Respiratory Medicine (2007) **101**, 1730–1737

ELSEVIER

respiratoryMEDICINE

Associations between reduced diffusing capacity and airflow obstruction in community-based subjects

Melanie C. Matheson[a,*], Joan Raven[b], David P. Johns[c], Michael J. Abramson[a], E. Haydn Walters[c]

[a]*Department of Epidemiology and Preventive Medicine, Monash University, Vic., Australia*
[b]*Department of Allergy, Immunology and Respiratory Medicine, The Alfred, Vic., Australia*
[c]*Cardio-Respiratory Research Group, Menzies Research Institute, University of Tasmania, Hobart, Australia*

Received 4 August 2006; accepted 25 February 2007
Available online 3 May 2007

KEYWORDS
COPD;
Diffusing capacity (DLco);
BHR;
Airflow obstruction;
Epidemiology

Summary
Introduction: The purpose of this analysis was to determine if abnormal diffusing capacity of the lung for carbon monoxide (DLco) identified a group of subjects with significantly different characteristics than those with normal lung function or airflow obstruction alone.
Methods: Participants were a random sample of adults aged 45–70 years. They completed a detailed respiratory questionnaire, spirometry, methacholine challenge and measurement of single breath DLco. Subjects were categorized into one of three groups: airflow obstruction only, reduced DLco only, or both airflow obstruction and reduced DLco.
Results: Individuals with airflow obstruction and reduced DLco in combination reported more symptoms than those with either condition alone. In subjects with a combination of both airflow obstruction and reduced DLco, a significantly higher proportion reported use of medication and laboratory tests. Current smoking was significantly associated with a reduced DLco alone and in combination with airflow obstruction, however, the association was stronger in those with DLco and airflow obstruction. Bronchial hyperreactivity (BHR) was found to be a risk factor while atopy was associated with a reduced risk of DLco and airflow obstruction.
Conclusions: Reduced DLco plus airflow obstruction together identifies a group of individuals with significantly more symptoms and worse lung function. Current cigarette smoking, early life serious respiratory infection and BHR were strongly associated with reduced DLco in combination with airflow obstruction.

*Corresponding author. Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, The University of Melbourne, Australia. Tel.: +61 3 8344 0713; fax: +61 3 9349 5815.
E-mail address: mcmat@unimelb.edu.au (M.C. Matheson).

0954-6111/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2007.02.020

Introduction

Chronic obstructive pulmonary disease (COPD) is a major contributor to the burden of disease internationally. The prevalence is continuing to increase and it is widely underdiagnosed particularly in the primary care setting.[1] Early diagnosis can lead to better treatment/intervention options that may modify the natural history of the disease and reduce the overall burden of COPD to the general community. In order to accurately assess the burden of disease and identify high-risk groups, risk factors for the development of COPD need to be determined using epidemiological approaches. This requires a consistent definition of COPD which has been lacking in the literature to date.

All the currently published guidelines have highlighted the importance of physiologically defining COPD using spirometry. The ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) is accepted as an indicator of airflow obstruction and percent predicted FEV_1 is used to grade severity. However, the prevalence of disease can vary with the cut-off level used to define airflow obstruction, which varies between the GOLD,[2] BTS,[3] ERS,[4] ATS,[5] Australian COPD-X[6] guidelines and clinical criteria.

High-resolution computed tomography (HRCT) of the chest is the most accurate imaging technique to detect pulmonary emphysema *in vivo*[7] and is considered the gold standard in defining emphysema clinically.[8] However, HRCT involves a substantial dose of ionising radiation and is prohibitively expensive for large epidemiological studies. Diffusing capacity of the lung for carbon monoxide (DLco) is a good predictor of emphysema when correlated with postmortem morphological measurements[9] and correlates well with the extent of emphysema on HRCT.[10] Measurement of DLco is a more feasible and acceptable alternative to HRCT for epidemiological studies and has already been used for occupational monitoring.[11]

Spirometry is considered the gold standard for detecting and quantifying airflow obstruction in the general population. However, several studies have failed to find a strong association between the parenchymal destruction seen in emphysema and airflow obstruction as measured by FEV_1.[12–14] This indicates that definitions that rely on measurement of FEV_1 alone may miss some cases of COPD. Including a measurement of DLco may be one way to detect early cases of emphysema that otherwise would go undetected.

Comparison of the different definitions for airflow obstruction for defining COPD for epidemiological studies have been evaluated previously.[15] Celli et al. found the different definitions of obstruction produced prevalence estimates that varied by as much as 200%. However, an epidemiological definition incorporating a measurement of DLco has not previously been widely used or evaluated. The purpose of this analysis was to determine if abnormal DLco identified a group of subjects with significantly different clinical characteristics than those with normal lung function or airflow obstruction alone.

