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COPD prevalence and its association with occupational exposures in a general population

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Short title for manuscript: COPD prevalence and occupational exposures.

ABSTRACT

Question of the study

The aim of this study was to ascertain the population prevalence of chronic obstructive pulmonary disease (COPD) in an area with past heavy industry and to establish the relative contributions of occupational and other risk factors.

Materials / patients and methods

We investigated respiratory symptoms and the prevalence of spirometrically-defined COPD in a population-based study in north east England between 2002 and 2004. Questionnaires were posted to 6,000 men and 6,000 women aged 45-69 randomly selected from a primary care database (response rate 64%, n=7,566). Spirometric measurements were performed on 845 randomly selected responders. We defined COPD by the Global Initiative for Obstructive Lung Disease II criteria.

Results

The prevalence of respiratory symptoms was 55%. Symptoms were strongly associated with smoking, occupational exposures and hay fever. COPD was present in 10% of subjects. Its presence was significantly associated with occupational exposures, smoking and hay fever.

Answer to the question

COPD is common in north east England. Respiratory effects of occupational exposures can be detected within the general population: there were clear associations between occupational exposures and respiratory symptoms. The association with COPD that was more marked in females.

Key words

Chronic obstructive pulmonary disease, epidemiology, occupational exposure, prevalence

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a global health problem that causes substantial morbidity and mortality. It is increasing in prevalence and by 2020 it will be the third leading cause of death worldwide.[1] Despite its considerable social and economic importance, population-based epidemiological studies of its prevalence have lagged behind those of other common health problems. Chapman *et al* recently noted that only 32 prevalence surveys of COPD had been reported up to 2001, compared with hundreds of studies of asthma and thousands relating to cancer and cardiovascular disease.[2]

The lack of generally-agreed diagnostic criteria has been an important limitation to the investigation of COPD. Symptoms relate poorly to lung function abnormalities limiting the value of questionnaires.[3] Variations in lung function diagnostic criteria can change prevalence estimates considerably [4] and the age distribution of the study population also has a marked effect.[3,5] Studies from different centres often cannot be compared directly, limiting conclusions about geographic variation and temporal trends. However, recently introduced guidelines such as those of the Global Initiative for Obstructive Lung Disease (GOLD) have helped standardise diagnostic practice and have facilitated national and international comparisons.[6]

In addition to uncertainties about the true prevalence of COPD and its geographic variability, some aetiological issues also remain unresolved. Cigarette smoking is the principal risk factor. However, smoking explains no more than two thirds of the variation in COPD prevalence in epidemiological studies, and often less.[2,3] Occupational exposures to dusts, vapours and fumes have been established as risk factors by studies of coal miners and other working groups.[7] They are believed to be responsible for approximately 15% of

COPD overall but their influence is likely to vary geographically depending on their extent and nature, and may be substantially higher in some areas.[8] Other COPD risk factors include atopy, social status, air pollution and genetic predisposition.[1,8-10]

Our study aimed to quantify the population prevalence of COPD in north east England, an area that until recently was characterised by heavy industry such as mining and shipbuilding. Many middle-aged and elderly local residents were heavily exposed to dust, fumes and vapours during their working lives. This population therefore offered the opportunity to explore the relative contribution of occupational exposures to COPD in one of the most industrialised areas of Western Europe.

MATERIALS AND METHODS

Study design

This was a two-phased cross-sectional community survey of an urban population of approximately 500,000 residents. The main study objective was to ascertain the prevalence of spirometrically-defined COPD and explore its association with occupational exposures. Appropriate ethical approval was obtained from the Newcastle and North Tyneside Ethics Committee.

Sampling frame

12,000 subjects (50% male) aged 45-69 years were randomly selected from the local Primary Care Trust database, and were stratified equally into five-year age bands.

Questionnaire design

The self-completed questionnaire contained twenty-one questions ascertaining information on demographic and occupational details, respiratory symptoms and smoking.

