RESPIRATORY DISEASE

Plasma fibrinogen and lung function: the CARDIA Study

Bharat Thyagarajan,1 David R Jacobs,1,2* George G Apostol,1 Lewis J Smith,3 Cora E Lewis4 and O Dale Williams4

Accepted 2 March 2006

Background We hypothesized that fibrinogen, as a marker of chronic inflammation, is inversely associated with forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) in healthy persons.

Methods The CARDIA cohort started in 1985 and included black and white men and women, aged 18–30, from the general population. Spirometry testing conducted at years 5 and 10 [FVC, FEV1, and their ratio (FEV1/FVC)] was studied relative to plasma fibrinogen levels measured at year 5 (cross-sectional n = 4040) and at year 7 (longitudinal n = 3001), controlling for race, sex, age, height, smoking, asthma, body mass index, physical activity, birth control pill use, and alcohol intake.

Results In cross-sectional analyses, FVC at year 5 was lower by 166 ml (95% confidence interval 116–216 ml) in the highest vs lowest year 5 fibrinogen quartile. At year 10, holding year 5 FVC and change in fibrinogen (year 7–year 5) constant, the difference in FVC between the highest and the lowest year 5 fibrinogen quartiles widened by 67 ml (95% CI 31–103 ml). The corresponding differences for FEV1 were 166 ml (95% CI 146–253 ml) at year 5 and 45 ml (95% CI 11–80 ml) widening by year 10. The FEV1/FVC ratio was unrelated to plasma fibrinogen.

Conclusion These findings are consistent with the hypothesis that fibrinogen, possibly as a marker for chronic low-grade inflammation, is associated with modest deterioration of lung function in healthy young adults.

Keywords Fibrinogen, FEV1, FVC, FEV1/FVC ratio, lung function, inflammation, smoking, asthma, BMI

In recent years, a correlation between fibrinogen and other markers of inflammation and heart disease has emerged. Several studies have shown that higher levels of fibrinogen are associated with the subsequent development of major atherosclerotic cardiovascular events like coronary heart disease, peripheral artery disease, and stroke.1–3 These diseases are also associated with reduced lung function.4 It is, therefore, plausible that chronic low-grade systemic inflammation adversely affects lung tissue, although the specific mechanism by which this may occur is unknown. There is little information on a relationship between plasma fibrinogen levels and lung function.5–7 A possible association between plasma fibrinogen levels and lung function is particularly important given the observation that hyperfibrinopenia is linked with obesity,8,9 asthma,10,11 and smoking.12–16 Although the prevalence of smoking was stable in the recent past, the prevalence of obesity in US adults increased from 15.0% in 1979 to 30.9% in 2000,17 across all age groups, races, genders, and educational levels,18 while asthma had a similarly upward trend.19

We hypothesized that low-level, systemic inflammation, as represented by the year 5 plasma fibrinogen levels, is associated with a cross-sectionally worse and longitudinally worsening lung function, as represented by forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1), in a generally healthy population.
Methods

Participants and measurements

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multi-centre cohort study occurring in Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota, and Oakland, California. At baseline, in 1985–86, CARDIA recruited 5115 participants, approximately equal numbers of blacks and whites, men and women, aged 18–24 and 25–30, and with more or less than high school education. Of these, 4352 were reexamined in 1990–91 (year 5), 4086 in 1992–93 (year 7), and 3950 in 1995–96 (year 10) (Figures 1 and 2). Measurements included demographic characteristics, lifestyle habits (e.g. cigarette smoking, average weekly alcohol intake), and physical activity. The latter used an interviewer-administered questionnaire concerning the frequency of participation in 13 different activities during the past 12 months. Because participants were not asked specifically about duration of physical activity, the activity score is expressed in ‘Exercise Units’ (EU). A score of 100 EU is roughly equivalent to participation in activities such as a vigorous exercise class or bicycling faster than 10 miles per hour, 2 or 3 h a week for 6 months of the year. Medical history and medication use were collected by self-report; asthma was diagnosed based on the use of anti-asthmatic medications and/or self-report of a medical diagnosis. Information regarding oral contraceptive use and use of other medications such as, antihypertensive medications, cholesterol lowering medications, and other prescription medications were collected using a questionnaire at both year 5 and year 7. At years 0, 2, 5, and 10, spirometry testing was conducted with the subjects standing, following American Thoracic Society (ATS) recommendations. Weight, height, and body mass index (BMI, kg/m²) were measured consistently across time. After blood samples were drawn by venipuncture, the plasma was separated by centrifugation, transferred into airtight vials, stored at −70°C and shipped on dry ice.