Methods

Participants

Recruitment and lung function testing have been described in detail elsewhere.[16,18] Briefly, 7005 adults aged between 45 and 70 years were randomly selected from the electoral rolls for three inner south eastern Melbourne electorates. A screening questionnaire was completed by 4923 subjects (70% response rate) and 2900 of these participants were invited to attend our lung function laboratory. A total of 1232 Caucasian subjects (42% response rate) attended. The study was approved by the Ethics Committees at Monash University and The Alfred Hospital, Melbourne, Australia. All participants gave written informed consent.

Lung function testing

Spirometry and single breath carbon monoxide diffusing capacity (DLco) were performed according to the American Thoracic Society (ATS) criteria.[17,18] Predicted values for FEV_1, FVC and FEF_{25-75} were calculated from age, height and gender using equations by Gore et al.,[19] and for FEV_1/FVC%, DLco and DLco/VA using the equations by Quanjer et al.[20] Methacholine (MCh) (USP Methapharm Inc., Brantford, Ontario, Canada) was delivered by a Mefar 3B dosimeter (Mefar, Bovezzi, Italy) until FEV_1 fell by 20% from the initial value (PD_{20}) or up to a cumulative dose of 2 mg.

Definitions

Morning cough was defined as a positive response to: "Do you usually cough first thing in the morning in the winter"? *Chronic cough* was defined as a positive response to: "Do you cough like this on most days for as much as 3 months each year"? *Morning sputum* was defined as a positive response to: "Do you usually bring up phlegm from your chest first thing in the morning in the winter"? *Chronic bronchitis* was defined as a positive response to: "Have you brought up phlegm on most days for as much as 3 months of a year for at least 2 successive years"? *Shortness of Breath-grade* 2 (*SOB grade* 2) was defined as a positive response to: "Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill"? *SOB Grade 3* was defined as a positive response to: "Do you have to stop for breath when walking at your own pace on level ground"? *Wheeze* was defined as a positive response to: "Have you had wheezing or whistling in your chest at any time in the last 12 months"? *Exertional SOB* was defined as a positive response to: "Have you been short of breath following strenuous activity in the last 12 months"? Serious early respiratory tract infection (*serious early RTI*) was defined by a positive response to the question "Did you have a serious respiratory infection before the age of 5 years"? (including croup requiring hospitalisation, bronchiolitis, wheezy bronchitis, pneumonia, diphtheria, tuberculosis, whooping cough)". *Current asthma* for this analysis was defined by a positive response to the question 'Have you had an attack of asthma in the last 12 months'?

Airflow obstruction was defined as FEV_1/FVC ratio < lower limit of normal (LLN).[21] Reduced diffusing capacity was defined as a DLco < LLN.[22] The LLN was calculated as the value falling 1.64 standard deviations (SD) below the predicted mean. Bronchial hyperresponsiveness (BHR) was defined as a provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}) less than 2 mg. Bronchial reactivity was also expressed as the dose response slope (DRS) = (percentage change in FEV_1+3.5)/MCh dose.[23,24] Pack years were calculated

as the average number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked.

Subject groupings

Subjects were categorized into one of four groups; (1) normal lung function ($FEV_1/FVC \geqslant LLN$, $DLco \geqslant LLN$), (2) reduced diffusing capacity only ($DLco < LLN$) (3) airflow obstruction only ($FEV_1/FVC < LLN$), (4) both airflow obstruction and reduced diffusing capacity (Both FEV_1/FVC and $DLco < LLN$). Body mass index (BMI) was calculated as the ratio of body weight (kg) to height squared (m^2). Height and weight were measured in the standing position in subjects wearing clothes, but without shoes.

Statistical analysis

The statistical package STATA (version 6.0; STATA Corporation, Texas) was used for all analyses. Intra-class (within individual) correlation was used to assess agreement between duplicate measurements of DLco, alveolar volume (V_A), and inspiratory vital capacity (VC_{insp}). All the variables listed in Table 2 were considered as possible covariates.

In the univariate analysis, the associations between variables listed in Table 2 and the four categories were analysed by either a χ^2-test or an exact test for binary variables or ANOVA for continuous variables. Multinomial (polytomous) logistic regression was used to identify those risk factors that were independently associated with disease risk. Group 1 normal lung function ($FEV_1/FVC \geqslant LLN$, $DLco \geqslant LLN$) was used as the base category. Age and gender were fitted to all models and subjects who reported an asthma attack in the last 12 months were excluded from the analysis.

Results

Characteristics of the study population

Table 1 presents lung function characteristics of the four groups. As would be expected those with a combination of both reduced diffusing capacity and airflow obstruction have a greater degree of obstruction and diffusing impairment than those with a single lung function defect. Bronchial reactivity (log DRS) was also highest in the pure airflow obstruction group.