The questions were based on the European Compendium of Respiratory Standard Questionnaires for adults.[11] Subjects were also asked to state if they had worked with any of the substances, or in any of the occupations illustrated in figure 1, and if so, for how long. UK census data from 2001 indicated that only 3.2% of the local population was non-white and no adjustment was made for ethnicity.[12]

Questionnaire administration

Questionnaires were mailed between July and October 2002. Up to two reminders were sent to non-responders. Data were coded by the Newcastle University Data Preparation Service and entered into a database.

Lung function measurements

Lung function measurements were carried out by the same trained personnel in two centres between September 2003 and August 2004. 1,516 subjects were invited to attend. 425 were selected at random from those mailed the questionnaire. The remainder were identified by stratifying questionnaire responders into 5 subgroups by the number of symptoms reported and selecting 24% from each subgroup. Participants were asked not to take inhaled short-acting bronchodilators for four hours and long-acting bronchodilators for 24 hours prior to testing. Height and weight were recorded. FEV_1 and FVC were measured using PK Morgan rolling seal volume displacement spirometers, with software supplied by Collingwood Measurement, Packington, Leicestershire, UK. The spirometers were calibrated daily in accordance with the manufacturer's instructions and all equipment complied with European Commission standards. Inter-laboratory assessments of consistency were undertaken by the supervising individuals measuring their own (stable) spirometry at the start of each session. FEV_1 and FVC were re-measured 15 minutes after the inhalation of 200mcg of Salbutamol

(Glaxo Smith Kline, Uxbridge, Middlesex, UK) via a metered dose inhaler and spacer device. All measurements were corrected to body temperature pressure saturated (BTPS) and compared with values derived from the European Community for Steel and Coal prediction equations.[13] The best of at least three technically satisfactory measurements was recorded.

Definition of COPD

COPD was defined as post-bronchodilator FEV_1 <80% of the predicted value and an FEV_1/FVC ratio <0.7) representing moderate or severe disease, ie stage II or above using GOLD criteria.[6]. Alternative definitions including FEV1/FVC <0.7 (GOLD stage 1), and FEV_1 below the lower limit of normal (LLN) [13] were explored.

Statistical analysis

The study was designed to have 80% power to detect a 5% difference in symptom prevalence in any subgroup that comprised 15% or more of the study population at the 5% level of significance. Statistical Package for Social Sciences (SPSS, version 15.0) and Stata were used for statistical analysis. Sub-groups were compared by χ^2 and t-tests. Binary logistic regression for complex samples was used for categorical dependant variables to allow for the stratification of the population by age and gender. Multiple logistic regression for complex samples was used when the dependant variables were continuous.

RESULTS

7,566 valid and 138 invalid questionnaire responses were received, a response rate of 64%. Characteristics of the questionnaire responders are detailed in table 1. As reported

previously from north east England,[14] the study population was largely static, with only 10% of individuals having lived the majority of their lives outside the region.

Table 1: Characteristics of questionnaire responders (%) by gender

	Men	Women
Demographic characteristics		
Gender	46%	54%
Median age, years (IQ range)	58 (52 to 64)	57 (52 to 64)[1]
Home ownership	75%	77%[1]
Lived locally most of life	89%	91%
Occupational exposure		
Any	67%	36%[1]
Smoking history		
Never smoked	30%	44%[1]
Ex-smoker	45%	32%[1]
Current smoker	25%	24%
Median (IQ range) pack-years for smokers	26 (13-44)	22 (9-36) [1]
Self-reported symptoms		
Any respiratory symptoms	57%	53%[1]
Cough	23%	18%[1]
Sputum	30%	20%[1]
Dyspnoea	33%	34%
Wheeze	42%	38%[1]
History of hay fever	24%	28%[1]

[1]Difference between men and women $p<0.001$

Older subjects and females were more likely to respond to the questionnaire: the median age of responders was 58 versus 56 years for non-responders ($p<0.001$). Differences in the response patterns between those responding to the first and to subsequent mailings of the questionnaire suggested that those with symptoms ($p=0.001$), lighter smokers ($p<0.001$), those of higher social class ($p<0.001$) and those without occupational exposures were more likely to respond ($p=0.01$).[15] There were differences between men and women in their exposure profiles (figure 1).