Plasma fibrinogen levels were available in 4196 participants examined at year 5. We excluded 52 participants who were not ages 18 through 30 at the time of their baseline exam. We also excluded 55 women who were pregnant during the year 5 exams; since, pregnancy might influence BMI, lung function, and fibrinogen levels (observations from these participants when not pregnant were included). After exclusion for missing covariates, 4040 participants entered the cross-sectional analyses. Fibrinogen levels were available at both year 5 and year 7 in 3454 participants. For longitudinal analyses, 3001 participants were included, given that attendance at both year 7 and year 10 was required, and after further exclusion for women who were pregnant during the exams following the year 5 exams and for missing covariates.

Year 5 plasma fibrinogen levels were measured by the Clauss method using reagents from the Dade Division, Baxter Healthcare Corp. (Deerfield, IL). A standard curve was prepared with universal reference plasma, and the results were reported as a percentage of the standard. The technical error as a percentage of the mean was 5.6% for fibrinogen. Internal reference plasmas showed no drift over time, but blind quality control suggested some increase. Adjustment for this possible laboratory drift in fibrinogen measurement was attempted using a covariate indicating month of examination, as suggested by Folsom et al. This adjustment did not alter findings for the relation between fibrinogen and lung function, and was not included in the final models. Year 7 plasma fibrinogen levels were measured in two ways. Concurrent with year 7 data collection, the Clauss method was used in two centres (Chicago and Minneapolis), as part of an ancillary study. During 2003, plasma fibrinogen was assayed in samples stored since year 7 (1992–93) in all examined participants, using the BNII method. Fibrinogen antigen was measured using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The amount of fibrinogen present in the sample was determined by an immunochemical reaction. The year 5 intra-assay and inter-assay coefficients of variation were 2.7 and 4.0%,
respectively. The correlation was 0.75 ($p < 0.0001$) between year 7 plasma fibrinogen levels in the subset of 1694 participants in whom values using both methods were available. Because values obtained using BNII were higher than those using the Clauss method, we rescaled the BNII values using a linear equation, estimated year 7 Clauss $\mu$mol/l (mg/dl) = $1.6956 + 0.01826 \times$ BNII $\mu$mol/l (57.674 + 0.62105 $\times$ BNII mg/dl). The measured year 5 plasma fibrinogen value and the estimated year 7 plasma fibrinogen value were used in data analysis.

Observed FVC, FEV$_1$, and FEV$_1$/FVC in millilitres, and FEV$_1$/FVC were adjusted for differences in age, race, sex, and height using Hankinson’s formula$^{29}$ to obtain predicted FVC, FEV$_1$, and FEV$_1$/FVC. The ratios of observed to predicted values of FVC, FEV$_1$, and FEV$_1$/FVC were analysed as dependent variables. To ease interpretation, results are reported in millilitres by multiplying predicted FVC, FEV$_1$, and FEV$_1$/FVC by the average FVC, FEV$_1$, and FEV$_1$/FVC estimated using Hankinson’s formula of the population (year 5 FVC: 4272 ml, year 5 FEV$_1$: 3563 ml; FEV$_1$/FVC: 82.95, year 10 FVC: 4229 ml, year 10 FEV$_1$: 3477 ml, and year 10 FEV$_1$/FVC: 82.91). We used quartiles of plasma fibrinogen at year 5 as the main predictor variable.

