ERJ Express. Published on June 25, 2008 as doi: 10.1183/09031936.00012408

Prevalence and Outcomes of Diabetes, Hypertension, and Cardiovascular Disease in Chronic Obstructive Pulmonary Disease

David M. Mannino, M.D.

Deborah Thorn, Pharm. D.

Andrine Swensen, PhD

Fernando Holguin, M.D.

From the Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, Lexington, KY, (D.M.) Emory University College of Medicine, Atlanta, GA (F.H.) and Novartis Pharmaceuticals Corporation, East Hanover, NJ (D.T., A.S.)

Corresponding Author: David M. Mannino, MD
Department of Preventive Medicine and Environmental Health
University of Kentucky College of Public Health,
121 Washington, Avenue
Lexington, KY 40536
Phone 1 859 323 6608
Fax 1 859 257 1044
E-mail: dmannino@uky.edu

Word Count:

Abstract:	272
Text :	2754
Figures:	4
Tables:	4
References :	34

Funded by a research grant from Novartis Pharmaceuticals.

Running Head: Comorbid Disease in COPD

Key Words: Lung Function, hypertension, diabetes, cardiovascular, mortality

ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is associated with important chronic comorbid diseases, including cardiovascular disease, diabetes, and hypertension.

Methods: We analyzed data on 20,296 participants in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS) aged 45 and older at baseline. The sample was stratified based on baseline lung function data, according to modified Global Initiative on Obstructive Lung Disease (GOLD) criteria. We then searched for comorbid disease at baseline and death and hospitalizations over 5 years of follow-up.

Results: Lung function impairment was found to be associated with more comorbid disease. In logistic regression models adjusting for age, sex, race, smoking, body mass index and education, people with GOLD stage 3 or 4 COPD had a higher prevalence of diabetes (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.1, 1.9), hypertension (OR 1.6, 95% CI 1.3, 1.9) and cardiovascular disease OR 2.4, 95% CI 1.9, 3.0). Comorbid disease was associated with a higher risk of hospitalization and mortality that was worse in people with impaired lung function.

Discussion: Lung function impairment is associated with a higher risk of comorbid disease which contribute to a higher risk of adverse outcomes of mortality and hospitalizations.

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality in the United States and around the world [1, 2]. In recent years the approach towards patients with COPD has moved away from nihilism and towards viewing this disease as both preventable and treatable [3].

An important factor in both the prognosis and functional capabilities of COPD patients is the role of comorbid disease [4, 5]. There are several important steps in evaluating comorbid disease in COPD. The first is to define the diseases that occur with an increasing frequency in subjects with evidence of COPD and the second is to determine the affect that comorbid disease has on health-related outcomes. The disease processes most closely linked to COPD include lung cancer[6], depression[7], congestive heart failure [5] and ischemic heart disease[5], although there are several other diseases potentially linked to respiratory disease or its treatment with a weaker association (i.e. osteoporosis[8], cataracts[9] , hypertension [10], and diabetes mellitus[11]).

OBJECTIVE

Our goal was to determine the relation between COPD and the common chronic comorbid conditions of cardiovascular disease, hypertension, and diabetes mellitus, and to determine how these affect the outcomes of hospitalizations and death. This analysis was done by combining two existing databases, the Atherosclerosis Risk in Communities Study (ARIC)[12] and the Cardiovascular Health Study (CHS) [13] which are described below.

METHODS

We combined data from the CHS and ARIC cohorts, both of which were population-based NIH cohorts initiated in the late 1980s. These cohorts were designed to study subjects of different ages (65 and older for CHS and 45—64 for ARIC) with comprehensive evaluations including lung function and longitudinal follow-up. We analyzed ARIC and CHS data that is publicly available from the National Heart Lung and Blood Institute.

Study Population CHS

The original CHS cohort of 5,201 men and women was selected using Medicare eligibility lists provided by the U.S. Health Care Financing Administration for four communities: Forsyth County, North Carolina; Pittsburgh, Pennsylvania; Sacramento County, California; and Washington County, Maryland during the period from May 1989 to May 1990 [13]. CHS participants underwent pulmonary function testing during a baseline clinical examination and provided information on history of respiratory symptoms and diagnoses, BMI, smoking history, and medical history. Study protocols were approved for protection of human subjects. Details of the CHS are published elsewhere [13]. Our analysis was limited to CHS participants who provided baseline information on respiratory symptoms, underwent pulmonary function testing at the baseline examination, and for whom follow-up data were available.

Study Population ARIC

The original ARIC cohort, initiated in 1986, including 15,792 adults aged 45-64 years-old, was a population-based study of the etiology and clinical sequelae of atherosclerosis. Study protocols were approved for protection of human subjects. Details of the ARIC study are published elsewhere.[12] Our analysis was limited to ARIC participants, who provided baseline information on respiratory symptoms, who underwent pulmonary function testing at the baseline examination, and for whom follow-up data were available.

Pulmonary Function Data

Spirometry was conducted using a volume displacement, water-sealed spirometer. At least three acceptable spirograms were obtained from a minimum of five forced expirations. The best single spirogram was identified by computer and confirmed by a technician. Quality assurance was provided by the CHS Pulmonary Function Center for the CHS cohort and the ARIC coordinating center for ARIC, and the procedures followed contemporary American Thoracic Society guidelines [14]. Several measures of lung function were used: the forced expiratory volume in 1 second (FEV_1), the forced vital capacity (FVC), and the FEV_1/FVC ratio. We used the prediction equations developed by Hankinson et al. to determine "predicted" levels of lung function.

Variable Definition

Age, sex, race and highest education level obtained were self-reported. Age was stratified into 4 -5 year categories, race was classified as white or black, and education level was classified as < 12 years, 12 years, or more than 12 years. Responses to the

questions “Have you ever smoked cigarettes?” and “Do you now smoke cigarettes?” were used to classify as “current-, former- and never-smokers. BMI was calculated as weight divided by height squared (kg/m^2) [15].