Predictors of respiratory symptoms are shown in table 2. The effect of occupational exposures was generally more marked in females, indicated by the significant gender-exposure interaction term. There were associations with the specific occupational exposures to coal mining ($p<0.01$), factory work ($p<0.05$), work with solvents ($p<0.05$), welding and shipyard work ($p<0.05$). Analyses using the duration of exposure for each category did not strengthen any of these associations.

Table 2: Significant predictors of respiratory symptoms (odds ratios and 95% confidence intervals)

	Cough	Sputum	Dyspnoea	Wheeze	Any symptom
Male gender		1.3 (1.1 to 1.6)	0.7 (0.6 to 0.9)		
Age (per 10 years)			1.3 (1.2 to 1.4)	0.9 (0.8 to 1.0)	1.2 (1.1 to 1.3)
Smoking (per 10 pack years)	1.3 (1.3 to 1.3)	1.3 (1.2 to 1.3)	1.3 (1.3 to 1.3)	1.3 (1.3 to 1.4)	1.3 (1.2 to 1.3)
Hay fever	1.8 (1.6 to 2.1)	1.9 (1.7 to 2.2)	1.8 (1.6 to 2.0)	2.9 (2.6 to 3.3)	2.5 (2.2 to 2.8)
Any occupational exposure	2.0 (1.6 to 2.1)	2.2 (1.8 to 2.8)	1.9 (1.5 to 2.3)	1.8 (1.5 to 2.2)	2.1 (1.7 to 2.5)
Gender-exposure interaction			1.3 (1.0 to 1.7)	1.3 (1.1 to 1.7)	
Property not owned	1.8 (1.6 to 2.1)	1.8 (1.6 to 2.1)	2.3 (1.9 to 2.5)	1.6 (1.4 to 1.8)	1.8 (1.6 to 2.1)

Potential explanatory variables considered in the final model: property ownership (the proxy for socio-economic status), current area of residence (Newcastle or North Tyneside), area lived majority of life, any occupational exposure, ever smoked (yes/no), pack years smoked, hay fever / allergies causing nasal stuffiness (the proxy for atopy), weight, gender-occupational exposure interaction.

The characteristics of those attending for lung function testing are shown in table 3. 15% reported an established diagnosis of asthma, 9% chronic bronchitis and 2% emphysema. 15% of men and 7% of women (11% overall) fulfilled the diagnostic criteria for COPD (fig 3). Logistic regression analysis showed associations with occupational exposures, smoking,

and hay fever (table 4). There was a strong gender-exposure interaction with a greater influence of occupational exposure in females compared with males. No significant smoking-exposure interaction was found.

Table 3: Characteristics of those attending for lung function

	n=845
Males (%)	49%
Median age, years (IQ range)	59 (52 to 64)
Occupational exposure	50%
Mean FEV_1 post-bronchodilator (litres)	Males 3.19 Females 2.38
Mean % predicted FEV_1 post-bronchodilator (95% CI)	100.1% (99 to 101)
% with COPD	10% (n=84)
% with COPD who had ever smoked	77%
Undiagnosed COPD	6%

Table 4: Univariate and multivariate analysis of COPD (FEV_1<80% predicted and FEV_1/FVC<0.7) against potential explanatory variables

	Univariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Gender	2.3	1.4 to 3.6	3.2	1.3 to 7.8
Age (per 10 years)	1.6	1.2 to 2.9		
Any occupational exposure	2.3	1.4 to 3.7	3.0	1.3 to 6.9
Exposure-gender interaction*			0.3	0.1 to 1.0
Hay fever	1.6	1.0 to 2.6	2.5	1.4 to 4.2
Smoking (per 10 pack years)	1.3	1.2 to 1.5	1.3	1.2 to 1.4

*Indicating a greater effect of exposure in females. Potential explanatory variables considered as in table 2.