Selected characteristics by disease group are presented in Table 2. There was a small but significant difference in mean age and proportion of males between the groups. Those with both a reduced diffusing capacity and airflow obstruction were significantly more likely to have ever smoked and be current smokers.

Those with pure airflow obstruction or in combination with reduced diffusing capacity were significantly more likely to be using inhaled steroids and bronchodilator medication. The mean BMI in all groups classified most subjects as overweight, with the exception of those with both a reduced diffusing capacity and airflow obstruction where the mean BMI was at the high end of the normal range.

The proportion of subjects who were atopic was significantly higher among those without reduced diffusing capacity. BHR was present in nearly half of subjects with both airflow obstruction and reduced DLco, and over half of those with airflow obstruction alone. In those with reduced DLco however BHR was not very common. A significantly greater proportion of subjects with both airflow obstruction and reduced DLco reported a serious respiratory infection before the age of 5 years. Significantly more subjects with a combination of reduced diffusing capacity and airflow obstruction had a paternal history of COPD and were retired. However, there was no difference between groups for occupational exposures to vapours, gases, dusts, or fumes.

Comparison of respiratory symptoms between groups

Individuals with a combination of a reduced diffusing capacity and airflow obstruction reported significantly more wheeze, morning and chronic cough, morning and chronic phlegm, Grade 2 and 3 SOB than other groups (Fig. 1).

Table 1 Lung function characteristics of the study population divided by disease group.

Lung function Mean (±SD)	Normal $n = 807$	$DLco < LLN$ only $n = 145$	$FEV_1/FVC < LLN$ only $n = 204$	Both $n = 66$
FEV_1 (L)	3.23±0.77	3.58±0.74	2.75±0.82	2.68±0.92
FEV_1% Predicted	109.8±14.1	99.0±15.2	91.1±17.4	77.3±19.8
FVC (L)	4.11±0.97	4.61±0.92	4.15±1.12	4.37±1.23
FVC % predicted	111.0±13.6	100.3±15.0	108.8±16.3	99.5±17.6
FEV_1/FVC %	78.6±4.27	78.0±4.18	65.6±5.39	59.4±10.6
FEF_{25-75} (L/s)	3.04±1.01	3.27±1.02	1.55±0.63	1.32±0.66
FEF_{25-75}% Predicted	2.83±0.53	3.32±0.43	2.86±0.59	3.05±0.48
DLco ml/min/mmHg	23.6±5.59	22.4±3.91	24.1±6.63	20.1±5.43
DLco % Predicted	101.1±12.4	77.9±8.04	100.0±13.3	72.9±12.4
DLco/VA ml/min/mmHg/L	4.18±0.61	3.63±0.50	4.05±0.64	3.20±0.62
DLco/VA % predicted	73.2±11.6	67.3±9.44	71.5±12.6	59.9±12.4
Bronchial reactivity (log dose response slope)	1.74±1.10 $n = 732$	1.34±0.76 $n = 123$	3.55±1.86 $n = 166$	3.08±1.95 $n = 41$

Table 2 Characteristics of the study population by group.

Symptom/history	Normal $n = 807$	DLco < LLN only $n = 145$	FEV_1/FVC < LLN only $n = 204$	Both $n = 66$	P^*
Age years (mean ± SD)	57.64 ± 7.35	56.9 ± 7.25	57.9 ± 8.03	60.8 ± 7.08	0.005‡
Sex (male)	347 (42.5)	138 (95.2)	97 (47.6)	55 (83.3)	0.0001
Ever smoker *n* (%)	371 (45.4)	95 (65.5)	97 (47.6)	52 (78.8)	0.0001
Current Smoker *n* (%)	81 (9.9)	41 (28.3)	25 (12.3)	26 (39.4)	0.0001
Pack years					
	$n = 364$	$n = 94$	$n = 97$	$n = 52$	
Ever smoker (Median, IQR)	11 (4.4, 26)	21 (8, 42)	17 (6.3, 33)	34 (19, 46)	0.0001††
	$n = 78$	$n = 41$	$n = 25$	$n = 26$	
Current smoker (Median, IQR)	15 (4.6, 33)	29 (11, 46)	30 (19, 43)	36 (20, 45)	0.0005††
	$n = 810$	$n = 145$	$n = 204$	$n = 66$	
BMI kg/m^2 (mean ± SD)	27.5 ± 4.47	27.8 ± 3.79	27.0 ± 5.37	25.9 ± 3.81	0.02‡
Treatment					
Inhaled steroids *n* (%)	39 (4.8)	1 (0.7)	46 (22.6)	13 (19.7)	0.0001
Inhaled bronchodilators *n* (%)	83 (10.2)	9 (6.2)	74 (36.3)	21 (31.8)	0.0001
Asthma attack *n* (%)	61 (7.5)	5 (3.5)	64 (31.4)	12 (18.2)	0.0001
Atopy *n* (%)	413 (51.0)	74 (51.0)	126 (61.8)	30 (45.5)	0.03
BHR *n* (%)	103 (13.9)	7 (5.6)	104 (53.6)	26 (42.6)	0.0001
Serious RI before 5 yrs *n* (%)	184 (22.7)	34 (23.5)	56 (27.7)	29 (43.9)	0.001
Employment status					
Employed *n* (%)	523 (64.0)	112 (77.2)	133 (65.2)	39 (59.1)	
Not employed *n* (%)	82 (10.0)	4 (2.8)	19 (9.3)	4 (6.1)	
Retired *n* (%)	212 (26.0)	29 (20.0)	52 (25.5)	23 (34.9)	0.02
Mother had COPD *n* (%)	98 (12.1)	13 (9.1)	26 (12.8)	3 (4.6)	0.21
Father had COPD *n* (%)	127 (16.0)	18 (13.1)	48 (23.9)	17 (26.2)	0.007
Occupational exposure to vapours, gases, dusts and fumes *n* (%)	493 (61.6)	91 (63.2)	107 (52.7)	44 (66.7)	0.07

