LUNG FUNCTION

Systemic inflammation and lung function in young adults

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Background: Impaired lung function is associated with systemic inflammation and is a risk factor for cardiovascular disease in older adults. It is unknown when these associations emerge and to what extent they are mediated by smoking, chronic airways disease, and/or established atherosclerosis. We explored the association between the forced expiratory volume in one second (FEV_1) and the systemic inflammatory marker C-reactive protein (CRP) in young adults.

Methods: Associations between spirometric lung function and blood CRP were assessed in a population based birth cohort of approximately 1000 New Zealanders at ages 26 and 32 years. Analyses adjusted for height and sex to account for differences in predicted lung function and excluded pregnant women.

Results: There were significant inverse associations between FEV_1 and CRP at both ages. Similar results were found for the forced vital capacity. These associations were similar in men and women and were independent of smoking, asthma, and body mass index.

Conclusions: Reduced lung function is associated with systemic inflammation in young adults. This association is not related to smoking, asthma, or obesity. The reasons for the association are unexplained, but the findings indicate that the association between lower lung function and increased inflammation predates the development of either chronic lung disease or clinically significant atherosclerosis. The association between poor lung function and cardiovascular disease may be mediated by an inflammatory mechanism.

Impaired lung function not only leads to increased respiratory mortality, but is also associated with adverse cardiovascular events including myocardial infarction, stroke, and cardiovascular death.[1–4] Indeed some studies have found a reduced forced expiratory volume in one second (FEV_1) to be a stronger indicator of cardiovascular risk than traditional measures such as blood cholesterol.[2 5] The link between impaired lung function and cardiovascular risk is poorly understood. Although part of the association will be because cigarette smoking causes both cardiovascular and lung disease, the association between poor lung function and cardiovascular risk persists when the analysis is adjusted for smoking history, and is present in people who have never smoked.[2 4 5]

It is possible that the link between poor lung function and cardiovascular risk is mediated by inflammation.[6] Atherosclerosis is now recognised to be an inflammatory condition and systemic inflammation is associated with an increased risk of cardiovascular disease.[7] People with chronic airflow obstruction also have elevated serum markers of inflammation and exacerbations of chronic obstructive pulmonary disease are associated with a systemic inflammatory response.[6 8–13] However, this seems unlikely to account for the association between lung function and cardiovascular mortality in people who have never smoked and are at a low risk of developing chronic obstructive pulmonary disease.

To date the links between lung function, systemic inflammation, and cardiovascular risk have been studied mostly in elderly or middle aged populations.[6 14] To shed more light on the issue we studied the association between lung function and C-reactive protein (CRP) in a population based cohort of young adults who are unlikely to have developed clinically significant atherosclerosis or chronic obstructive pulmonary disease. We hypothesised that a low FEV_1 would be associated with systemic inflammation in young adults independently of smoking, asthma, and body weight.

METHODS

Study members were born in Dunedin between April 1972 and March 1973.[15] Assessments have been conducted throughout childhood and into adulthood.[16] This analysis assesses the association between CRP and FEV_1 collected when the study members were aged 26 and 32 years. At each age 96% of living study members were assessed (980/1018 at age 26 and 972/1015 at age 32 years), although not all consented to both blood and lung function tests. The study members are mostly of New Zealand/European ethnicity with 7.5% identifying as Maori. Few study members identified with other ethnicities. The Otago ethics committee approved the study. Written informed consent was obtained at each assessment.

Information obtained about respiratory health throughout the life course was updated at ages 26 and 32 years. Self administered and interviewer administered questionnaires included selected questions from the American Thoracic Society and the European Community Respiratory Health Survey questionnaires.[17 18] Current asthma is defined as self reported asthma with symptoms in the previous year. Current smoking was defined as smoking daily for at least one month during the past year. Cumulative smoking was calculated as the number of pack years (20 cigarettes per day for 1 year = 1 pack year). At both ages 26 and 32 years, participants were asked if they currently had any kind of cancer, arthritis, heart problems, had ever been told that they had diabetes or high blood sugar (excluding gestational), or had had either a kidney or bladder infection or a surgical operation requiring a general anaesthetic in the past 12 months. Study members reporting any of these problems were regarded as having a recent or current health problem. At both ages, Study members were also asked if they had smoked cannabis in the previous year.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IQR, interquartile range