Including all subjects with FEV_1/FVC <70% (GOLD stage I), increased the apparent prevalence of COPD to 25% and generally weakened associations though those with cigarette smoking (OR 1.3 per 10 pack years; 95% CI: 1.2 to 1.4), gender (OR 1.5 for males; 95% CI: 1.0 to 2.5) and age (OR 1.8 per 10 years; 95% CI: 1.3 to 2.5) remained significant. Using pre-bronchodilator measurements increased the apparent prevalence of COPD to 14%. Defining COPD as FEV_1 <LLN and FEV_1/FVC ratio <LLN, identified fewer cases of COPD (50 versus

84) but the associations with occupational exposure (OR 2.99; 95% CI 1.43 to 6.26), smoking (OR 1.26 per 10 pack years; 95% CI 1.11 to 1.42) and hay fever (OR 2.58; 95% CI 1.37 to 4.88) were unchanged. Defining COPD as FEV_1<80% predicted and FEV_1/FVC<LLN identified even fewer cases of COPD (44 versus 84). Relations between occupational exposure (OR 3.53; 95% CI 1.58 to 7.89), smoking (OR 1.21 per 10 pack years; 95% CI 1.06 to 1.38) and hay fever (OR 1.85; 95% CI 0.94 to 3.63) were again maintained but the association with hay fever was of borderline significance. The relationship between occupational exposure and COPD strengthened as the definition of COPD became tighter. Only 7 subjects (0.8%) had a restrictive abnormality (FEV_1 and FVC below the LLN and FEV_1/FVC ≥70%).

DISCUSSION

We identified COPD in 10% of our 45-69 year old population of north east England, a rate that is within the wide range of COPD prevalences reported by previous studies. For example Matheson *et al* identified COPD in 7% of 45-70 year olds in Australia,[16] whereas Murtagh *et al* identified COPD in 14% of 40-69 year olds in Northern Ireland.[17]. The range of recent European COPD prevalence estimates varies at least two-fold, and worldwide estimates vary about ten-fold.[2]

The lack of standardised study methodology is likely to contribute substantially to variations in reported COPD prevalence [18] though not all such variations can be explained in this way. Pena *et al* reported prevalences ranging from 5% to 18% in seven regions of Spain [19]. Similar study methods were used in each region and little if any of the variation was explained by differences in smoking rates. The 2005 PLATINO study reported prevalences ranging from 8% to 20% in five Latin American cities [20]. Approximately half of those prevalences remained unexplained after adjustment for covariates. Caballero *et al*

found prevalences of GOLD stage I COPD (FEV1/FVC <70%) ranging from 6% to 13% in Colombia [21] and the international BOLD study [22] identified prevalences in men ranging from 11% in China to 24% in South Africa. Overall, the evidence suggests substantial geographical variation in COPD prevalence that remains largely unexplained.

Under some circumstances occupational exposures are likely to contribute to variations in COPD prevalence. Dusts, fumes and vapours are recognised to cause COPD and are believed to contribute approximately 15% to its overall prevalence.[8] Coal miners have been the most extensively studied occupational group, and a number of workplace studies have suggested that heavy exposures to coal mine dust and smoking are of similar potency in causing COPD.[23] Effects of equal magnitude have been seen in studies of silica-exposed gold miners and a range of other workplace dusts and fumes has been shown to contribute to COPD.[23] Such effects are likely to be detectable in general population surveys if the subjects have experienced heavy occupational exposures.

Our study adds to a growing body of evidence that respiratory effects of occupational exposures can be detected not only within specific industrial sectors but also within the general population. We identified clear associations between a range of occupational exposures and respiratory symptoms. Overall, those with a history of occupational exposures were approximately 50% more likely than unexposed subjects to report respiratory symptoms. There were significant associations with some specific occupational exposures, *ie.* coal mining, welding, factory work, and solvent exposure. Two of these exposures (welding fume and coal mining) are established causes of COPD, [7,24] and factory work in our region is likely to have been associated with a range of exposures that are plausibly associated with COPD. Solvent exposures have previously been identified as being associated with COPD.[25] A wide range of associations with other specific exposures has been reported but no consistent pattern has yet emerged. The most relevant exposures are likely to vary

depending on the nature of local industries. The notion that so many exposures have been linked to COPD is consistent with the view that the disease is a potential consequence of exposure to any airborne dust, fume or vapour.