Using a modification of the criteria developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [16, 17], we classified subjects at baseline according to their GOLD stages of chronic obstructive pulmonary disease (COPD): GOLD stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC< 0.70$ and $FEV_1 >= 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 >= 80\%$), restricted ($FEV_1/FVC >= 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease. We defined a participant as having a respiratory symptom (used to classify GOLD 0 lung function status) if they responded positively to any of the following questions: Do you usually have a cough?; Do you usually bring up phlegm from your chest?; Does your chest ever sound wheezy or whistling apart from colds?; Do you have to walk slower than people of your age on the level because of breathlessness?; Are you too breathless to leave the house or breathless on dressing or undressing? GOLD Stage 0 does not appear in the most recent guideline revisions but it is included it in our analysis as we have previously demonstrated adverse outcomes among people in this category [17, 18]. Bronchodilator response was not evaluated in this survey so classification is based on the “prebronchodilator” level. Some subjects may have taken a bronchodilator prior to spirometry, but data on this were not available.

Subjects were classified as having diabetes if they either reported a diagnosis of diabetes at baseline or had impaired fasting or post glucose load glucose levels (> 140) at

the examination. Subjects reporting a diagnosis of a previous myocardial infarction, stroke, heart failure, angina, or transient ischemic attacks were classified as have cardiovascular disease at the baseline examination. Subjects were classified as having hypertension if they either reported a physician diagnosis of hypertension, were on treatment for hypertension, or had evidence of hypertension at the examination (either a diastolic blood pressure >= 90 mmHG or a systolic blood pressure >- 140, based on three measurements). In addition, we summed the three comorbid conditions (cardiovascular disease, hypertension, and diabetes) and classified each subject as having 0, 1, 2 or 3 diseases. Only comorbid disease at baseline was included in the analysis.

Analyses were limited to subjects in whom we had complete data on demographic factors, risk factors, and baseline comorbid disease.

Hospitalizations and Deaths

Hospitalization data were searched and events were defined as any hospitalizations that occurred during five years of follow-up after the baseline evaluation. We determined the time interval from study entry to the initial hospitalization for each subject. For decedents, follow-up was counted from the date of the baseline survey to either the date of death or 5 years.

Analysis

All analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC), SUDAAN version 9.0 (RTI, Research Triangle Park, NC) and SPSS version 10 (SPSS Inc, Chicago, IL, USA).

Our main outcomes were the prevalence of diabetes mellitus, hypertension, and cardiovascular disease or combinations of these diseases at the baseline evaluation. We also determined the relation between respiratory impairment, comorbid disease and mortality and hospitalizations using Cox proportional hazard models.

We developed logistic and multinomial logistic regression models, using the SUDAAN procedures RLOGIST and MULTILOG, to determine the association between our categories of respiratory impairment and diabetes mellitus, hypertension, and cardiovascular disease (RLOGIST) or combinations of disease (MULTILOG). These models adjusted for age, sex, race, smoking status, education level, and body mass index.

Cox proportional hazard regression models for death and hospitalization were developed using the SUDAAN procedure SURVIVAL to account for differential follow up in cohort participants. Time of follow up was used as the underlying time metric. Censoring occurred at the date of death reported on the death certificate or date the participant was last known to be alive for death. For the hospitalization models we censored at the date of first hospitalization, date of death reported on the death certificate or date the participant was last known to be alive. Plots of the log-log survival curves for each covariate were produced to evaluate the proportional hazards assumptions. We used these models to determine the association between our categories of respiratory impairment, comorbid disease, and death or hospitalizations. Age, sex, race, smoking status, education level, and body mass index were included in the adjusted models. Models were evaluated for interaction between the class of lung function impairment, comorbid disease, and the outcomes of death or time to first hospitalization.

RESULTS

Our final cohort consisted of 15,341/15,792 (97.1%) of the ARIC participants and 4,955/5,201 (95.3%) of the CHS participants. The demographics of the studied population are shown in Table 1.

Overall, GOLD stage 3 or 4 COPD was present in 530 subjects (2.6%), GOLD Stage 2 COPD was present in 2,076 subjects (10.2%), and restriction on spirometry was present in 2,868 subjects (14.1%). Diabetes was present in 2,570 subjects (12.7%), hypertension was present in 8,137 (40.1%) and cardiovascular disease was present in 3,091 subjects (15.2%) (Table 1).

Analyses showed that increasing age, a higher body mass index, lower education status, and male sex were associated with a higher risk of diabetes, hypertension and cardiovascular disease (Table 1). In multivariate analyses, GOLD stage 3 or 4 COPD was associated with a higher risk of diabetes (Odds Ratio [OR] 1.5, 95% confidence interval [CI] 1.1, 1.9), hypertension (OR 1.6, 95% CI 1.3, 1.9), and cardiovascular disease (OR 2.4, 95% CI 1.9, 3.0). Similar findings were seen for GOLD Stage 2 COPD, GOLD stage 0 COPD, and restricted subjects (Table 2).

In our study cohort, 9,925 (48.9%) had no comorbid disease, 7,359 (36.3%), had one comorbid disease, 2,597 (12.8%) had 2 comorbid diseases, and 415 (2.0%) had 3 comorbid diseases (Table 3). Multinomial logistic regression showed that compared to people with normal lung function, those with GOLD Stage 3 or 4 COPD were more likely to have 1 (OR 1.8, 95% CI 1.5, 2.3), 2 (OR 2.9, 95% CI 2.2, 3.8) or 3 (OR 3.5, 95% CI 1.9, 6.4) comorbid diseases, with similar effects seen among restricted subjects and those with GOLD 2, and GOLD 0 COPD (Table 4).