### Statistical methods

We used linear regression in the SAS statistical package, version 9. Initially, a cross-sectional analysis was done to evaluate the association between year 5 lung function and year 5 fibrinogen levels. Subsequently, prospective analyses were conducted to evaluate the associations between year 7 fibrinogen levels and year 5 lung function. We used linear regression in the SAS statistical package, version 9. Initially, a cross-sectional analysis was done to evaluate the association between year 5 lung function and year 5 fibrinogen levels. Among the race–sex categories, black women had the highest level of fibrinogen at year 5, 8.53 $\mu$mol/l (290.3 mg/dl). Quartile cutpoints for fibrinogen were 25th percentile 6.56 (223 mg/dl), median 7.50 $\mu$mol/l (255 mg/dl), and 75th percentile 8.67 $\mu$mol/l (295 mg/dl). In the highest quartile, 110 participants had fibrinogen levels over 11.76 $\mu$mol/l (400 mg/dl). Among the race–sex categories, black women had the highest level of fibrinogen at year 5, 8.53 $\mu$mol/l (290.3 mg/dl). Mean FVC or FEV$_1$ at year 0 was somewhat lower but not statistically significantly different in 4196 participants who attended only year 0 compared with 4040 who attended year 5 and had their fibrinogen levels measured (4.16 l vs 4.33 l, $P = 0.09$ and 3.44 l vs 3.54 l, $P = 0.20$, respectively).

In a model including age, race, sex, asthma, smoking status, BMI, physical activity, birth control pill use, and alcohol

### Table 1 Clinical characteristics [mean (standard deviation) or percentage] of the participants according to race–sex group

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Black male ($n = 843$)</th>
<th>Black female ($n = 1092$)</th>
<th>White male ($n = 1014$)</th>
<th>White female ($n = 1091$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (ml)</td>
<td>4234 (537)</td>
<td>3651 (510)</td>
<td>5003 (539)</td>
<td>4225 (455)</td>
</tr>
<tr>
<td>FEV$_1$ (ml)</td>
<td>3534 (493)</td>
<td>3057 (461)</td>
<td>3976 (487)</td>
<td>3477 (397)</td>
</tr>
<tr>
<td>FEV$_1$/FVC</td>
<td>81.3% (6.6%)</td>
<td>83.9% (7.4%)</td>
<td>79.6% (6.4%)</td>
<td>82.5% (6.2%)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>26.5 (5.1)</td>
<td>28.2 (7.4)</td>
<td>25.6 (4.1)</td>
<td>24.3 (5.2)</td>
</tr>
<tr>
<td>Physical activity score (exercise units)</td>
<td>488 (350)</td>
<td>264 (230)</td>
<td>456 (288)</td>
<td>350 (256)</td>
</tr>
<tr>
<td>Birth control pill use (%)</td>
<td>Not applicable</td>
<td>25.0</td>
<td>Not applicable</td>
<td>27.9</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>19.5 (33.7)</td>
<td>5.8 (20.0)</td>
<td>16.2 (32.8)</td>
<td>6.4 (11.3)</td>
</tr>
<tr>
<td>Plasma fibrinogen ($\mu$mol/l (mg/dl)]</td>
<td>$[249.0 (48.5)]$</td>
<td>$[290.3 (61.2)]$</td>
<td>$[240.9 (47.5)]$</td>
<td>$[265.3 (55.7)]$</td>
</tr>
</tbody>
</table>