Table 1 Study member characteristics at age 26 and 32 years

Age		Women			Men		
26		n	Yes	%	n	Yes	%
	Smokers	442	165	37.3	494	178	36.0
	Asthma	448	90	20.1	499	92	18.4
		n	Median	IQR	n	Median	IQR
	CRP* (mg/l)	390	3	1–7	451	2	1–3
		n	Mean	SD	n	Mean	SD
	FEV_1 (litres)	426	3.38	0.48	476	4.65	0.69
	BMI (kg/m^2)	445	24.9	4.9	494	25.1	3.9
32		n	Yes	%	n	Yes	%
	Smokers	444	152	34.2	495	184	37.2
	Asthma	442	73	16.5	493	89	18.1
		n	Median	IQR	n	Median	IQR
	CRP* (mg/l)	406	1.39	0.56–3.33	455	1.01	0.52–1.90
		n	Mean	SD	n	Mean	SD
	FEV_1 (litres)	434	3.33	0.48	480	4.43	0.65
	BMI (kg/m^2)	439	25.9	5.6	488	26.3	4.3

Pregnant women are excluded. CRP, C-reactive protein; FEV_1, forced expiratory volume in one second; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

At both assessments height and weight in light clothing without shoes were measured. Spirometry was performed using SensorMedics body plethysmograph (Yorba Linda, CA, USA) according to American Thoracic Society standards before and after 200 μg salbutamol via a large volume spacer.[19] Study members were seated in the plethysmograph and wore nose pegs. At least three acceptable manoeuvres were obtained with the best FEV_1 and forced vital capacity (FVC) from any of the acceptable tests reported and used for calculation of FEV_1/FVC. A portable spirometer (Spiropro, Sensormedics, Yorba Linda CA, USA) was used to test study members (n = 27) who refused to sit in the plethysmograph or were unable to attend the research unit. Participants were asked to avoid using any of their inhalers on the day of the test. Tests were reviewed by a senior technician to ensure only acceptable and reproducible results were entered for analysis. Equipment was calibrated daily and weekly quality control measures were obtained to ensure accuracy and precision of equipment.

At both ages blood samples were obtained approximately 4 hours after lunch. The following assays were performed using a Hitachi 917 analyser: at age 26 years serum CRP by immunoturbidimetric assay (coefficient of variation 5.6–12.9%, Boehringer Mannheim, Germany); at age 32 years, CRP was measured using a high sensitivity particle enhanced immunoturbidimetric assay (coefficient of variation 2.8%, Roche Diagnostics, Germany).

Analyses

Mean values of percentage predicted FEV_1, were compared across groups with low, medium, and high CRP values at each age. Cross sectional associations between CRP and FEV_1 were further analysed by multiple linear regression using absolute values of FEV_1 (in ml) as the dependent variable and CRP as the main predictor with adjustment for height and sex. CRP values were transformed using natural logarithms to approximate normal distributions (a value of 1 was added to all age 26 CRP values to allow log transformation of zero values). All analyses adjusted for sex. Plots of residual versus fitted values were visually inspected to ensure an approximately random distribution of residuals around the fitted values. The linearity assumptions of the models were checked by fitting quadratic and cubic terms for log-CRP. Neither was significant at either age. Supplementary analyses tested for interactions between sex and FEV_1, analysed sexes separately, and were restricted to those who had never smoked and had never had asthma and reported no recent other health problems. Analyses were repeated including terms for body mass index, current smoking, and current asthma in the model. Analyses were repeated using the FVC, the FEV_1/FVC ratio, and the post-bronchodilator FEV_1 as dependent variables.

To test the hypothesis that systemic inflammation leads to an accelerated decline in lung function, we used linear regression to test if log-CRP at age 26 predicted the change in FEV_1 (ml) from age 26 to age 32 years, adjusting for sex, smoking between age 26 and 32, and asthma at either age. To test the alternative hypothesis that a decline in FEV_1 leads to an increase in inflammation, we used linear regression to test whether the change in FEV_1 between ages 26 and 32 years predicted log-CRP at age 32, adjusting for sex, smoking between age 26 and 32 years, and asthma at either age.