Within five years of the baseline evaluation, 1,202 (5.9%) study participants died. The presence of respiratory impairment and comorbid disease predicted higher mortality, with cardiovascular disease and diabetes mellitus demonstrating a larger effect on mortality than hypertension (Figure 1). The combination of multiple comorbid diseases, along with respiratory impairment, also resulted in a higher risk of death (Figure 2). For example, a person with GOLD stage 3 or 4 COPD and all 3 comorbid diseases had a 20-fold higher risk of death than a person with normal lung function and no comorbid disease (Figure 2). There was no significant interaction between respiratory impairment, comorbid disease, and death ($p > 0.10$ for all models).

At least one hospitalization during the first 5 years of follow-up occurred in 4,537 (22.4%) study participants. The risk of any hospitalization was increased among study participants with respiratory impairment and comorbid disease, either alone or in combination (Figures 3 and 4). There was a significant interaction between respiratory impairment, comorbid disease, and hospitalization ($p < 0.05$ for all models).

DISCUSSION

In this analysis, the presence of respiratory impairment, as determined using both lung function measurement and the presence of respiratory symptoms, was associated with a higher risk of having comorbid hypertension, cardiovascular disease, and diabetes and of also having 2 or all of these comorbid diseases. In addition, the presence of these comorbid diseases further modified the effect that respiratory impairment had on our outcomes of all-cause mortality and hospitalization during 5 years of follow-up. While we found a significant interaction between respiratory impairment , comorbid disease and hospitalizations, but not deaths, this may have been related to the far larger number of hospitalizations (4,537 vs. 1,202).

The association between respiratory disease and cardiovascular disease is an area of research that has received a great deal of attention in recent years [19-21]. The reasons for this association are unclear, but may be related to systemic inflammation, chronic infections, shared risk factors (such as smoking), or other undefined factors [22-24]. A recent analysis of the ARIC data demonstrates that respiratory impairment predicts the development or recurrence of cardiovascular disease[25]. This relation, however, is decreased after adjusting for fibrinogen, a marker of systemic inflammation, which suggests that the relation between COPD and cardiovascular disease may be, in part, related to other factors [25]. In addition, there is evidence that smoking can also increase susceptibility to infection [26] and can increase levels of inflammatory markers in the serum [27].

An interesting finding in this analysis was that people with normal lung function but respiratory symptoms (formerly known as GOLD Stage 0) had a risk of

cardiovascular disease as high as people with GOLD Stage 3 or 4 COPD (Table 2). The presence of respiratory symptoms in the absence of lung function impairment is found in a significant proportion of patients [28]. Many of these people probably have cough or wheeze associated with asthma, gastroesophageal reflux, or sinusitis [29]. In some cases this may be an early manifestation of COPD [30]. In others, as this analysis suggests, this may be an indication of comorbid cardiovascular disease. Thus, the presence of respiratory symptoms, whether or not lung function is abnormal, is important both epidemiologically and clinically.

Similarly, the presence of restriction on spirometry has been found to be both associated with diabetes [31-33] and predictive of the development of diabetes [11, 31]. A novel finding in this analysis was a modest association of people with GOLD Stage 2 or higher COPD and those with GOLD Stage 0 COPD with diabetes (Table 2). This relationship is interesting and merits further investigation, with the potential to reveal new information on the development of both COPD and diabetes. Potential mechanisms explaining the relation between respiratory impairment and diabetes might be an increased body mass index and altered respiratory compliance, weakness of the respiratory muscles, neuropathies, or other undefined factors.

In addition, this analysis found an association between GOLD Stage 2 and higher COPD and restriction on spirometry and the presence of hypertension. Hypertension is an early manifestation of cardiovascular disease so a possible explanation of this association are that the same factors explaining the link between respiratory and cardiovascular disease are important here.

We also found that the presence of multiple comorbid diseases was significantly

increased among people with most classes of respiratory impairment (GOLD 0, GOLD 2 or higher, and restricted, Table 4). This is an area of particular interest given the recent attention to the presence of a "chronic systemic inflammatory syndrome" that hypothesizes the role of a chronic inflammatory process that results in the development of multiple chronic diseases [34]. Our data support this concept and also provide data suggesting that additive comorbid conditions affect outcomes in COPD. These findings raise the possibility that interventions in early COPD may best target the "inflammatory" and systemic component of the disease, rather than the lung disease per se.

LIMITATIONS

Strengths of this study include the two large cohorts of subjects, a reasonable length of follow-up, and well-defined outcome events. The study participants were not chosen to reflect a national sample, however, so these results do not necessarily reflect what might be seen in the US population. Even though this is a large study, however, subgroups of interest could be small, for example, only 14 subjects with GOLD stage 3 or 4 COPD had all three comorbid diseases present. Subjects were classified by COPD stage based on initial prebronchodilator spirometry, which may not have represented a true baseline for various reasons. In addition, our restricted category was included based on a decreased FVC alone rather than the gold standard, total lung capacity measurements.

CONCLUSIONS

In conclusion, we found a significant relation between respiratory impairment and

the presence of comorbid cardiovascular disease, diabetes mellitus, and hypertension. We also found that people with respiratory impairment are more likely to have two or all of these conditions and a significantly higher risk of death and hospitalizations, especially when comorbid disease is present. These findings suggest that the presence of respiratory impairment could provide a rationale to look for other comorbid disease and, conversely, that the presence of diabetes, hypertension, or cardiovascular disease might be the basis to evaluate patients for respiratory impairment.

Acknowledgement

The authors thank the staff and participants in the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS) for their important contributions. The ARIC Study and CHS are conducted and supported by the National Heart Lung and Blood Institute (NHLBI) in collaboration with the ARIC and CHS Investigators. This Manuscript was not prepared in collaboration with investigators of the ARIC or CHS and does not necessarily reflect the opinions or views of the ARIC, CHS, or the NHLBI.

Reference List

(1) Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. *MMWR Surveill Summ* 2002; 51: 1-16.

(2) Chen JC, Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 1999; 5: 93-99.

(3) Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932-946.

(4) Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM. Spectrum of heart failure in older patients: results from the National Heart Failure project. *Am Heart J* 2002; 143: 412-417.