Results

### Description of study population

The study sample at year 5 in 1990–91 was aged ~30 years (Table 1). The participants were generally healthy and, by design, nearly equally distributed among the race-sex groups. About 31% had no education past high school. Of the 4040 participants with no missing data, 1935 had never smoked by year 0 and never had asthma during the study. For the entire sample, the mean year 5 fibrinogen level was 7.72 ± 1.68 $\mu$mol/l (262.5 ± 57.2 mg/dl). Quartile cutpoints for fibrinogen were 25th percentile 6.56 (223 mg/dl), median 7.50 $\mu$mol/l (255 mg/dl), and 75th percentile 8.67 $\mu$mol/l (295 mg/dl). In the highest quartile, 110 participants had fibrinogen levels over 11.76 $\mu$mol/l (400 mg/dl). Among the race–sex categories, black women had the highest level of fibrinogen at year 5, 8.53 $\mu$mol/l (290.3 mg/dl). Mean FVC or FEV$_1$ at year 0 was somewhat lower but not statistically significantly different in 4196 participants who attended only year 0 compared with 4040 who attended year 5 and had their fibrinogen levels measured (4.16 l vs 4.33 l, $P = 0.09$ and 3.44 l vs 3.54 l, $P = 0.20$, respectively).

In a model including age, race, sex, asthma, smoking status, BMI, physical activity, birth control pill use, and alcohol...
intake, year 5 plasma fibrinogen levels did not differ between the three asthma categories ($P = 0.94$), but increased with BMI [0.12 μmol/l (4 mg/dl) per kg/m², $P < 0.0001$] and was higher in smokers: 8.00 μmol/l (272.2 mg/dl) in current smokers, 7.59 μmol/l (258.3 mg/dl) in ex-smokers, and 7.61 μmol/l (258.9 mg/dl) in those who never smoked ($P < 0.0001$ for current vs former or never smokers). Plasma fibrinogen decreased with physical activity [7.82 μmol/l (266.1 mg/dl) for the lowest physical activity quartile as compared with 7.62 μmol/l (259.2 mg/dl) for the highest physical activity quartile $P = 0.008$] and alcohol intake [7.81 μmol/l (265.8 mg/dl) for lowest quartile of alcohol intake as compared with 7.61 μmol/l (258.9 mg/dl) for the highest alcohol intake quartile $P = 0.0006$]. Mean plasma fibrinogen level was significantly higher ($P < 0.0001$) among women who consumed birth control pills as compared with those who did not [8.10 μmol/l (275.5 mg/dl) among women who consumed birth control pills as compared with 7.66 μmol/l (260.4 mg/dl) among women who did not]. Plasma fibrinogen at year 7 had mean 7.83 ± 1.40 μmol/l (266.6 ± 47.5 mg/dl), with a correlation of $r = 0.61$ between the fibrinogen levels at years 5 and 7 in the 3454 participants measured at both times.

**Cross-sectional analysis**

Cross-sectional analysis (Table 2) between year 5 fibrinogen and year 5 FVC showed that plasma fibrinogen level was a significant predictor of FVC at year 5 ($P < 0.0001$). Mean FVC levels were 166 ml lower in the highest fibrinogen quartile as compared with the lowest fibrinogen quartile (4411 ml in the lowest fibrinogen quartile compared with 4245 ml in the highest fibrinogen quartile). All pairwise comparisons of FVC between fibrinogen quartiles were significantly different from each other ($P < 0.04$) except for differences in FVC between the lowest two fibrinogen quartiles ($P = 0.38$). Findings were similar for FEV1. In contrast, cross-sectional analysis between year 5 fibrinogen and year 5 FEV1/FVC shows that the ratio varied little across fibrinogen levels ($P = 0.20$). Mean FEV1/FVC levels were close to 82% in all fibrinogen quartiles.