*P value χ^2-test; ‡t-test test; ††Kruskal–Wallis test; IQR = inter quartile range.

Notably, those with a reduced DLco only reported more morning and chronic phlegm than those with only airflow obstruction. Table 3 shows the symptoms that were independently associated with airflow obstruction and/or reduced diffusing capacity. None of the respiratory symptoms were associated with low diffusing capacity only. Wheeze was associated with airflow obstruction in those with and without reduced diffusing capacity. Morning cough and SOB Grade 2 were also significantly associated with having both airflow obstruction and a reduced DLco.

Comparison of health care utilisation between groups

Health care utilisation between the groups was also compared (Fig. 2). We observed that airflow obstruction was the main determinant of the usage of health services. In subjects with airflow obstruction alone a significantly higher proportion reported use of inhaled or oral medications. However those subjects with both airflow obstruction and a reduced diffusing capacity were more likely to have seen a doctor, spent a night in hospital, visited a specialist and undergone laboratory tests of some sort in the last 12 months. The majority had chest X-rays or lung function tests performed.

Risk factors for reduced DLco in those with and without airflow obstruction

Table 4 reports the odds ratios (OR) and 95% CIs for risk factors found to be significantly associated with disease risk. Females had a lesser risk of a reduced diffusing capacity in those with and without airflow obstruction. Current smoking was significantly associated with a reduced diffusing capacity alone and in those with both a reduced diffusing capacity and airflow obstruction. Pack years as a measure of smoking intensity was also found to be an important risk factor for a reduced diffusing capacity in combination with airflow obstruction. Having a lower BMI was associated with a lesser risk of airflow obstruction in those with and without a reduced diffusing capacity. Bronchial hyperreactivity was found to be a risk factor for both airflow obstruction alone and in combination with a reduced diffusing capacity. Atopy was associated with a lesser risk of the combination of airflow obstruction and a reduced diffusing capacity. A serious respiratory tract infection before 5 years of age was significantly associated with the combination of airflow obstruction and reduced diffusing capacity.

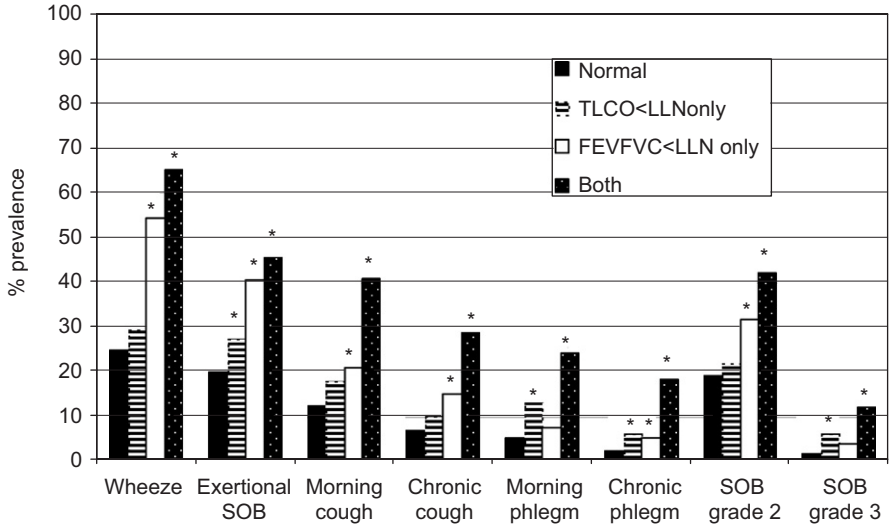

Figure 1 Comparison of respiratory symptoms between disease groups. $^{*}P<0.001$ for a comparison to the normal group.