There was a less clear association between occupational exposures and COPD as defined by lung function abnormalities. Overall, we found statistically significant effects to be more marked in females compared with males. It is not clear whether the gender difference is related to differences in exposure or to differences in susceptibility. There is an increasing body of evidence that females respond differently to environmental agents [26] and are possibly more susceptible. [27] There are previous reports of occupational COPD specifically affecting females.[16] Matheson *et al* demonstrated a 4 to 6-fold increased risk of chronic obstructive bronchitis in females exposed to mineral dusts, biological dusts, gases and fumes but no significantly increased risk in males in an Australian study.[16]

There are some inevitable limitations to investigations such as ours. The response rate of 64% is within the range reported in similar studies.[28] The primary care database we used is known to contain inaccuracies because of changes in address, migration and death. Devereux *et al* in 1996 suggested that 79% of non-responders had not received a questionnaire when using the same database.[29] We were unable to verify receipt of the questionnaire within this study, but if the rate of inaccuracy was similar to that in the Devereux study the response rate could have been as high as 87%. Murtagh *et al* used a similar primary care database and reported that at least 7% of their patients did not receive a questionnaire because of incorrect addresses.[17] There was some further loss of participation for those invited for the laboratory studies, with 56% attending. This was similar to that reported in the study by Matheson *et al*.[16]

The recruitment process was complicated by an initial attempt to stratify the population according to symptoms. This was abandoned and subjects were selected randomly within each

symptom subgroup and in proportion to the frequency of symptoms in the overall population. The overall effect was equivalent to an entirely random sample. Correcting for the age and gender distribution of the local population [12] reduced our COPD prevalence estimate slightly to 10%.

There was some evidence of bias in recruitment with females and older subjects over-represented. Such response patterns are frequently seen in epidemiological studies.[30] There was no evidence of bias in favour of those most likely to have been most affected by workplace exposure. A letter mailed with the questionnaire advised potential subjects that occupational exposures were being investigated together with other environmental factors but this was not given undue prominence. The possibility of recall bias, with symptomatic subjects more likely to report occupational exposures leading to a spurious association with COPD is of potential concern. Our assessment of occupational exposures was relatively crude, but previous studies suggested that in general population settings associations can be demonstrated as readily with subject-reported exposures as with more complex assessments such as job-exposure matrices.[25]

We did not exclude those with asthma because of the potentially unreliable nature of the diagnosis, because asthma and COPD co-exist in many subjects, and since asthma and airway hyperresponsiveness may be important risk factors for COPD.[2] Atopy which is closely associated with asthma appeared to be an important risk factor for COPD.

The epidemiology of COPD is complex and changing. The current focus is rightly on increased smoking in developing countries and the increasing worldwide prevalence of COPD. Adult smoking is declining in many industrialized countries but other potential risk factors for COPD such as asthma, atopy, diet, and atmospheric pollution are increasing or changing, making it difficult to predict and the overall trends in prevalence of the disease.

Occupational exposures currently contribute substantially to COPD in some areas and might continue to do so unless carefully controlled and regulated.

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Figure 1: Specific occupational exposures by gender