**Prospective analysis**

Prospective analysis, in which year 10 FVC or FEV1 levels were predicted adjusting for year 5 FVC or FEV1 and other year 5 variables including age, race, sex, height, BMI, physical activity, birth control pill use, and alcohol consumption, and year 0 smoking status and year 0–10 asthma, showed that both fibrinogen levels 5 years earlier and change in fibrinogen levels from year 5 to year 7 were significant predictors of future FVC levels ($P < 0.0001$ for fibrinogen levels 5 years earlier and $P = 0.01$ for change in fibrinogen levels from year 5 to year 7). Mean year 10 FVC levels were 67 ml lower in the highest vs the lowest year 5 plasma fibrinogen quartile ($P = 0.004$), representing a widening of the FVC difference from year 5 according to plasma fibrinogen level. Pairwise comparisons of FVC amongst the other fibrinogen quartiles also revealed statistically significant differences ($P < 0.03$) between FVC in the lowest quartile and FVC in the two higher quartiles (31 ml decrease between first and second quartile; 43 ml decrease between first and third quartile). Adjusted year 10 FVC was non-significantly higher by 31 ml in those in the lowest quartile of change in plasma fibrinogen as compared with the highest quartile ($P = 0.06$) but significantly higher by 46 ml in the second quartile of change compared with the highest quartile ($P = 0.002$). Pairwise comparisons between FVC of other quartiles revealed no significant differences in FVC across different quartiles of change in fibrinogen except the decrease between the second and third fibrinogen quartiles (11 ml, $P = 0.01$). Consistent with these observations, the mean FVC levels among people in the lowest fibrinogen quartile and the lowest quartile of change in fibrinogen levels were estimated to be 101 ml higher than in those in the highest fibrinogen quartile and the highest change in fibrinogen quartile (4318 ml vs 4217 ml, $P = 0.81$, data not tabulated). Mean FEV1 at year 10 was estimated to be 45 ml higher in the lowest vs highest year 5 plasma fibrinogen quartile ($P = 0.01$). FEV1 in the lowest fibrinogen quartile was also significantly different from FEV1 in the third quartiles (41 ml). No other significant differences in FEV1 were observed across different fibrinogen quartiles. Year 10 FEV1 was not significantly related to the change in fibrinogen levels ($P = 0.05$) after adjustment for year 5 FEV1 and other covariates. The FEV1/FVC ratio showed no relation to fibrinogen in prospective analyses (Table 3).

**Analyses without adjustment for BMI**

If increased fibrinogen levels were caused by increased BMI and increased fibrinogen level in turn caused an accelerated decline in lung function, then control for BMI would represent

| Table 2 Cross-sectional analysis at year 5 of lung function according to quartile of year 5 plasma fibrinogen |
|---------------------------------|-------------------------------------------------|---------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                | ≤6.53 μmol/l (222 mg/dl) | 6.54–7.47 μmol/l (223–254 mg/dl) | 7.48–8.64 μmol/l (255–294 mg/dl) | ≥8.65 μmol/l (295 mg/dl) |
|                                | (n = 1018) | (n = 957) | (n = 1014) | (n = 1051) |
| Year 5 FVC (ml)                 | 4411 [103.25] | 4579 [102.51] | 4526 [101.26] | 4245 [99.36] |
| Year 5 FEV1 (ml)                | 3606 [101.22] | 3570 [100.20] | 3524 [98.91] | 3440 [96.55] |
| Year 5 FEV1/FVC                 | 82.20% [97.91] | 81.95% [97.62] | 81.94% [97.60] | 81.52% [97.10] |
| Mean and 95% CI of difference   | 166.6 [3.89] | 166.0 [3.83] | 166.4 [3.87] | 166.6 [3.87] |
| (lowest–highest)                | [2.72–5.07] | [2.72–5.07] | [3.42–5.92] | [3.42–5.92] |

% Predicted FVC, FEV1, and FEV1/FVC are given in [ ]. 4040 participants at the year 5 examination. The CARDIA Study, 1990–91. Based on three separate linear regression analyses, adjusting for year 5 age, race, sex, height, smoking status, physical activity, birth control pill use, alcohol use, and BMI, plus year 0–10 asthma.

$^a$ Test for linear trend $P < 0.0001$; all pairwise differences $P < 0.04$ except first compared with second quartile, $P > 0.05$.

$^b$ Test for linear trend $P = 0.11$; all pairwise differences $P > 0.05$ except lowest quartile compared with highest quartile, $P = 0.03$. 