(5) Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; 128: 2005-2011.

(6) Mannino DM, Doherty D, Buist AS, Holguin F. Global initiative on obstructive lung diseases (GOLD) classification of COPD and incident lung cancer: Findings from a cohort study. *Chest* 2004; 126: 853S.

(7) Di Marco F., Verga M, Reggente M, Maria CF, Santus P, Blasi F, Allegra L, Centanni S. Anxiety and depression in COPD patients: The roles of gender and disease severity. *Respir Med* 2006; 100: 1767-1774.

(8) Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* 2003; 114: 10-14.

(9) Ernst P, Baltzan M, Deschenes J, Suissa S. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. *Eur Respir J* 2006; 27: 1168-1174.

(10) Antonelli-Incalzi R., Fuso L, DeRosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 2794-2800.

(11) Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, Speizer FE, Barr RG, Camargo CA, Jr. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27: 2478-2484.

(12) The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* 1989; 129: 687-702.

(13) Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, . The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991; 1: 263-276.

(14) American Thoracic Society. Standardization of Spirometry. *Am Rev Respir Dis* 1979; 119: 831-838.

(15) Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998; 158: 1855-1867.

(16) World Health Organization. Global Strategy for Diagnosis, Management, and Prevention of COPD. *http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989* . 2006. (Date accessed 6-3-2008.)

(17) Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van WC, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532-555.

(18) Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. *Thorax* 2006; 61: 472-477.

(19) Sin DD, Man SF. Chronic obstructive pulmonary disease: a novel risk factor for cardiovascular disease. *Can J Physiol Pharmacol* 2005; 83: 8-13.

(20) Mancini GB, Etminan M, Zhang B, Levesque LE, Fitzgerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006; 47: 2554-2560.

(21) Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, She D. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; 16: 63-70.

(22) Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; 49: 171-180.

(23) Kiechl S, Werner P, Egger G, Oberhollenzer F, Mayr M, Xu Q, Poewe W, Willeit J. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke* 2002; 33: 2170-2176.

(24) Naunheim KS, Wood DE, Krasna MJ, DeCamp MM, Jr., Ginsburg ME, McKenna RJ, Jr., Criner GJ, Hoffman EA, Sternberg AL, Deschamps C.

Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial. *J Thorac Cardiovasc Surg* 2006; 131: 43-53.

(25) Johnston AK, Mannino DM, Hagan GW, Davis KJ, Kiri VA. Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort. *Thorax* 2008.

(26) Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med* 2004; 164: 2206-2216.

(27) Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. *Chest* 2005; 127: 558-564.

(28) Kohler D, Fischer J, Raschke F, Schonhofer B. Usefulness of GOLD classification of COPD severity. *Thorax* 2003; 58: 825.

(29) Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, Brown KK, Canning BJ, Chang AB, Dicpinigaitis PV, Eccles R, Glomb WB, Goldstein LB, Graham LM, Hargreave FE, Kvale PA, Lewis SZ, McCool FD, McCrory DC, Prakash UB, Pratter MR, Rosen MJ, Schulman E, Shannon JJ, Smith HC, Tarlo SM. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129: 1S-23S.

(30) de Marco R., Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, Kunzli N, Leynaert B, Janson C, Gislason T, Vermeire P, Svanes C, Anto JM, Burney P. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. *Thorax* 2004; 59: 120-125.

(31) Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004; 27: 2966-2970.

(32) Bolton CE, Evans M, Ionescu AA, Edwards SM, Morris RH, Dunseath G, Luzio SD, Owens DR, Shale DJ. Insulin resistance and inflammation - A further systemic complication of COPD. *COPD* 2007; 4: 121-126.

(33) Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Intern Med* 2003; 253: 574-581.

(34) Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; 370: 797-799.

Table 1 – Demographics of the studied population and proportion with diabetes mellitus, hypertension, and cardiovascular disease (mean proportion of each row and standard error [SE] of the mean) at baseline. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990 . N=20,296 study participants

	N (%)	Diabetes Mellitus % (SE)	Hypertension % (SE)	Cardiovascular Disease % (SE)
Age Group				
45-49	4,096 (20.2)	8.1 (0.4)	24.5 (0.7)	9.7 (0.5)
50-54	3,978 (19.6)	10.6 (0.5)	32.0 (0.7)	11.9 (0.5)
55-59	3,751 (18.5)	12.9 (0.5)	38.1 (0.8)	14.8 (0.6)
60-64	3,516 (17.3)	16.5 (0.6)	46.4 (0.8)	17.0 (0.6)
65-71	437 (2.2)	16.2 (1.8)	49.9 (2.4)	16.0 (1.7)
72-75	1,680 (8.3)	13.9 (0.8)	51.3 (1.2)	17.3 (0.9)
76-79	1,168 (5.8)	15.9 (1.1)	58.0 (1.4)	21.1 (1.2)
80 and older	1,670 (8.2)	15.4 (0.9)	62.4 (1.2)	27.4 (1.1)
Sex				
Female	11,258 (55.5)	12.0 (0.3)	40.8 (0.5)	13.1 (0.3)
Male	9,038 (44.5)	13.5 (0.4)	39.2 (0.5)	17.9 (0.4)
Race				
White	16,040 (79.0)	10.7 (0.2)	35.7 (0.4)	16.1 (0.3)
Black	4256 (21.0)	20.1 (0.6)	56.6 (0.8)	12.0 (0.5)
Smoking Status				
Current Smoker	8,290 (40.9)	13.1 (0.4)	42.6 (0.5)	13.1 (0.4)
Former Smoker	7,052 (34.8)	13.2 (0.4)	41.2 (0.6)	18.2 (0.5)
Never Smoker	4,954 (24.4)	11.1 (0.4)	34.3 (0.7)	14.6 (0.5)
Education (years)				
< 12	4,996 (24.6)	18.9 (0.6)	50.8 (0.7)	19.9 (0.6)
12	6,372 (31.4)	11.9 (0.4)	39.0 (0.6)	14.8 (0.4)
> 12	8,928 (44.0)	9.7 (0.3)	34.9 (0.5)	12.9 (0.4)
Body Mass Index				
< 20	811 (4.0)	5.1 (0.8)	30.6 (1.6)	14.3 (1.2)

