore might be a goal for intervention to improve the prognosis in COPD.

Resting heart rate has been shown to be a risk factor in both general populations^{6, 7, 17, 18} and in populations with cardiovascular disease^{4, 8}. COPD and heart failure share many of the same features. Both are characterized by dyspnea, fatigue, decreased stroke volume and increased heart rate. However, in contrast to the clinical classification of heart failure¹⁹, heart rate has so far played no role in the risk stratification or management of patients with COPD.

Heart rate-reducing agents, such as beta-blockers, have in cardiovascular clinical medicine long proven its beneficial effects on mortality and morbidity but the effect of heart rate reducing agents specifically for COPD is unexplored. Clinicians commonly avoid use of β -blockers in subjects with COPD²⁰. However, a recent retrospective study of 6000 patients with COPD suggested that β -blockers may have a beneficial effect on mortality³. New agents (I_f -inhibitors) with selective sinus node inhibition and heart rate reducing properties without systemic effects have recently been introduced in heart failure and ischemic heart disease^{21, 22}. It is possible, that reducing heart rate in subjects with COPD

could increase myocardial performance and thereby improve symptoms and prognosis. A clinical trial of heart rate reduction in COPD seems warranted at this point in time. Several hemodynamic factors, such as hypoxia and decreased stroke volume probably play a role in the relationship between high resting heart rate and COPD. Low arterial oxygen saturation leads to an increase in cardiac output²³. Furthermore, pulmonary dysfunction in COPD is associated with incremental decrease in left ventricular size and stroke volume^{24, 25}. When stroke volume is decreased, cardiac output can be maintained by an increase in heart rate. COPD is additionally known to be associated with autonomic dysfunction resulting in decreased parasympathetic and increased sympathetic activity^{26, 27}. Smoking is the leading cause of COPD. We have recently shown that former and current smokers are at increased risk of elevated heart rate compared to never smokers⁷. These findings are in line with Barr et al who found a significant interaction between smoking status and stroke volume in subjects with pulmonary dysfunction; smokers were found to have lower ventricular dimensions compared to non-smokers⁶. Vascular abnormalities with intimal hypertrophy, endothelial dysfunction, decreased vascular relaxation, and as a consequence, an increase in pulmonary pressure and myocardial impairment may play a role. This has been observed in both subjects with COPD as well as in smokers with normal pulmonary function²⁸. However, this subject needs further study.

Study limitations

Resting heart rate was assessed from the ECG. It is possible that other assessments of heart rate, e.g. 24-hour ambulatory ECG, could provide more accurate heart rate measurements. The current findings can, however, easily be translated into a normal

clinical setting; also, misclassification of RHR from a single ECG would bias the results toward the null hypothesis.

A possible limitation may also be that diagnosis of asthma in our study was made by an affirmative answer to the question: “Do you have asthma?”. We have no data on reversibility of FEV₁ and thus some misclassification between asthma and COPD is possible. Yet, we do not think that this possibility affects our general findings regarding heart rate and mortality.

Bronchodilators are known to increase heart rate and could be an important confounder in this study; however we found that adjusting for use of asthma or bronchitis medication in addition to other possible confounding factors did not change the association between elevated heart rate and severity of pulmonary dysfunction.

In epidemiological studies residual confounding can never be excluded. Inflammatory markers have previously been shown to be associated with subclinical disease²⁹⁻³¹; including these markers of chronic low-grade inflammation in the multivariate adjustments did not change the results. The possible contribution from underlying subclinical disease may therefore have been minimized.

In conclusion, we demonstrate that resting heart rate increases with the severity of COPD. In multivariate analyses, resting heart rate is associated with both cardiovascular and all-cause mortality in subjects with COPD. High resting heart rate is associated with decreased median life expectancies across all stages of COPD and provides improved risk prediction above that of pulmonary function alone measured either as GOLD stage or FEV₁%p.

Resting heart rate can easily, with minimal clinical training, and without cost be included in the clinical assessment of patients with COPD as a risk marker. Resting heart rate is a potentially modifiable risk factor. Clinical trials with heart rate lowering in COPD seem warranted.