Table 2 Percentage predicted FEV_1 values in CRP categories

		Women			Men		
Age	CRP category	No (% FEV_1)	95% CI	p Value	No (% FEV_1)	95% CI	p Value
26	Low (⩽1 mg/l)	104 (107.3)	105.0 to 109.6		190 (101.6)	99.7 to 103.5	
	Medium (1–3 mg/l)	108 (102.8)	100.4 to 105.2		154 (99.2)	97.0 to 101.4	
	High (>3 mg/l)	167 (100.0)	97.9 to 102.0	<0.001	94 (100.1)	97.3 to 102.9	0.093
32	Low (⩽1 mg/l)	166 (106.6)	104.8 to 108.4		224 (99.8)	98.2 to 101.5	
	Medium (1–3 mg/l)	126 (105.7)	103.6 to 107.9		161 (96.7)	94.9 to 98.6	
	High (>3 mg/l)	110 (101.7)	99.2 to 104.1	0.004	63 (95.0)	91.9 to 98.2	0.001

Pregnant women are excluded. CRP, C-reactive protein; FEV_1, forced expiratory volume in one second; 95% CI = 95% confidence intervals for mean. p values for trend across CRP categories.

Table 3 Regression of FEV_1 on log-CRP

Age	Adjustments and model restrictions	No	Coefficient (95% CI)	p Value
26	Sex, height	816	−86 (−125 to −48)	<0.001
	Height (women only)	379	−89 (−130 to −49)	<0.001
	Height (men only)	437	−78 (−145 to −10)	0.024
	Sex, height (never asthma, never smokers)	315	−85 (−147 to −24)	0.007
	Sex, height, BMI, smoking*, asthma*	811	−75 (−115 to −35)	<0.001
32	Sex, height	850	−82 (−116 to −49)	<0.001
	Height (women only)	402	−72 (−108 to −35)	<0.001
	Height (men only)	448	−94 (−151 to −38)	0.001
	Sex, height (never asthma, never smokers)	309	−58 (−109 to −7)	0.027
	Sex, height, BMI, smoking*, asthma*	850	−73 (−108 to −38)	<0.001

CRP, C-reactive protein; FEV_1, forced expiratory volume in one second; BMI, body mass index.
Coefficients refer to the change in FEV_1 in ml for each standard deviation increase in log-CRP. Analyses exclude pregnant women. *Adjustment for current (past year) smoking and asthma. BMI, body mass index (kg/m^2).

Pregnant women (n = 33 at age 26, n = 31 at 32) were excluded from all analyses, which were performed using Stata 9.1 (StataCorp, College Station, TX, USA).

RESULTS

Cross sectional associations

The characteristics of the study population at ages 26 and 32 are shown in table 1. CRP levels at both ages were significantly higher in women than men ($p<0.001$). The mean FEV_1 was lower at age 32 than age 26 ($p = 0.0003$) and the fall in FEV_1 between age 26 and 32 was greater in men (0.22 litres) than women (0.05 litres) ($p<0.0001$). Based on local reference equations[20] the mean (SD) FEV_1 values were 102.4% (12.8) and 100.4% (13.3) predicted at age 26 years and 104.9% (12.4) and 97.9% (12.5) predicted at age 32 years in women and men, respectively. The sex adjusted partial correlation coefficients between measurements at age 26 and age 32 years were $r = 0.88$ ($p<0.001$) for FEV_1 and $r = 0.37$ ($p<0.001$) for log-CRP. Analyses of categorised low, medium, high CRP values (as defined by the American Heart Association/Centers for Disease Control[21]) demonstrated decreasing percentage predicted FEV_1 with increasing CRP in women at both ages ($p<0.01$) and in men at age 32 ($p<0.01$) but this was not significant in 26-year-old men ($p = 0.09$) (table 2).

FEV_1 values were inversely associated with log-CRP at both age 26 and age 32 years in regression analyses adjusting for sex and height (table 3). Associations between lung function and CRP were not significantly different between women and men (p value for interaction = 0.29 at age 26, $p = 0.83$ at age 32) or between Maori and non-Maori (p value for interaction = 0.61 at age 26, $p = 0.51$ at age 32). The findings were similar when the analysis was restricted to study members who had never had asthma and had never smoked (table 3). The associations between FEV_1 and log-CRP remained significant after including terms in the regression model to adjust for body mass index, current asthma, and current smoking (table 3). Analyses excluding all those reporting other health problems, past year cannabis smoking, current smoking or current asthma also provided similar findings (age 26; n = 205, coefficient = −96, $p = 0.016$: age 32; n = 285, coefficient = −70, $p = 0.006$).