20-24	6,288 (31.0)	6.3 (0.3)	30.1 (0.6)	13.4 (0.4)
25-29	8,100 (39.9)	11.7 (0.4)	39.9 (0.5)	15.4 (0.4)
>= 30	5,097 (25.1)	23.2 (0.6)	54.3 (0.7)	17.3 (0.5)
GOLD Category*				
GOLD 3 or 4	530 (2.6)	14.5 (1.5)	51.1 (2.2)	22.1 (1.8)
GOLD 2	2,076 (10.2)	12.6 (0.7)	43.8 (1.1)	19.4 (0.9)
GOLD 1	2,892 (14.3)	10.1 (0.6)	40.4 (0.9)	18.7 (0.7)
GOLD 0	4,511 (22.2)	14.9 (0.5)	41.6 (0.7)	19.7 (0.6)
Restricted	2,868 (14.1)	19.0 (0.7)	47.7 (0.9)	16.6 (0.7)
Normal	7,419 (36.6)	9.7 (0.3)	34.3 (0.6)	9.0 (0.3)
Total	20,296	12.7 (0.2)	40.1 (0.3)	15.2 (0.3)

* Modified Global Initiative on Obstructive Lung Disease (GOLD) stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC< 0.70$ and $FEV_1 >= 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 >= 80\%$), restricted ($FEV_1/FVC >= 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease. FEV_1 is the forced expiratory volume in one second and FVC is the forced vital capacity.

Table 2. Multivariate regression, predictors of diabetes mellitus, hypertension and cardiovasacular disease. Models are adjusted for age, sex, race, smoking status, education level, and body mass index. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990. N=20,296 study participants.

	Diabetes Mellitus OR (95% CI)	Hypertension OR (95% CI)	Cardiovascular Disease OR (95% CI)
GOLD Category*			
GOLD 3 or 4	1.5 (1.1, 1.9)	1.6 (1.3, 1.9)	2.4 (1.9, 3.0)
GOLD 2	1.4 (1.2, 1.6)	1.4 (1.3, 1.6)	2.2 (1.9, 2.5)
GOLD 1	0.9 (0.8, 1.1)	1.1 (0.9, 1.2)	1.7 (1.5, 1.9)
GOLD 0	1.4 (1.3, 1.6)	1.2 (1.1, 1.3)	2.4 (2.1, 2.8)
Restricted	2.1 (1.9, 2.5)	1.5 (1.4, 1.7)	2.4 (2.1, 2.7)
Normal	1	1	1

* See Table 1 for description of categories

Table 3 – Demographics of the studied population and proportion with 0, 1 , 2 or 3 comorbid diseases (diabetes mellitus, hypertension, and cardiovascular disease, mean proportion of each row and standard error [SE] of the mean) at baseline. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990 . N=20,296 study participants.

	N (%)	No Comorbid Disease Mean % (SE)	One Comorbid Disease Mean % (SE)	Two Comorbid Diseases Mean % (SE)	Three Comorbid Diseases Mean % (SE)
Age Group					
45-49	4,096 (20.2)	65.2 (0.7)	27.9 (0.7)	6.2 (0.4)	0.7 (0.1)
50-54	3,978 (19.6)	57.4 (0.8)	31.9 (0.7)	9.5 (0.5)	1.3 (0.2)
55-59	3,751 (18.5)	50.2 (0.8)	35.6 (0.8)	12.5 (0.5)	1.8 (0.2)
60-64	3,516 (17.3)	41.6 (0.8)	39.6 (0.8)	15.9 (0.6)	2.8 (0.3)
65-71	437 (2.2)	41.2 (2.4)	38.2 (2.3)	17.8 (1.8)	2.7 (0.8)
72-75	1,680 (8.3)	39.6 (1.2)	42.1 (1.2)	14.6 (0.9)	3.8 (0.5)
76-79	1,168 (5.8)	31.1 (1.4)	46.4 (1.5)	18.8 (1.1)	3.7 (0.6)
80 and older	1,670 (8.2)	24.9 (1.1)	48.1 (1.2)	23.8 (1.0)	3.2 (0.4)
Sex					
Female	11,258 (55.5)	49.9 (0.5)	35.9 (0.5)	12.6 (0.3)	1.6 (0.1)
Male	9,038 (44.5)	47.7 (0.5)	36.7 (0.5)	13.1 (0.4)	2.5 (0.2)
Race					
White	16,040 (79.0)	52.7 (0.4)	33.9 (0.4)	11.5 (0.3)	1.9 (0.1)
Black	4256 (21.0)	34.5 (0.7)	45.2 (0.8)	17.6 (0.6)	2.8 (0.3)
Smoking Status					
Current Smoker	8,290 (40.9)	53.7 (0.7)	34.0 (0.7)	11.0 (0.4)	1.4 (0.2)
Former Smoker	7,052 (34.8)	46.5 (0.6)	37.2 (0.6)	13.6 (0.4)	2.7 (0.2)
Never Smoker	4,954 (24.4)	48.1 (0.5)	36.9 (0.5)	13.2 (0.4)	1.9 (0.1)
Education (years)					
< 12	4,996 (24.6)	35.8 (0.7)	41.9 (0.7)	19.0 (0.6)	3.2 (0.2)
12	6,372 (31.4)	49.7 (0.6)	36.5 (0.6)	12.0 (0.4)	1.8 (0.2)