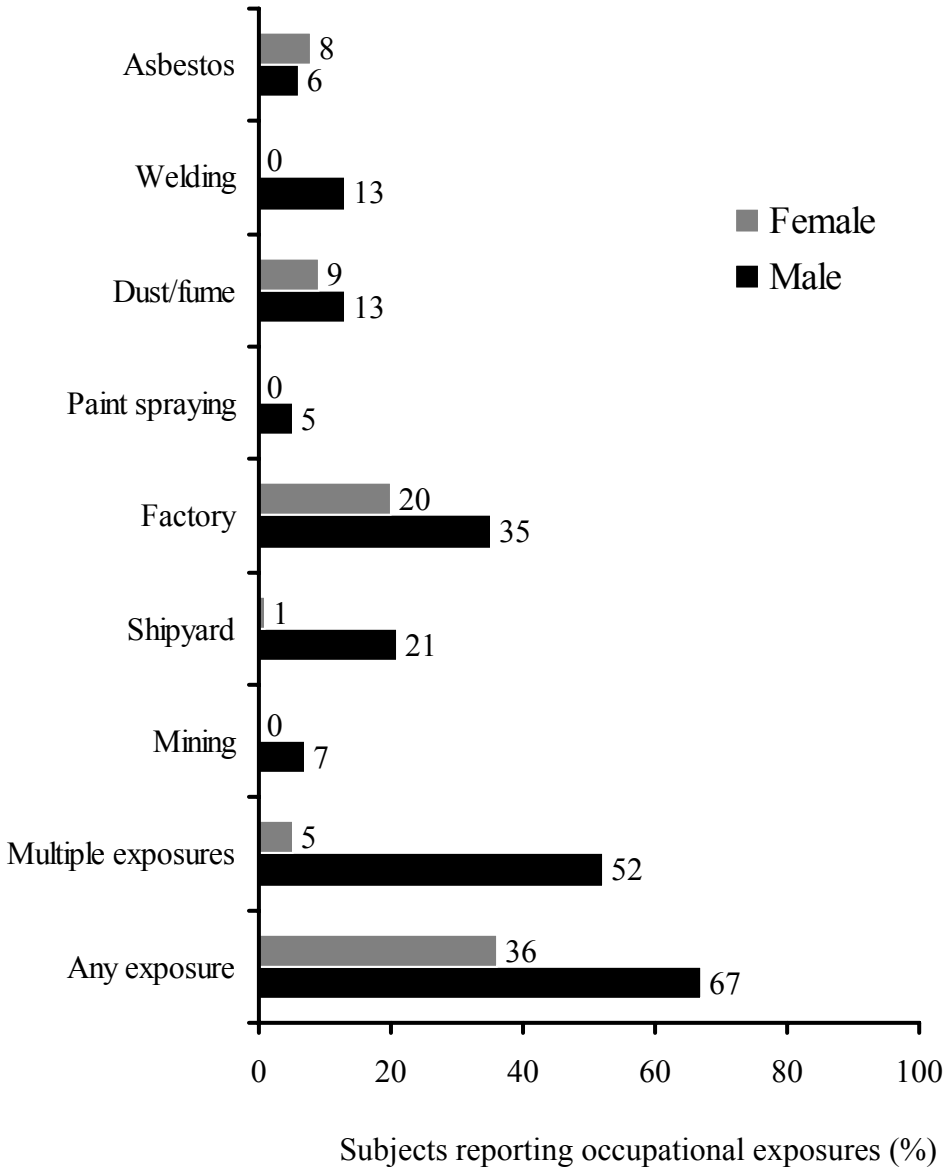
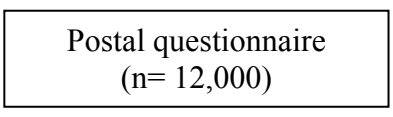
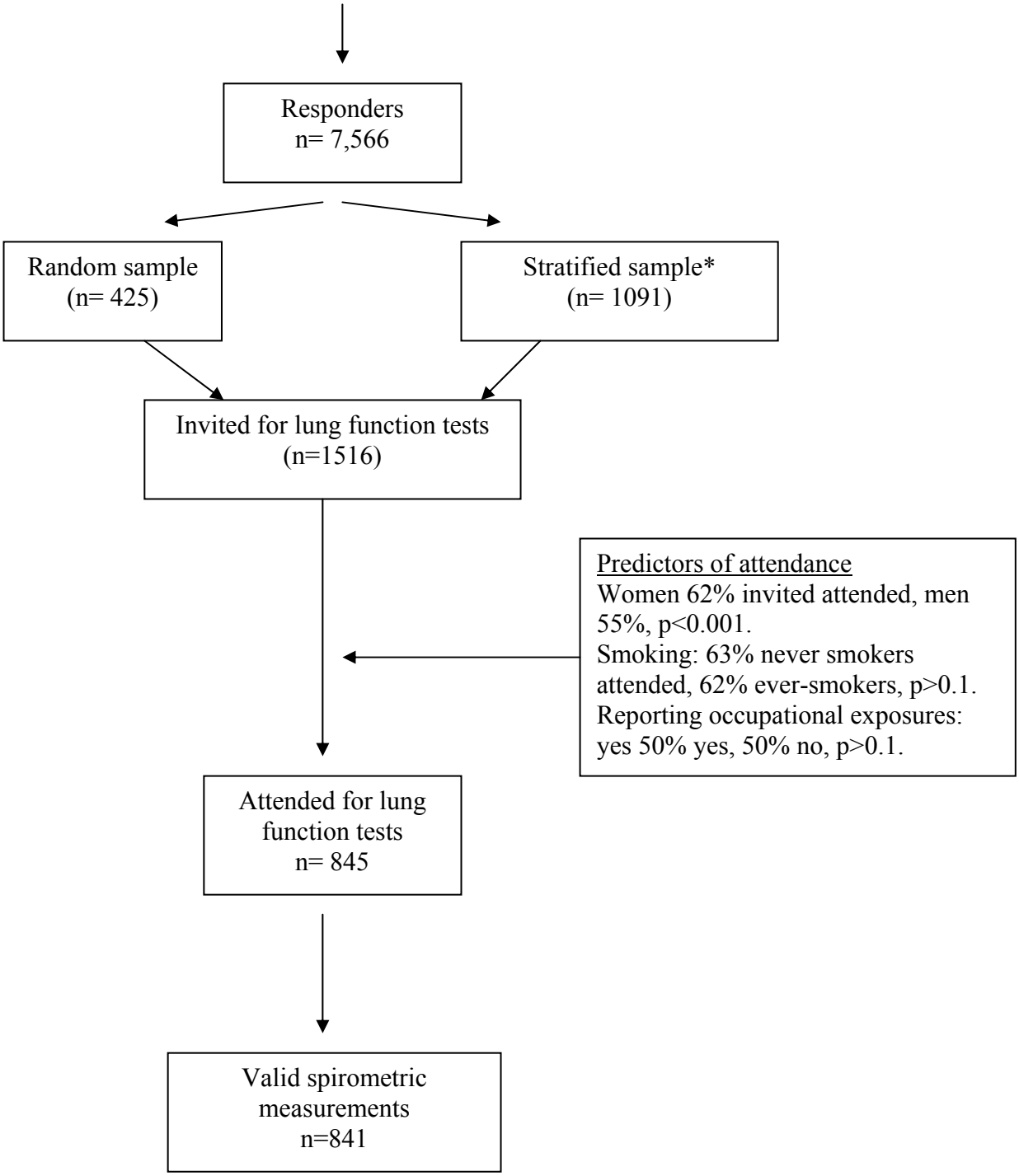