Similar associations between lung function and log-CRP were found for the post-bronchodilator FEV_1 (data not shown). For the FVC there was a significant sex×log-CRP interaction at age 32 ($p = 0.03$) and although both sexes showed significant inverse associations between log-CRP and FVC at both ages, these tended to be greater in men (see *Thorax* website, http://thorax.bmj.com/supplemental, table 1). There were also significant interactions between sex and log-CRP for the FEV_1/FVC ratio at both ages. The FEV_1/FVC ratio was inversely associated with CRP only in women. At age 32 this association was no longer significant after adjusting for smoking status (see *Thorax* website, http://thorax.bmj.com/supplemental table 2).

Longitudinal associations between age 26 and 32

Log-CRP at age 26 was not a significant predictor of the change in FEV_1 between ages 26 and 32 adjusting for sex and height (table 4). By contrast, the decrease in FEV_1 between age 26 and 32 years was a significant predictor of log-CRP at age 32 years. The sex×change in FEV_1 interaction term was not significant ($p = 0.72$) indicating that this longitudinal association was of similar magnitude in men and women. This association remained significant after adjusting for log-CRP at age 26, history of smoking between age 26 and 32, and asthma diagnosis at either age (table 4).

DISCUSSION

We have identified an association between spirometric lung volumes, and systemic inflammation, measured by serum C-reactive protein, in young adults aged 26 and 32 years. This

Table 4 Longitudinal analyses of the association between decline in FEV_1 from age 26 to 32 and CRP at age 26 and 32

Outcome	Predictor	Covariates	n	Coefficient (95% CI)	p Value
Fall in FEV_1 (ml)	Age 26 log-CRP	Sex, height	766	−3.30 (−25.1 to 18.5)	0.77
		Sex, height, smoking*, asthma*	765	−2.55 (−24.4 to 19.3)	0.82
Age 32 log-CRP	Fall in FEV_1 (litres)	Sex, height	788	0.48 (0.25 to 0.71)	<0.001
		Sex, height, smoking*, asthma*, age 26 CRP	739	0.49 (0.26 to 0.71)	<0.001

CRP, C-reactive protein; FEV_1, forced expiratory volume in one second.
CRP values were log transformed for analysis and are expressed as standard deviation scores. Analyses exclude women who were pregnant at either age. *Analyses adjusted for history of smoking between age 26 and 32 years and current asthma diagnosis at either age.

association was of similar magnitude in women and men and was independent of smoking, asthma and body mass index.

To our knowledge, this is the first report of an inverse association between lung function and CRP in young adults. There are numerous reports of increased markers of systemic inflammation in older adults with stable chronic obstructive pulmonary disease.[8 10 11] These markers appear to reflect disease severity and functional status,[10–12] This has usually been interpreted as being the result of the inflammatory nature of the airway disease.[22 23] Since systemic inflammation is a risk factor for atherosclerosis, it has been suggested that this is one reason why patients with chronic obstructive pulmonary disease have an increased risk of cardiovascular disease.[6 23] However, we have found that the association of a higher serum CRP with lower lung function is present as early as age 26 years. By this age it is very unlikely that members of this cohort will have developed either clinically significant atherosclerosis or chronic obstructive pulmonary disease. A recent report identified an inverse association between plasma fibrinogen and lung function in apparently healthy young American adults (average age 30).[24] Taken together, these findings indicate that there is an association between lung function and systemic inflammation, which predates the clinical development of either disease. Moreover, the associations are equally strong in those who have never smoked and do not have asthma. Although these are prominent risk factors for the development of chronic lung disease it is clear that they do not explain the association between lung function and systemic inflammation in these young adults. The finding that association between lower lung function and CRP was independent of body mass index is important because obesity is an established risk factor for systemic inflammation in young people, a finding that has been confirmed in an earlier report from this cohort,[25] and body size measurements may also influence lung function.[26]

These findings may help to explain epidemiological observations that have been made in older populations and are consistent with the hypothesis that systemic inflammation mediates the association between reduced lung function and cardiovascular disease. Firstly, the association between FEV_1 and systemic inflammation was present in those who had never smoked and did not have asthma or other health problems. This is consistent with several observations that reduced lung function predicts cardiovascular mortality independently of smoking[2] and is also consistent with the inverse association between CRP and lung function recently reported among apparently healthy older adults (mean age 50) attending for health screening[14] and in general population surveys (mean ages 37 and 44).[27 28] Secondly, the fall in FEV_1 between age 26 and 32 was a significant predictor of blood CRP at age 32 years. This may help to explain the association between rapid FEV_1 decline and cardiovascular mortality.[29]