> 12	8,928 (44.0)	55.6 (0.5)	32.9 (0.5)	9.9 (0.3)	1.6 (0.1)
Body Mass Index					
< 20	811 (4.0)	58.6 (1.7)	33.4 (1.7)	7.5 (0.9)	0.5 (0.2)
20-24	6,288 (31.0)	60.4 (0.6)	30.5 (0.6)	8.2 (0.3)	1.0 (0.1)
25-29	8,100 (39.9)	48.6 (0.6)	37.6 (0.5)	12.0 (0.4)	1.8 (0.1)
>= 30	5,097 (25.1)	33.7 (0.7)	41.7 (0.7)	20.6 (0.6)	4.0 (0.3)
GOLD Category*					
GOLD 3 or 4	530 (2.6)	35.1 (2.1)	44.7 (2.2)	17.5 (1.7)	2.6 (0.7)
GOLD 2	2,076 (10.2)	44.5 (1.1)	37.6 (1.1)	15.6 (0.8)	2.4 (0.3)
GOLD 1	2,892 (14.3)	47.3 (0.9)	37.7 (0.9)	13.6 (0.6)	1.4 (0.2)
GOLD 0	4,511 (22.2)	45.5 (0.7)	36.1 (0.7)	15.3 (0.5)	3.2 (0.3)
Restricted	2,868 (14.1)	40.8 (0.9)	38.4 (0.9)	17.7 (0.7)	3.2 (0.3)
Normal	7,419 (36.6)	57.0 (0.6)	34.0 (0.6)	8.0 (0.3)	1.0 (0.1)
Total	20,296	48.9 (0.4)	35.3 (0.3)	12.8 (0.2)	2.0 (0.1)

* See Table 1 for description of categories

Table 4 – Results of Multinomial Logistic regression predicting the presence of 1, 2 or 3 comorbid diseases (diabetes mellitus, cardiovascular disease or hypertension). Models are adjusted for age, sex, race, smoking status, education level, and body mass index From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990 and follow-up. N=20,296 study participants.

	One Comorbid Disease OR (95% CI)	Two Comorbid Diseases OR (95% CI)	Three Comorbid Diseases OR (95% CI)
GOLD Category*			
GOLD 3 or 4	1.8 (1.5, 2.3)	2.9 (2.2, 3.8)	3.5 (1.9, 6.4)
GOLD 2	1.4 (1.3, 1.6)	2.4 (2.0, 2.9)	3.2 (2.2, 4.6)
GOLD 1	1.1 (0.96, 1.2)	1.4 (1.2, 1.7)	1.0 (0.7, 1.5)
GOLD 0	1.3 (1.2, 1.4)	2.1 (1.9, 2.4)	3.6 (2.7, 4.9)
Restricted	1.5 (1.4, 1.7)	3.0 (2.6, 3.5)	6.1 (4.3, 8.7)
Normal	1.0	1.0	1.0

* See Table 1 for description of categories

Figure 1. Results from Cox-proportional hazard models that predict death within 5 years by modified GOLD* category and the presence of comorbid diabetes (A), hypertension (B), or cardiovascular disease (C). Reference group for each graphic is people with normal lung function who do not have the comorbid disease of interest and models are adjusted for age, sex, race, smoking status, education level, and body mass index. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990

* See Table 1 for description of categories

Figure 2. Results from Cox-proportional hazard models that predict death within 5 years by modified GOLD* category and the presence of no, one, two or three comorbid diseases (diabetes, hypertension, or cardiovascular disease). Reference group for each graphic is people with normal lung function any comorbid disease and models are adjusted for age, sex, race, smoking status, education level, and body mass index. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990

* See Table 1 for description of categories

Figure 3. Results from Cox-proportional hazard models that predict first hospitalization within 5 years by modified GOLD* category and the presence of comorbid diabetes (A), hypertension (B), or cardiovascular disease (C). Reference group for each graphic is people with normal lung function who do not have the comorbid disease of interest and models are adjusted for age, sex, race, smoking status, education level, and body mass index. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990

* See Table 1 for description of categories

Figure 4. Results from Cox-proportional hazard models that predict first hospitalization within 5 years by modified GOLD* category and the presence of no, one, two or three comorbid diseases (diabetes, hypertension, or cardiovascular disease). Reference group for each graphic is people with normal lung function any comorbid disease and models are adjusted for age, sex, race, smoking status, education level, and body mass index. From the Atherosclerosis Risk in Communities Study 1986-1989 and Cardiovascular Health Study 1989-1990