Table 3 Respiratory symptoms associated with the three disease groups (Odds ratios and 95% confidence intervals).

Respiratory symptoms	DLco < LLN only	FEV_1/FVC < LLN only	Both
Wheeze	1.12 (0.70, 1.82)	2.12 (1.41, 3.21)††	3.19 (1.67, 6.13)††
Exertive SOB	1.42 (0.84, 2.40)	1.32 (0.82, 2.11)	1.35 (0.66, 2.79)
Morning cough	1.23 (0.63, 2.38)	1.44 (0.80, 2.59)	2.70 (1.20, 6.10)‡
Chronic cough	0.81 (0.32, 2.07)	1.35 (0.65, 2.80)	0.99 (0.35, 2.80)
Morning sputum	2.13 (0.95, 4.79)	0.75 (0.30, 1.87)	1.95 (0.73, 5.23)
Chronic bronchitis	2.14 (0.54, 8.48)	0.98 (0.24, 3.94)	1.77 (0.40, 7.72)
SOB Grade 2	1.59 (0.85, 2.96)	1.42 (0.88, 2.31)	2.72 (1.27, 5.81)‡
SOB Grade 3	4.10 (0.89, 18.9)	0.29 (0.03, 2.34)	2.35 (0.45, 12.4)
Age	0.97 (0.95, 1.00)	1.01 (0.99, 1.04)	1.04 (0.99, 1.08)
Sex (female)	0.03 (0.01, 0.07)††	0.83 (0.57, 1.22)	0.07 (0.03, 0.18)††

$^{\ddagger}P = 0.02$; $^{\dagger}P = 0.001$; $^{\dagger\dagger}P = 0.0001$.

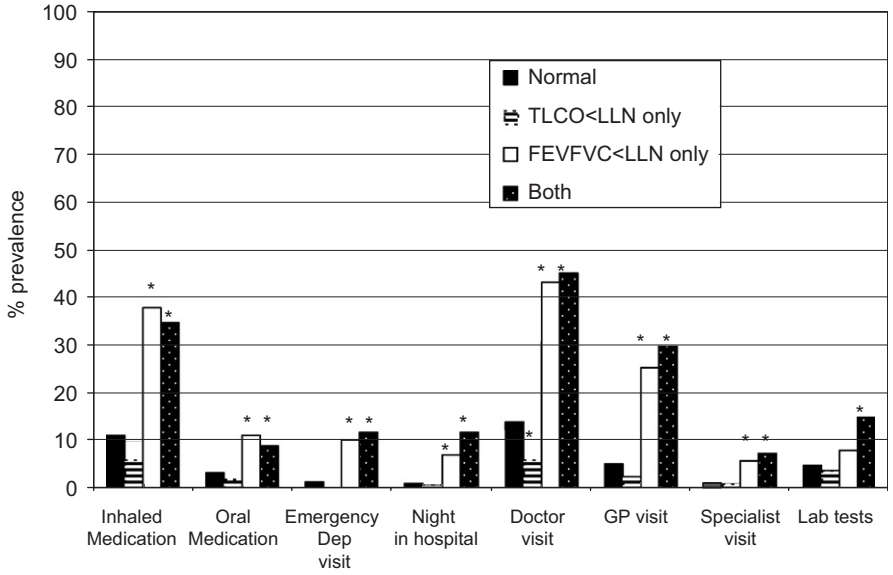

Figure 2 Comparison of health care utilisation between disease groups. $^{*}P<0.001$ for a comparison to the normal group.

Table 4 Independent risk factors for the three disease groups (Odds ratios and 95% confidence intervals).

Risk factors	DLco < LLN only	FEV_1/FVC < LLN only	Both
Age	0.97 (0.94, 1.00)	1.00 (0.98, 1.03)	1.04 (0.99, 1.09)
Sex (female)	0.04 (0.01, 0.09)††	0.66 (0.43, 1.01)	0.07 (0.03, 0.19)††
Current smoking	4.38 (2.42, 7.93)††	1.04 (0.54, 2.02)	3.88 (1.72, 8.74)†
Pack years	1.01 (0.99, 1.02)	1.01 (1.00, 1.02)	1.03 (1.01, 1.05)†
BMI	0.98 (0.93, 1.04)	0.95 (0.90, 0.99)‡	0.84 (0.76, 0.93)†
Atopy	0.95 (0.60, 1.50)	0.75 (0.49, 1.14)	0.50 (0.24, 1.00)‡
BHR	0.51 (0.20, 1.30)	6.67 (4.22, 10.5)††	5.65 (2.63, 12.1)††
Serious RTI	1.06 (0.59, 1.89)	1.28 (0.80, 2.05)	2.32 (1.14, 4.75)‡
Mother COPD	0.87 (0.39, 1.95)	0.87 (0.45, 1.71)	0.45 (0.09, 2.13)
Father COPD	0.58 (0.28, 1.21)	1.06 (0.62, 1.81)	1.74 (0.77, 3.94)
Vapours, gases, dusts and fumes	1.04 (0.65, 1.66)	0.78 (0.52, 1.18)	1.21 (0.58, 2.51)