Establishing whether systemic inflammation leads to reduced lung function or whether lower lung function leads to inflammation is difficult. In the longitudinal analyses CRP at age 26 did not predict the decline in FEV_1 over the following six years. By contrast, the decline in FEV_1 between ages 26 and 32 was a strong and significant predictor of CRP at age 32. Two other longitudinal studies in older adults also found that baseline CRP levels did not predict changes in lung function over the following 8–9 years but both found associations between decline in FEV_1 and rising CRP levels.[27 28] This suggests that systemic inflammation may be a consequence of a decline in lung function rather than the cause of the decline. However, CRP is an acute phase protein with a short half life[30] and a much less stable measure than FEV_1. Moreover, the CRP measurements at age 26 used a low sensitivity assay. Therefore the measurement taken at age 26 may not accurately reflect the level of inflammation over the following six years. In the CARDIA study, plasma fibrinogen measured at mean age 30 appeared to predict the decline in spirometric lung volumes over the subsequent five years.[24] This study did not have repeat measurements of fibrinogen after five years in order to test whether decline in lung function predicted systemic inflammation.

The association of lower spirometric lung volumes and systemic inflammation could have several explanations. It is possible that systemic inflammation damages pulmonary tissue and hence leads to deteriorating lung function. However, we found that the association was equally strong in apparently healthy study members (excluding ever smokers and those with asthma, arthritis, heart disease, cancer, diabetes, and recent major surgery or urinary tract infections). Although we will have missed some undiagnosed problems and conditions affecting other systems, this suggests that the association is unlikely to be mediated by a systemic inflammatory response to another disease process. An alternative explanation is that inflammation within the lungs may be the cause of the systemic inflammatory response, although it is clear from our findings that this inflammation is not caused by either asthma or smoking. The lungs may also have an anti-inflammatory role, particularly as a primary defence organ against environmental toxins and it is possible that this is why people with lower lung function have increased systemic inflammation. Finally, it is possible that other factors cause both a reduction in lung function and systemic inflammation. For example, a reduced dietary intake of anti-oxidants and vitamins has been linked to both lower lung function[31–33] and higher levels of CRP.[34–36] Alternatively CRP levels and lung function are likely to be influenced by genes and it is possible that these genetic influences overlap.

We analysed the data using the absolute value of FEV_1 adjusting for height in the analyses rather than use FEV_1 as a percentage of predicted. This is in accordance with the recommendations of Vollmer *et al*.[37] Repeat analyses using the FEV_1 as percentage predicted produced the same pattern of results as did analyses using FVC and the post-bronchodilator FEV_1. The association between the FEV_1/FVC ratio and CRP was weaker and only significant in women (see *Thorax* website, http://thorax.bmj.com/supplemental, table 2). Similarly, plasma fibrinogen has been found to be associated with lower FEV_1 and FVC measurements but not with reduced FEV_1/FVC ratios.[24] This suggests that the association between lung function and systemic inflammation is more closely related to spirometric lung volumes rather than airflow obstruction.

A limitation of this study is that the measurement of CRP at age 26 years used a low sensitivity assay. It is now believed that low grade inflammation, which may impact on cardiovascular risk, may be associated with CRP levels that are not accurately detected by standard CRP assays.[7] The low sensitivity assay at age 26 may have reduced our chance of detecting a prospective association between the initial CRP value and the subsequent decline in FEV_1. The differences in the assay methods may also explain the apparent fall in mean CRP levels between age 26 and 32 years. Nevertheless, CRP measurements taken at age 32 years using a high sensitivity assay provided similar cross sectional associations between CRP and FEV_1 to those found at age 26 using a low sensitivity assay.

This investigation has a number of strengths. We have found similar results at two ages in a general population based cohort with a high rate of participation. The cohort members have similar health status to nationally representative samples of young adult New Zealanders[38] and the distribution of CRP values is similar to that described for similar age participants in

other studies.[39] We have prospectively collected information on smoking and asthma and have directly measured height and weight. Lung function was measured using the same equipment for all study members and the blood samples were assayed in the same laboratory at each age.

In summary, there is a significant inverse relation between spirometric lung volumes and systemic inflammation in young adults. This association is independent of smoking and asthma history and is also independent of body mass index. While the underlying reason for this association is uncertain, the findings suggest a plausible mechanism by which a reduced FEV_1 is associated with an increased risk of cardiovascular disease in a manner that is independent of smoking and known respiratory disease.

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Further tables can been found on *Thorax* website, http://thorax.bmj.com/supplemental

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