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TABLES and FIGURES

Table 1: Demographics

Table 2: Resting heart rate, All-Cause and Cardiovascular Mortality

Table 3: Risk Reclassification, GOLD Stage versus GOLD Stage with Resting Heart Rate

Table 4: Risk Reclassification, FEV₁%p versus FEV₁%p with Resting Heart Rate

Figure 1: Resting Heart Rate and Severity of COPD

Figure 2: Life Expectancy by COPD Severity and Resting Heart Rate

TABLE AND FIGURE LEGENDS

Table 1: Baseline Demographics

Table 2: Risk of mortality from elevated resting heart rate. Risk of both cardiovascular and all-cause mortality increase significantly with increase in resting heart rate. This relationship remains after multivariate adjustments. a; reference. *Multivariate: adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol drinking habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischemic heart disease, electrocardiographic evidence of ischemic heart disease, previous stroke, previous diagnosis of any cancer), self-reported diabetes or fasting glucose higher than 11.1 mmol/L.*

Table 3: Resting heart rate improves the risk prediction when added to a model with GOLD stage alone. This is shown by the greater number of subjects in the blue squares compared to number of subjects in the red squares for both non-events and events.

White squares: Subjects classified in the same risk category by both models. Blue squares: Subjects without events reclassified into a lower risk category and subjects with events reclassified into a higher risk category after inclusion of resting heart rate to the model with GOLD stage alone. Red squares: Subjects without events reclassified into a higher risk category and subjects with events reclassified into a lower risk category after inclusion of resting heart rate to the model with GOLD stage alone.

Table 4: Resting heart rate improves the risk prediction when added to a model with FEV₁%p alone. This is shown by the greater number of subjects in the blue squares compared to number of subjects in the red squares for both non-events and events.

White squares: Subjects classified in the same risk category by both models. Blue squares: Subjects without events reclassified into a lower risk category and subjects with events reclassified into a higher risk category after inclusion of resting heart rate to the model with FEV₁%p alone. Red squares: Subjects without events reclassified into a higher risk category and subjects with events reclassified into a lower risk category after inclusion of resting heart rate to the model with FEV₁%p alone.

Figure 1: Resting heart rate by severity of COPD. Resting heart rate increase significantly with severity of COPD ($p < 0,001$).

a) *Unadjusted* **b)** *adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol drinking habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischemic heart disease, electrocardiographic evidence of ischemic heart disease, previous stroke, previous diagnosis of any cancer), self-reported diabetes or fasting glucose higher than 11.1 mmol/L.*

Figure 2: Median life expectancies decreased with increase in resting heart rate across all stages of COPD.