‡$P = 0.02$; †$P = 0.001$; ††$P = 0.0001$.

Discussion

The purpose of this analysis was to determine if measuring DLco in combination with airflow obstruction would add clinically relevant information to an epidemiological study of the general population. Measurement of DLco proved practical in this large scale epidemiological study. This is one of the first studies to investigate factors that were independently associated with a reduced DLco in individuals with airflow obstruction in a randomly selected community sample.

Tobacco smoking is the single most important risk factor for COPD.[25,26] In this population, 39% of individuals with both reduced diffusing capacity and airflow obstruction were current smokers and nearly 80% had ever been smokers. Notably current smoking was significantly associated with a reduced diffusing capacity in those with and without airflow obstruction. Pack years of smoking was also significantly associated with a reduced DLco with airflow obstruction. These results are consistent with the well known association between current cigarette smoking and the parenchymal lung damage that results in emphysema and reduced diffusing capacity.[27,28] Longitudinal studies of decline in DLco have not demonstrated significant differences in rate of decline between never, ever and current smokers, but have demonstrated that current smokers have lower mean levels of DLco.[28–30] The results of our study are consistent with the finding that only current smoking but not ever smoking is associated with reduced DLco levels, whether airflow obstruction is present or not.

BHR was found to be a significant risk factor for airflow obstruction with or without a reduced DLco. The association with BHR remained significant even when individuals with an ''attack of asthma'' in the last 12 months were removed from the analysis. BHR is regarded as a cardinal feature of asthma, but it is also observed in some subjects with COPD.[31] Whether BHR is a risk factor for the development of COPD or develops because of airflow obstruction caused by other factors has yet to be fully determined.[32] We observed a lesser risk of the development of airflow obstruction combined with a reduced diffusing capacity among those with atopy. They were less likely to be current or past smokers. Previous studies have also found a decreased current smoking prevalence with increasing degree of skin reactivity.[33] This suggests that atopic individuals are less likely to be regular smokers because of increased susceptibility to bronchial irritants. There appears to be little published information examining the relationship between BHR and DLco or DLco/VA, in subjects with airflow obstruction. The implication that BHR may predispose to chronic airway disease fits into the ''Dutch Hypothesis'' of COPD aetiology.[34]

A previous general population study found early childhood respiratory infection to be a risk factor for airflow obstruction.[35] There is evidence to suggest that childhood respiratory infections result in slower lung growth and lower maximal attained pulmonary function in adulthood.[36] It has also been shown that pneumonia in early life can result in permanent lung scarring and impaired lung growth.[37] Viral infections are capable of persisting after an acute infection and it has been suggested that latent virus is capable of amplifying cigarette smoke-induced lung damage.[38] Our data would support such conclusions as both serious childhood respiratory tract infection and cigarette smoking were independent risk factors for a reduced DLco with airflow obstruction.

Reduced diffusing capacity with airflow obstruction identified a group of individuals with significant respiratory morbidity. They reported more symptoms and had worse lung function than subjects with airflow obstruction alone, which supports the value of adding reduced DLco to the definition of COPD. However we did not find much difference between the two groups in health care utilisation, which is likely to reflect the low proportion of these subjects with a doctor's diagnosis of COPD.

We used the lower limit of normal as the cut-off to define those with evidence of a reduced diffusing capacity or airflow limitation. This is commonly used in the clinical setting due to its statistical validity.[39] The lower limit of normal definition has statistical validity in that by definition 97.5% of the general healthy population will meet or exceed this value and people falling below this level can be reliably defined as having pulmonary disease.[40]

Some previous studies have suggested that full single breath DLco manoeuvres can be successfully performed in between 50% and 80% of subjects. A Norwegian study found that all subjects were able to maintain a breath hold time for between 9 and 11 s and 98% were able to provide

reproducible measurements of DLco.[41] In the present study good agreement was observed between duplicate manoeuvres for DLco and V_A. Haemoglobin (Hb) measurement was not available from 21 subjects due to failed or refused venipuncture and in these subjects an uncorrected DLco value was used. The intraclass (within subject) correlation between the corrected and uncorrected DLco values was very good (0.98), so it is unlikely that this has substantially affected the results.