P
an overadjustment and might attenuate the true magnitude of association between fibrinogen and lung function. Hence, we repeated the analyses described above without adjustment for BMI. The cross-sectional analyses for year 5 FVC and year 5 FEV₁ without adjustment for BMI were very similar to the results obtained when BMI was included as a covariate in the model except that the FEV₁/FVC ratio decreased significantly from 82.37 to 81.36% from the lowest to the highest fibrinogen quartiles when BMI was not included as a covariate (P = 0.01). For the prospective analyses, the difference in adjusted mean year 10 FVC levels between the highest fibrinogen quartile and the lowest fibrinogen quartile was 119 ml without adjustment for year 5 BMI, as compared with 67 ml when year 5 BMI was included in the model. Similarly, the difference in the adjusted mean year 10 FEV₁ levels between the highest fibrinogen quartile and the lowest fibrinogen quartile was 75 ml without adjustment for BMI as compared with 45 ml when BMI was included in the model.

Models in never smokers who never had asthma
The prospective analyses described above were repeated restricted to the 1935 participants who never smoked before year 5 and who never had asthma during the study. Cross-sectional analysis of year 5 FVC showed results very similar to those observed in the entire population. Year 5 fibrinogen levels were inversely associated with both year 5 FVC and year 5 FEV₁ levels. On average, the year 5 FVC and FEV₁ were similar in never smokers who never had asthma as compared with all participants. The extent of the decline in FVC over 5 years between the lowest and highest year 5 plasma fibrinogen categories in never smokers who never had asthma was around one-third the decline seen in all participants [33 ml in never smokers who never had asthma (P = 0.18) as compared with 94 ml in participants who were ever smokers or who had had asthma (P = 0.002)]. However, this difference (33 ml vs 94 ml) did not achieve statistical significance (P = 0.42 for interaction). In the prospective analyses, the decline in year 10 FEV₁ from lowest to highest fibrinogen quartiles in never smokers who never had asthma was <50% of the decline observed in participants who were ever smokers or who had had asthma [24 ml in never smoker non-asthmatics (P = 0.02) as compared with 55 ml in smoker asthmatics (P = 0.04) and P for interaction = 0.56]. As observed for all participants, fibrinogen levels were not associated with FEV₁/FVC levels among never smokers who never had asthma.

Models excluding lung disease
Following definitions of Mannino et al.,³⁵ only five participants were classified as having mild COPD at both years 5 and 10.
and 35 participants were shown to have restrictive lung disease at both examinations. Repeating the analyses without participants with COPD or restrictive lung disease did not substantially change the results of the study.

**Discussion**

Fibrinogen is associated with a significantly decreased lung function (as measured by FVC and FEV₁) in a sample of young healthy adults aged 22–36, both cross-sectionally and prospectively in 5 year follow-up, consistent with a causal role for fibrinogen in the determination of future lung function in healthy adults.

Fibrinogen is a clotting factor and a marker of inflammation. Its association with atherosclerotic disease is well documented.1–3 Since reduced lung function is also associated with atherosclerotic disease,30,31 the hypothesis that chronic low-grade inflammation, as marked by fibrinogen, is associated with and possibly causally related to reduced lung function is plausible. However, no previous study has linked fibrinogen levels and lung function in a population of generally healthy, racially diverse, young adults.

In 1988 Geiger et al.32 showed that interleukin (IL)-6, an inflammatory cytokine synthesized in airway epithelium, macrophages, and other cells involved in inflammation, increased hepatic synthesis of fibrinogen 5-fold. Even when produced chronically in lesser amounts, (IL)-6 has major systemic effects on the acute-phase response.33 Therefore, moderately increased levels of IL-6 are likely to determine highly increased levels of fibrinogen.33 Thus, as proposed by Dahl et al.,3 fibrinogen can be used as a non-invasive marker of chronic inflammation not only in smokers or patients with COPD but also in the general population. The interest in the association of fibrinogen with lung function is enhanced in the context of the current increased prevalence of obesity, given that increased BMI is associated with higher fibrinogen levels.8,9