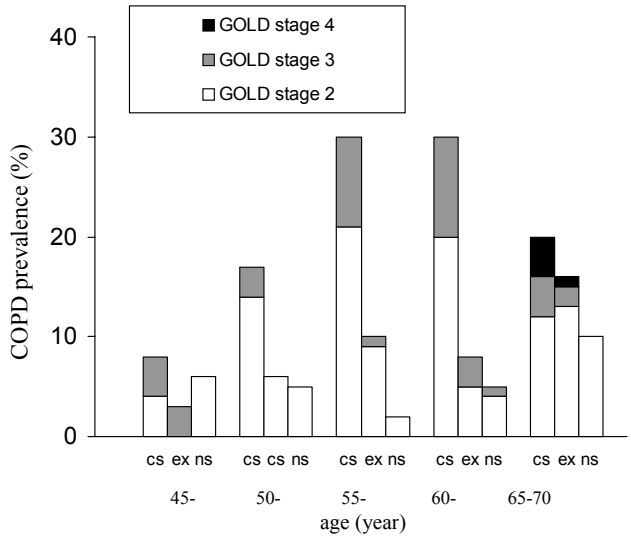
Figure 2: Study design





* see text for details

Figure 3: Prevalence of chronic obstructive disease by smoking history



cs = current smoker
ex = ex-smoker
ns = never smoked