It is important that DLco measurements are corrected for the presence of a significant CO back pressure and COHb which are known to reduce DLco in heavy smokers.[11] While we did ask subjects not to smoke for 6 h before the test to reduce this bias, we did not confirm compliance with this request. It is therefore possible that DLco in our smokers was systematically underestimated, but it has been shown that this is unlikely to fully account for the lower DLco in smokers.[28] Furthermore, DLco remains a useful measure in epidemiological studies even when CO back pressure is not measured.[42] We did not ask female participants about their date of last menses, so we could not correct for the affects of menstrual cycle on DLco,[43] but because of the age-group studied this is unlikely to have any meaningful affect on the results.

Bronchodilator reversibility was not assessed in all subjects with airflow limitation. A bronchodilator was only administered where there was substantial airflow obstruction, which precluded methacholine challenge. The GOLD definition of COPD specifies that all FEV_1 values should be post bronchodilator.[2] This may have introduced some bias into the assessment of airflow obstruction and may have been a possible explanation for the associations with BHR if we take this as a surrogate for asthma i.e. significant bronchodilator response. It has been shown that the BHR and the bronchodilator response are two different phenotypic markers and are not interchangeable in epidemiological studies.[44] Without the assessment of reversibility it is unclear whether potentially reversible airflow obstruction influenced our results. We did exclude asthmatics from the analysis, furthermore a high proportion of COPD patients have 'significant' bronchodilator reversibility,[45] so it is not easy to differentiate COPD and asthma on this basis.

In conclusion, reduced DLco plus airflow obstruction identifies a group of individuals with significantly more symptoms, and worse lung function than subjects with airflow obstruction alone. Current rather than former cigarette smoking was found to be strongly associated with a reduced DLco, highlighting the need to actively promote smoking cessation even where airflow obstruction is not evident. The prevention of serious respiratory infections with the progressive and sustained introduction of pertussis, measles and pneumococcal vaccines to early childhood immunisation schedules may reduce the burden of COPD in the future.

Acknowledgments

The study was funded by the National Health and Medical Research Council of Australia. Malcolm Sim assisted in securing funding for the study. We wish to thank Cathryn Wharton, Judi Wicking and Billy Skoric for assistance with data collection.

References

1. Voelkel NF. Raising awareness of COPD in primary care. *Chest* 2000;**117**:372S–5S.
2. World Health Organization NH, Lung and Blood Institute. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Report no. 2001. 〈www.goldcopd.com〉.
3. British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;**52**:S1–S28.
4. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;**8**:1398–420.
5. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;**152**:S77–S121.
6. McKenzie DK, Frith PA, Burdon JG, et al. The COPDX Plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease 2003. *Med J Australia* 2003;**178**:S7–S39.
7. Thurlbeck WM, Muller NL. Emphysema: definition, imaging, and quantification. *Am J Roentgenol* 1994;**163**:1017–25.
8. Boschetto P, Miniati M, Miotto D, et al. Predominant emphysema phenotype in chronic obstructive pulmonary. *Eur Respir J* 2003; **21**:450–4.
9. Park SS, Janis M, Shim CS, et al. Relationship of bronchitis and emphysema to altered pulmonary function. *Am Rev Respir Dis* 1970;**102**:927–36.
10. Baldi S, Miniati M, Bellina CR, et al. Relationship between extent of pulmonary emphysema by high-resolution computed tomography and lung elastic recoil in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**164**:585–9.
11. Make B, Miller A, Epler G, et al. Single breath diffusing capacity in the industrial setting. *Chest* 1982;**82**:351–6.
12. Clark KD, Wardrobe-Wong N, Elliott JJ, et al. Patterns of lung disease in a ''normal'' smoking population: are emphysema and airflow obstruction found together? *Chest* 2001;**120**:743–7.
13. Petty TL, Silvers GW, Stanford RE. Mild emphysema is associated with reduced elastic recoil and increased lung size but not with air-flow limitation. *Am Rev Respir Dis* 1987;**136**:867–71.
14. Klein JS, Gamsu G, Webb WR, et al. High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest radiographs and isolated low diffusing capacity. *Radiology* 1992;**182**:817–21.
15. Celli BR, Halbert RJ, Isonaka S, et al. Population impact of different definitions of airway obstruction. *Eur Respir J* 2003; **22**:268–73.
16. Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax* 2005;**60**:645–51.
17. American-Thoracic-Society. Standardization of spirometry. 1994 update. *Am J Respir Crit Care Med* 1996;**152**:1107–36.
18. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique—1995 update. *Am J Respir Crit Care Med* 1995;**152**:2185–98.
19. Gore CJ, Crockett AJ, Pederson DG, et al. Spirometric standards for healthy adult lifetime nonsmokers in Australia. *Eur Respir J* 1995;**8**:773–82.
20. Quanjer PH, Dalhuijsen A, van Zomeren BC. Summary equations of reference values. *Bull Eur Physiopathol Respir* 1983;**19**: 45–51.
21. Quanjer P, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows: report of working party. Standardisation of lung function tests. European Community for Steel and Coal. *Eur Respir J* 1993;**6**:4–5.