Five articles have explored the relationship between fibrinogen and lung function, all using cross-sectional designs.5–7,34,35 In a sample of 8955 mostly white participants, aged 20–93 years old, Dahl et al.5 showed that participants in the upper tertile of plasma fibrinogen had a lower FEV₁ (by 169 ml in smokers and 121 ml in non-smokers) and higher COPD hospitalization rates when compared with the lowest fibrinogen tertile. They also found that age and BMI were the most important predictors of fibrinogen levels, in agreement with our suggestion that including BMI as a covariate might have overadjusted the fibrinogen–lung function correlation that we found. In another study, Engström et al.6 found that among participants aged 28–61 those in the lowest FVC quartile had significantly higher levels of fibrinogen when compared with participants in the highest FVC quartile both in smokers (3.76 g/l vs 3.60 g/l) and non-smokers (3.44 g/l vs 3.27 g/l), even after adjusting for age and BMI. Sin et al.7 also found that individuals over the age of 50 with severe airflow obstruction had higher fibrinogen levels than the controls but, given the focus of their paper, they did not describe the relationship between lung function and fibrinogen levels with age. Gan et al.34 showed that increased levels of inflammatory markers such as CRP and fibrinogen were independently associated with decreased FEV₁ levels and smoking status in the NHANES III dataset. Participants in this study were older than 40 years and given the cross-sectional nature of the study no conclusions could be drawn regarding the temporal nature of the observed relationships. Furthermore, since the data included participants who had lung disease (COPD or restrictive lung disease), as well as participants without lung disease, the association between lung function and inflammatory markers among healthy individuals could not be evaluated in this study. Mannino et al.35 showed a cross-sectional association between lung disease (COPD and restrictive lung disease) and increased levels of markers of inflammation such as C-reactive protein and fibrinogen in the NHANES III dataset. Few CARDIA participants met the criteria for COPD or restrictive lung disease,35 so that the results of Mannino et al. could not be confirmed in this current study.

Systemic low-grade inflammation is also associated with adiposity, perhaps through release of adipocytokines.36,37 For example, among the race–sex categories, the black women had the highest level of fibrinogen at year 5; they also had the highest level of adiposity at baseline (Table 1) and their adiposity increased most rapidly during CARDIA follow-up.18 Therefore, we adjusted the association of plasma fibrinogen with lung function for year 5 BMI. As seen in prior studies,5,16 BMI was associated with fibrinogen in this study and the effect of fibrinogen on lung function (FVC and FEV₁) was accentuated in models that did not adjust for BMI. These findings are in agreement with our hypothesis that inflammation, whether in response to increased adiposity or otherwise, plays a role in determining future lung function.

The cross-sectional analyses showed a larger change in lung function occurring between the third and fourth quartiles than between the first and second or second and third quartiles. Such an evolution would be expected if most damage to the lung occurs only after the degree of inflammation, represented by the elevated levels of fibrinogen, overcomes the natural protective mechanisms. However, prospective analyses of fibrinogen levels and lung function did not show a larger decrease in year 10 lung function between the third and fourth fibrinogen quartiles as compared with the other quartiles. A longer duration of follow-up would aid in understanding the role of fibrinogen in determining future lung function.

The results of our study suggest that the inverse relationship between fibrinogen levels and lung function in a generally healthy population is most likely due to a ‘restrictive’ rather than an ‘obstructive’ mechanism because of the increased loss of FVC as compared with FEV₁ in the highest fibrinogen quartile and the unchanged FEV₁/FVC ratio.38 The unchanged FEV₁/FVC ratio may also reflect the young mean age of the participants in the study (30 years) when obstructive or restrictive diseases are very uncommon or represent very early changes in lung function that are too subtle to be identified by the FEV₁/FVC ratio. BMI is hypothesized to reduce lung function through two mechanisms: a decreased mobility of the diaphragm and thoracic cage and increased secretion of inflammatory cytokines35; the latter would provide a direct link to fibrinogen. The specific pathophysiological mechanisms involved, however, remain a matter of debate, as it is difficult to speculate in the absence of other data such as measurements...
of cytokines, diffusing capacity, high-resolution chest CT scans, or lung biopsies.