* See Table 1 for description of categories

Figure 1

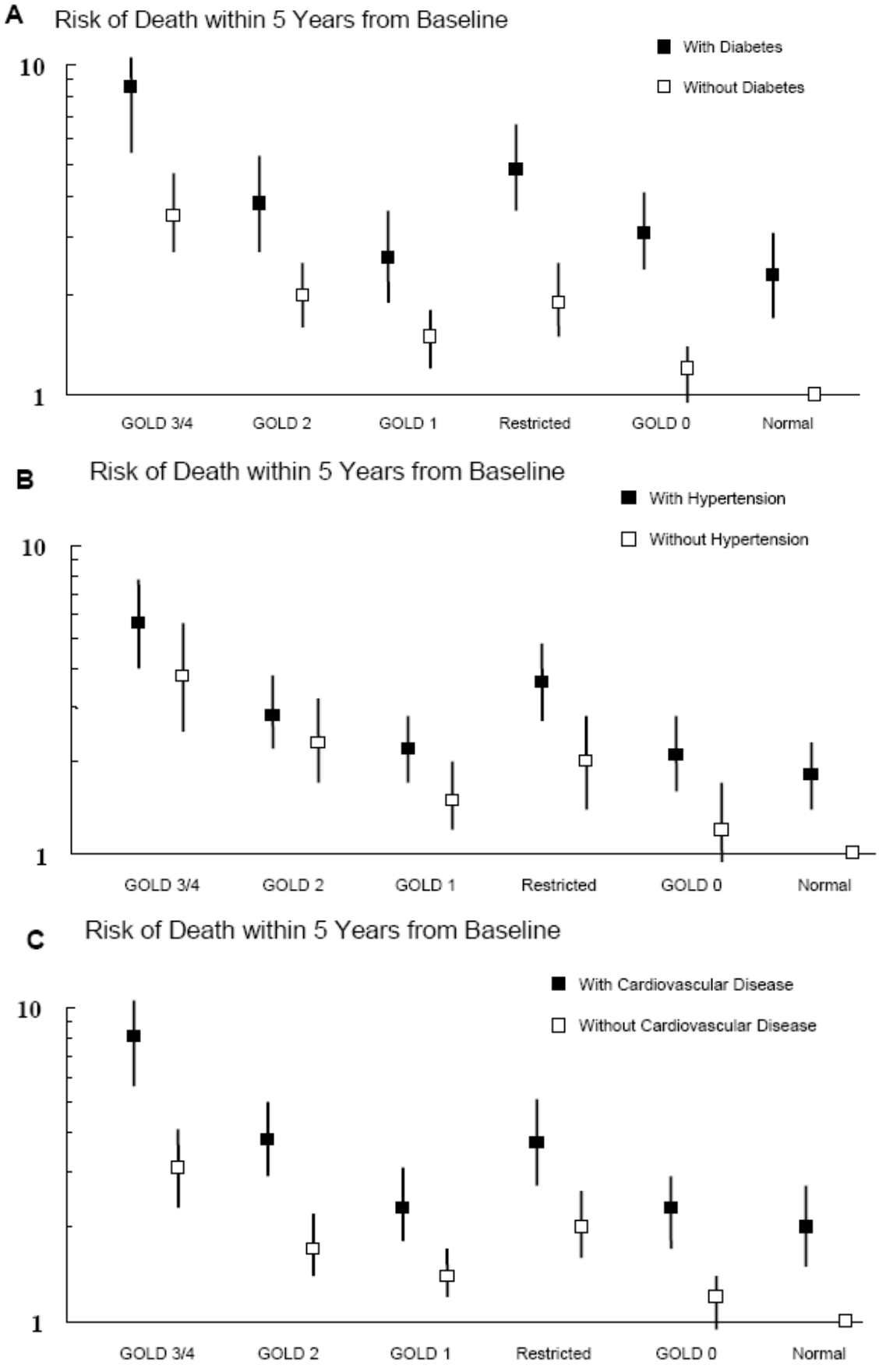

A
Risk of Death within 5 Years from Baseline
With Diabetes
Without Diabetes
10
1
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal
B
Risk of Death within 5 Years from Baseline
With Hypertension
Without Hypertension
10
1
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal
C
Risk of Death within 5 Years from Baseline
With Cardiovascular Disease
Without Cardiovascular Disease
10
1
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal

Figure 2

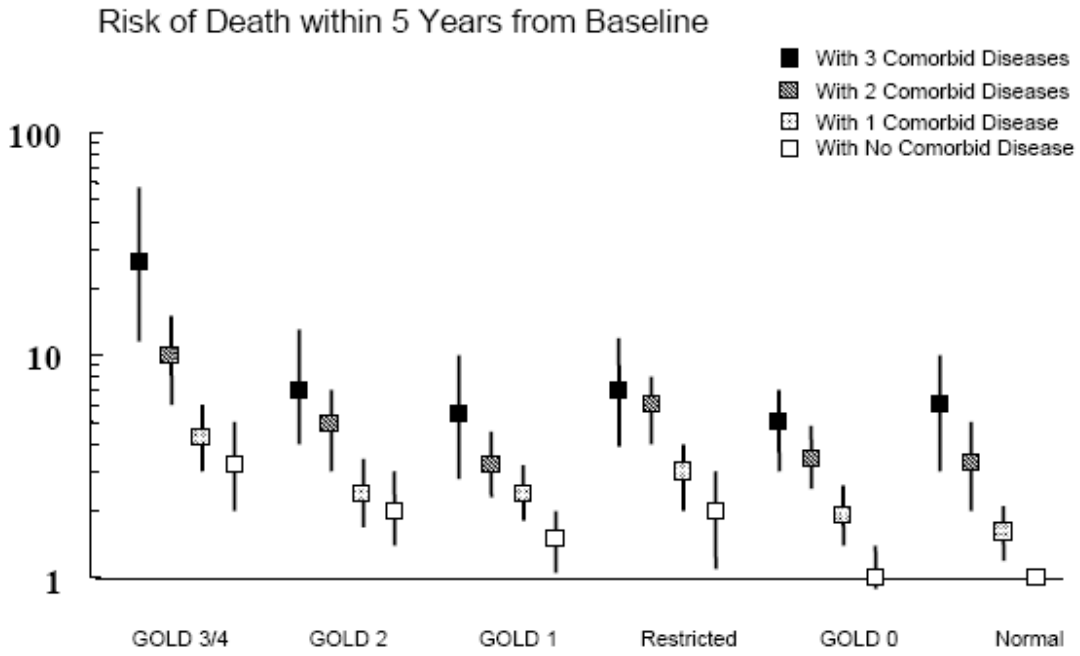

Risk of Death within 5 Years from Baseline
With 3 Comorbid Diseases
With 2 Comorbid Diseases
With 1 Comorbid Disease
With No Comorbid Disease
100
10
1
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal

Figure 3

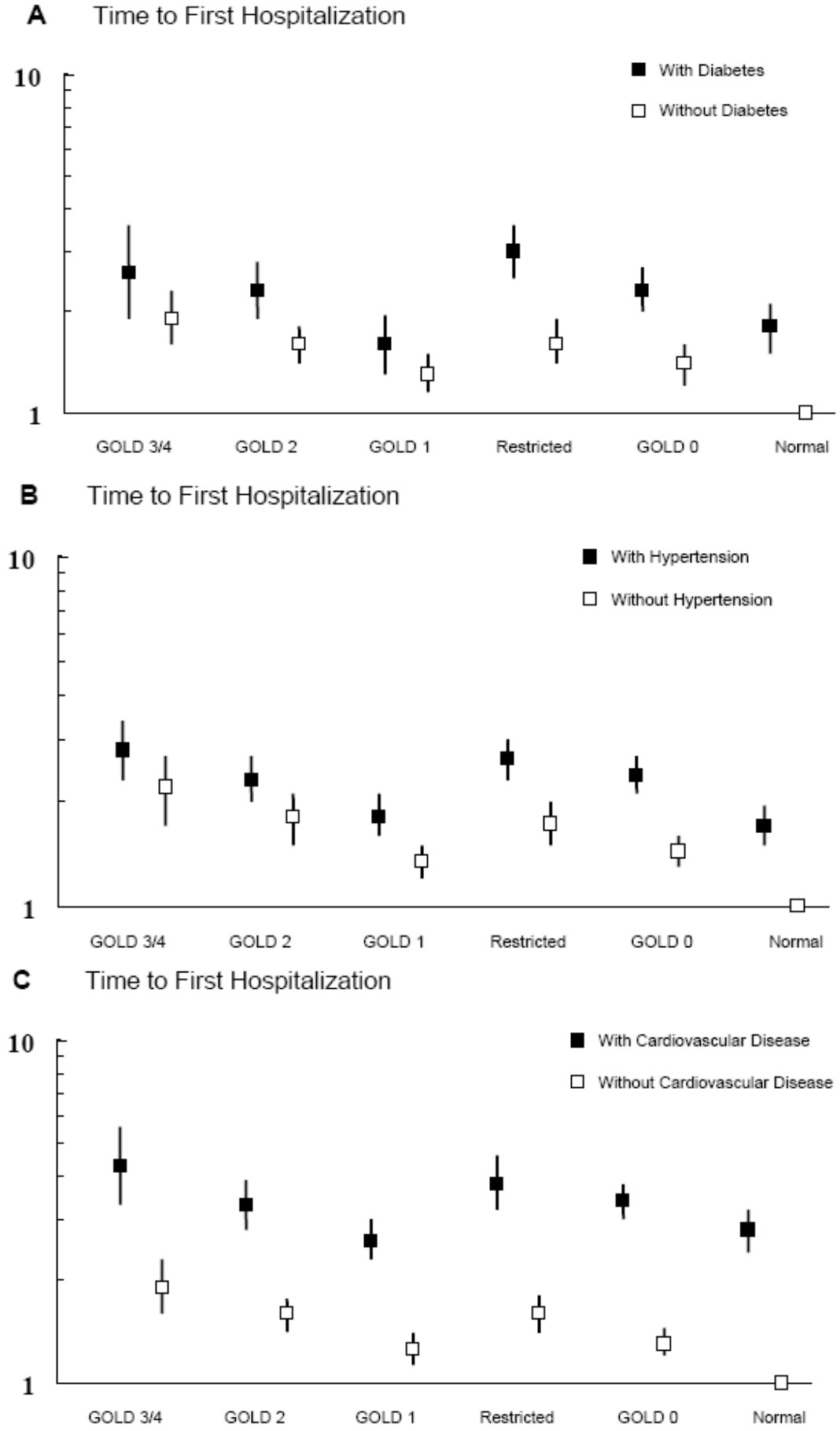
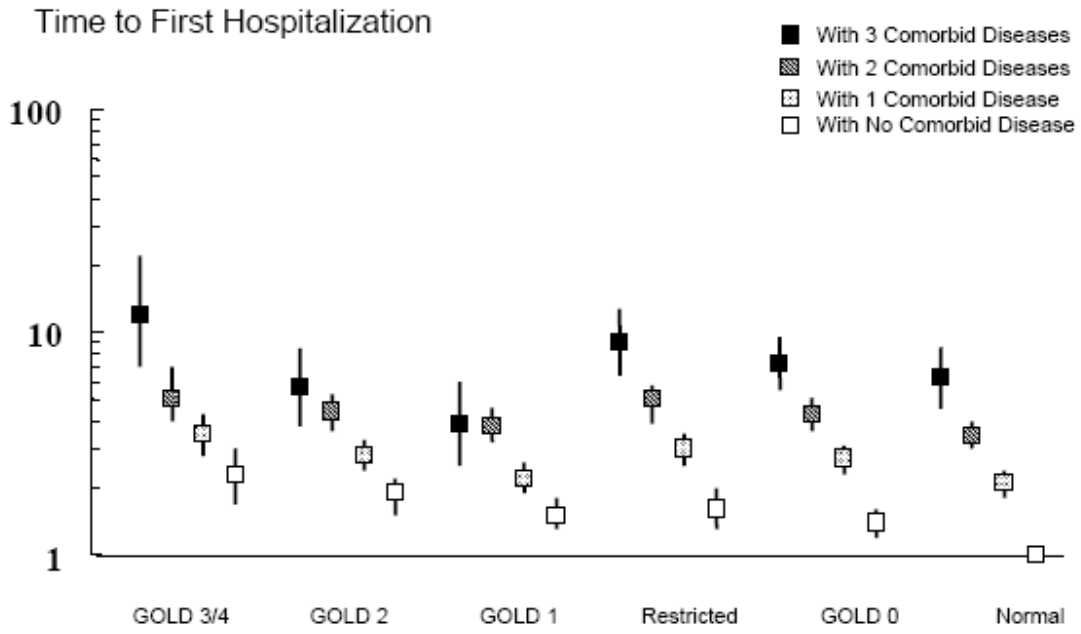

A
Time to First Hospitalization
10
1
With Diabetes
Without Diabetes
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal
B
Time to First Hospitalization
10
1
With Hypertension
Without Hypertension
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal
C
Time to First Hospitalization
10
1
With Cardiovascular Disease
Without Cardiovascular Disease
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal

Figure 4


Time to First Hospitalization
With 3 Comorbid Diseases
With 2 Comorbid Diseases
With 1 Comorbid Disease
With No Comorbid Disease
100
10
1
GOLD 3/4
GOLD 2
GOLD 1
Restricted
GOLD 0
Normal