22. Beck KC, Offord KP, Scanlon PD. Comparison of four methods for calculating diffusing capacity by the single breath method. *Chest* 1994;**105**:594–600.
23. O'Connor G, Sparrow D, Taylor D, et al. Analysis of dose–response curves to methacholine. An approach suitable for population studies. *Am Rev of Respiratory Dis.* 1987;**136**: 1412–7.
24. Abramson MJ, Saunders NA, Hensley MJ. Analysis of bronchial reactivity in epidemiological studies. *Thorax* 1990;**45**:924–9.
25. Fletcher CM, Peto R, Tinker C, et al. *The natural history of chronic bronchitis and emphysema: an eight year study of early chronic obstructive lung disease in working men in London*. Oxford: Oxford University Press; 1976.
26. Doll R, Peto R, Wheatley K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;**309**:901–11.
27. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of US adults. *Am J Respir Crit Care Med* 1996;**153**:656–64.
28. Knudson RJ, Kaltenborn WT, Burrows B. The effects of cigarette smoking and smoking cessation on the carbon monoxide diffusing capacity of the lung in asymptomatic subjects. *Am Rev Respir Dis* 1989;**140**:645–51.
29. Watson A, Joyce H, Hopper L, et al. Influence of smoking habits on change in carbon monoxide transfer factor over 10 years in middle aged men. *Thorax* 1993;**48**:119–24.
30. Sherrill DL, Enright PL, Kaltenborn WT, et al. Predictors of longitudinal change in diffusing capacity over 8 years. *Am J Respir Crit Care Med* 1999;**160**:1883–7.
31. Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985;**132**:25–9.
32. Tashkin DP, Altose MD, Bleecker ER, et al. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study Research Group. *Am Rev Respir Dis* 1992;**145**:301–10.
33. Burrows B, Lebowitz MD, Barbee RA. Respiratory disorders and allergy skin-test reactions. *Ann Intern Med* 1976;**84**:134–9.
34. Orie NGM. The Dutch hypothesis. *Chest* 2000;**117**:299S.
35. Viegi G, Pedreschi M, Pistelli F, et al. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. *Chest* 2000; **117**:339S–45S.
36. Shaheen SO, Sterne JAC, Tucker JS, et al. Birth weight, childhood lower respiratory tract infection, and adult lung function. *Thorax* 1998;**53**:549–53.
37. Tager AM, Luster AD. BLT1 and BLT2: the leukotriene B4 receptors. *Prostagland, Leukotrienes Essential Fatty Acids* 2003;**69**:123–34.
38. Hogg JC. Childhood viral infection and the pathogenesis of asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 1999;**160**:S26–8.
39. Cotes JE, Chinn DJ, Quanjer PH, et al. Standardization of the measurement of transfer factor (diffusing capacity). Report working party standardization of lung function tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993;**16**(Suppl.): 41–52.
40. Roberts CM, MacRae KD, Winning AJ, et al. Reference values and prediction equations for normal lung function in a non-smoking white urban population. *Thorax* 1991;**46**:643–50.
41. Welle I, Eide GE, Bakke P, et al. Applicability of the single-breath carbon monoxide diffusing capacity in a Norwegian Community Study. *Am J Resp Critl Care Med* 1998;**158**:1745–50.
42. Viegi G, Paoletti P, Prediletto R, et al. Carbon monoxide diffusing capacity, other indices of lung function, and respiratory symptoms in a general population sample. *Am Rev Respir Dis* 1990;**141**:1033–9.
43. Sansores RH, Abboud RT, Kennell C, et al. The effect of menstruation on the pulmonary carbon monoxide diffusing capacity. *Am J Respir Crit Care Med* 1995;**152**:381–4.
44. Douma WR, de Gooijer A, Rijcken B, et al. Lack of correlation between bronchoconstrictor response and bronchodilator response in a population-based study. *Eur Respir J* 1997;**10**: 2772–7.
45. Reid DW, Soltani A, Johns DP, et al. Bronchodilator reversibility in Australian adults with chronic obstructive pulmonary disease. *Intern Med J* 2003;**33**:572–7.