Figure 1: Resting Heart Rate and Severity of COPD

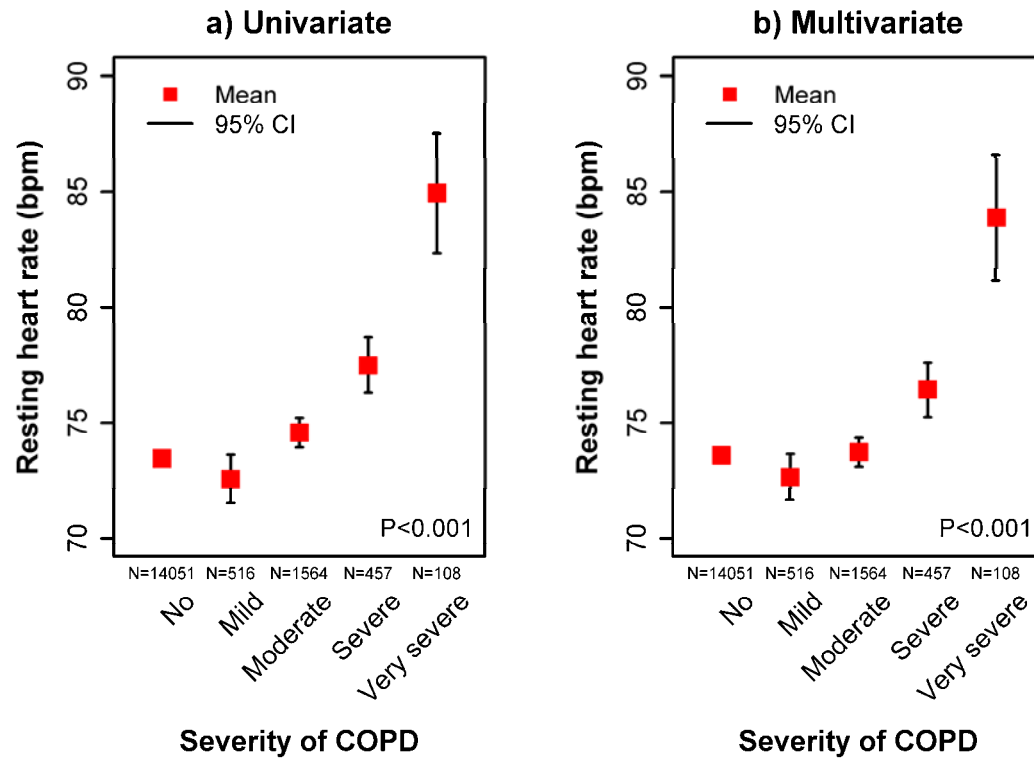


Figure 2: Life Expectancy by COPD Severity and Resting Heart Rate

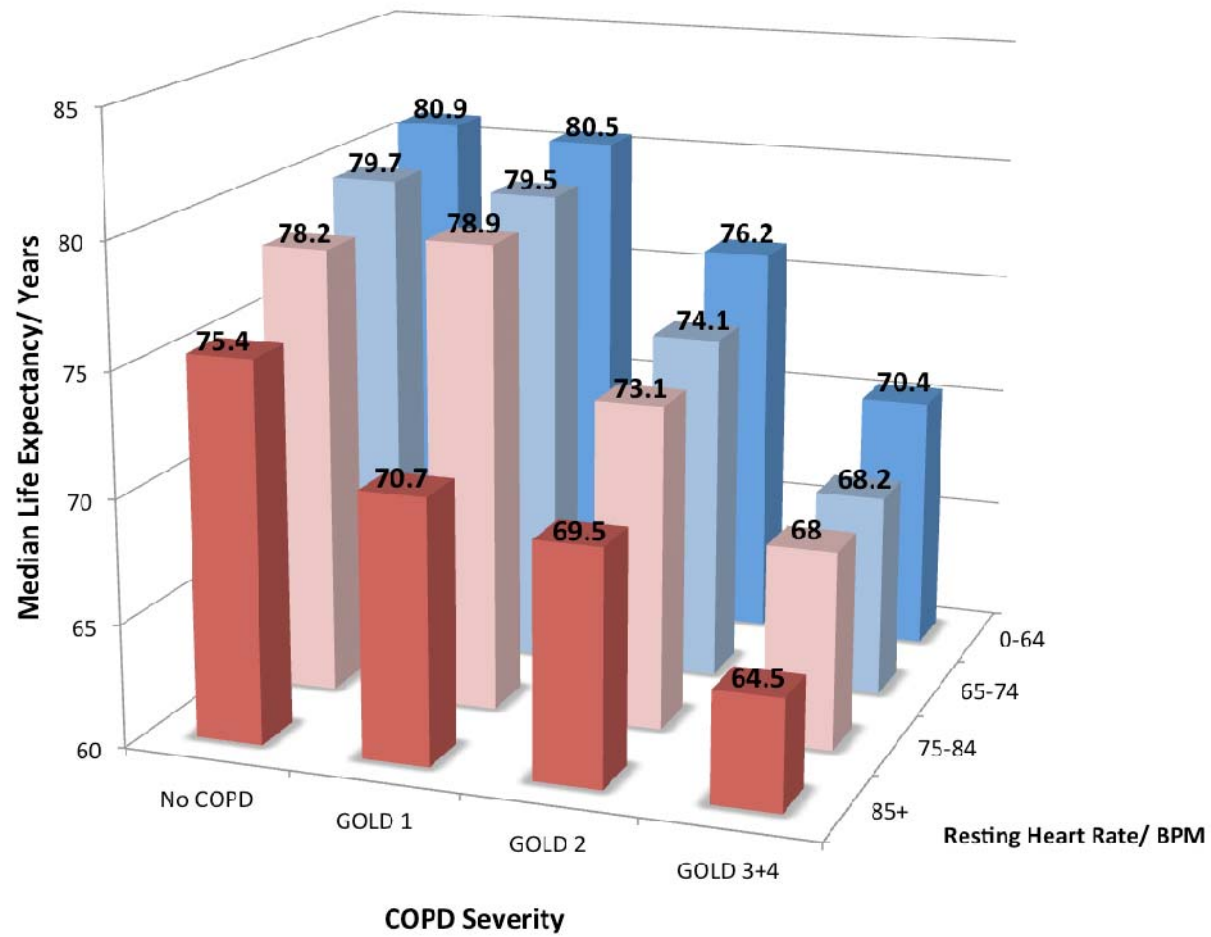


Table 1: Demographics

	GOLD Stage/ COPD Severity					P
	<i>0</i>	<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	
	<i>No COPD</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>	<i>Very Severe</i>	
Number of subjects	14051	516	1564	457	108	
Male sex, No. (%)	6251 (44.5)	313 (60.7)	866 (55.4)	261 (57.1)	75 (69.4)	<0.001
Age (Years) Mean (SD)	54 (9)	57 (10)	57 (10)	59 (9)	62 (9)	<0.001
Resting Heart Rate (BPM) mean (SD)	73.4 (13)	72.6 (12)	74.6 (13)	77.5 (13)	84.9 (14)	<0.001
Systolic Blood Pressure (mmHg)	137 (22)	138 (22)	141 (23)	141 (22)	144 (20)	<0.001
Mean (SD)						
Body Mass Index (kg/m ²) Mean (SD)	25.5 (4.2)	24.4 (3.2)	25.1 (4.2)	25.1 (4.8)	24.6 (5.1)	0.894
FEV ₁ %p Mean(SD)	89 (17)	89 (16)	65 (8)	42 (6)	24 (5)	<0.001
Sedentary physical activity, %,	17.6	21.4	24.3	31.1	47.7	<0.001
Smoking status:						

	August 20th 2012					
Never, %	21.9	15.6	10.9	7.3	7.5	<0.001
Former, %	19.2	19.9	12.9	15.4	34.9	<0.001
Current, %	58.9	64.5	76.2	77.3	57.5	<0.001
Daily alcohol drinking,	24.3	32.5	33.6	34.4	38.3	<0.001
Cholesterol (mmol/L) Mean (SD)	6.1 (1.2)	6.0 (1.2)	6.0 (1.2)	6.0 (1.1)	5.9 (1.2)	0.009
Use of heart medication, %	9.0	7.8	10.1	15.0	16.8	<0.001