The present study has several strengths, including the large number of generally healthy participants, inclusion of blacks and whites and men and women, and follow-up soon after peak lung function is achieved. It also assured high-quality data collection through strict quality control across examinations. Because the sample studied by CARDIA included young people, few individuals were lost owing to disease, avoiding survivorship biases. Furthermore, there was an excellent retention of the original cohort. Only 557 participants who attended the year 5 exam did not attend the year 10 exam. Participants who attended the year 10 exam were more likely to be white and female and had higher alcohol intake (14.4 g/day) as compared with those who did not attend the year 10 exam (10.9 g/day). None of the other covariates, fibrinogen levels, or demographic variables were different between the two groups of participants.

A limitation of the study is that other inflammatory markers, such as IL-6, were not measured. The short duration of follow-up between initial (year 5) fibrinogen level measurement and year 10 lung function (5 years) does not allow a full understanding of the prospective relationship between fibrinogen and lung function. In addition, concurrent changes in lung function and inflammatory activity would have been better assessed if fibrinogen had been repeatedly measured in the whole study population or if other markers of inflammation were measured and produced similar findings.

In conclusion, we found among a sample of young adults with very little lung disease a significantly greater lung function loss in those who had the highest levels of fibrinogen, independent of smoking and asthma status, BMI, physical activity, birth control pill use, alcohol intake, race, and sex. As fibrinogen was measured at an average age of 30, before the age-related loss of lung function begins, our findings are consistent with the hypothesis that inflammatory processes are involved early in lung pathophysiology, similar to that seen in cardiovascular diseases. Therefore, a reduction in systemic inflammation could have beneficial effects on the lungs as well as the heart. Further studies are required to evaluate possible mechanisms to explain this association between chronic low-grade inflammation and loss of lung function in generally healthy young adults. Subsequent measurements of lung function performed within the CARDIA cohort will further help our understanding of the relationship between fibrinogen levels measured early in life and future lung function.

Acknowledgements

Supported by National Heart, Lung, and Blood Institute contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050, and N01-HC-95095 (CARDIA) and R01-HL053560-08 (YALTA).

References


Commentary: Fuelling the fire—systemic inflammation and development of lung disease in the general community

Don D Sin1,2* and SF Paul Man1,2

Airway inflammation is associated with reduced lung function.1 With progressive loss in lung function, the inflammatory process intensifies.1 Individuals with increased airway inflammation have a faster decline in lung function, leading to the development of chronic airway diseases such as chronic obstructive pulmonary disease (COPD).2 Once COPD is firmly established, the airways become more vulnerable to additional damage, leading to a further deterioration in lung function, which in turn becomes a substrate for more inflammation.3 The only known therapy that can mitigate this process is smoking cessation.4

Although it has been recognized for more than 30 years that airway inflammation plays a central role in COPD progression (and reduction in lung function), the potential importance of systemic inflammation has not been fully appreciated until quite recently. Systemic inflammation is present in individuals with reduced lung function, as assessed by forced expiratory volume in 1 s (FEV1) and the intensity of systemic inflammation varies inversely along the FEV1 gradient.5 In those with reduced lung function, systemic inflammation has been implicated with a variety of poor clinical outcomes 

1 The James Hogg Icapture Center For Cardiovascular, Pulmonary Research, St Paul’s Hospital, Vancouver, BC, Canada.
2 Division of Respirology, The Department of Medicine, The University of British Columbia, Vancouver, BC, Canada.
* Corresponding author. James Hogg Icapture Center for Cardiovascular and Pulmonary Research, St Paul’s Hospital, Room #368A, 1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6. E-mail: dsin@mrl.ubc.ca