Previous CHD, %	2.2	1.7	3.0	2.8	3.7	0.219
Previous Stroke, %	1.0	1.4	1.5	1.5	2.8	0.152
Previous cancer, %	4.1	2.9	5.4	5.9	8.3	0.004
Diabetes, %	3.1	1.8	4.2	5.4	10.6	<0.001

Table 2:

<i>Hazard Ratio (95% CI)/ Resting heart rate (BPM)</i>	<64 bpm	65-74 bpm	75-84 bpm	≥85 bpm
All-cause mortality				
Univariate	1 ^a	1.11 (1.05-1.17)	1.30 (1.23-1.37)	1.51 (1.42-1.60)
Multivariate	1 ^a	1.16 (1.10-1.22)	1.31 (1.24-1.38)	1.51 (1.43-1.60)
Cardiovascular mortality				
Univariate	1 ^a	1.08 (1.00-1.17)	1.34 (1.24-1.45)	1.57 (1.45-1.70)
Multivariate	1 ^a	1.16 (1.07-1.25)	1.36 (1.26-1.48)	1.57 (1.45-1.71)
<i>a: reference</i>				

Table 3:

Model with GOLD Stage and Resting Heart Rate

Model with GOLD Stage	<25 %	25%-35%	35%-50%	≥50%	Total
<u>Subjects without event</u>					
<25 %	0	0	0	0	0
25%-35%	55	900	82	0	1037
35%-50%	0	49	179	4	232
≥50%	0	0	1	36	37
Total	55	949	262	40	1306
<u>Subjects with event</u>					
<25 %	0	0	0	0	0
25%-35%	7	329	51	0	387
35%-50%	0	25	110	0	135
≥50%	0	0	0	35	35
Total	7	354	161	35	557

Table 4:

Model with FEV₁%p and Resting Heart Rate

Model with FEV₁%p	<25 %	25%-35%	35%-50%	≥50%	Total
<u>Subjects without event</u>					
<25 %	111	35	1	0	147
25%-35%	117	613	60	1	791
35%-50%	0	65	250	21	336
≥50%	0	0	10	22	32
Total	228	713	321	44	1306
<u>Subjects with event</u>					
<25 %	25	20	0	0	45
25%-35%	25	216	45	0	286
35%-50%	0	36	144	15	195
≥50%	0	0	7	24	31
Total	50	272	196	39	557