Adult height and cryptogenic fibrosing alveolitis: a case-control study using the UK General Practice Research Database

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Abstract
Background—The reasons why cryptogenic fibrosing alveolitis has emerged as a new clinical entity during the second half of the 20th century are unclear. Some environmental exposures have been identified as potential risk factors including occupational dust, cigarette smoking and antidepressants, but there have been no studies of the role of early life exposures. Since adult height reflects, in part, early life experience, we have examined the relationship between adult height and the risk of cryptogenic fibrosing alveolitis.

Methods—A case-control study of 569 cases and 3669 age, sex, and community matched controls drawn from the UK General Practice Research Database was undertaken.

Results—Evidence was found of an inverse association between quintile of height and cryptogenic fibrosing alveolitis (odds ratio (OR) per increase in height quintile 0.93, 95% CI 0.86 to 0.99). This association was not diminished by adjustment for smoking status (OR 0.93, 95% CI 0.87 to 1.00), but some minor attenuation did occur after adjustment for oral corticosteroid use (OR 0.94, 95% CI 0.88 to 1.02). There was a significant interaction with sex such that the effect of height was strong in women (OR 0.85, 95% CI 0.75 to 0.97) and absent in men (OR 1.00, 95% CI 0.91 to 1.09).

Conclusions—These findings raise the possibility that early life exposures may be important in determining the lifetime risk of developing cryptogenic fibrosing alveolitis.

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Keywords: cryptogenic fibrosing alveolitis; adult height; early life experience; UK General Practice Research Database

The registered mortality from cryptogenic fibrosing alveolitis has increased markedly during the second half of the 20th century and the reasons for this are not clear. There is evidence from epidemiological studies that occupational dust exposures, cigarette smoking, and antidepressant use may be risk factors for the disease, but there have been no studies on the importance of early life experience. Adult height has consistently been shown to have an inverse association with all-cause mortality and mortality from respiratory disease, and this effect has generally been interpreted as reflecting the importance of early life events on long term health. To investigate whether early life events may be important in the lifetime risk of cryptogenic fibrosing alveolitis, we have determined the association between adult height and cryptogenic fibrosing alveolitis in a population based case-control study using data from the UK General Practice Research Database (GPRD).

Methods

Our subjects consisted of 890 cases of cryptogenic fibrosing alveolitis and 5884 age, sex, and community matched controls which have been described elsewhere. Briefly, cases were identified using the GPRD, which is the largest primary care population database in the UK and includes data from over seven million patients. Cases were defined as having cryptogenic fibrosing alveolitis if a diagnosis of the condition was recorded anywhere in the GPRD record and controls were matched by sex and general practice. We have previously established that the diagnosis of cryptogenic fibrosing alveolitis in the GPRD appears to be accurate. Cases and controls with a recorded diagnosis of any connective tissue disease were excluded from the analysis since connective tissue disease is a strong risk factor for cryptogenic fibrosing alveolitis and may be a cause of lost height.

Data on height and weight before the first recorded diagnosis of cryptogenic fibrosing alveolitis (matching date for controls) were extracted from the dataset. Where there was more than one measurement, the first was used. Height and weight were recoded into quintiles for men and women separately. We estimated the association between quintile of height and cryptogenic fibrosing alveolitis using conditional logistic regression, and looked for evidence of confounding by smoking habit (using smoking status data from our previous study), body mass index, and oral corticosteroid use before the first recorded diagnosis of cryptogenic fibrosing alveolitis. Multiplicative terms were added as appropriate.
to test for possible interactions with age (in ter-
tiles) and sex. All analyses were conducted
using STATA (version 5.0) and likelihood ratio
tests were used for all tests of significance.

Results
The median age of our cases at diagnosis was
71 years (interquartile range 64–78) and 553
(62%) were men. Data were available on height
for 569 cases (64%) and 3669 (63%) controls.
The mean (SD) age at which height was
recorded for cases was 66.4 (10.9) years and
for controls was 66.4 (10.7) years. The mean
(SD) recorded height for women was 159
(7) cm and for men was 173 (7) cm. The
distribution of cases and controls by height
quintile are shown in table 1. For controls with
available smoking data 1016 (27%) were
current smokers and 2736 (73%) were non-
current smokers, and for cases 178 (29%) were
current smokers and 446 (71%) were non-
current smokers.11 There was no evidence of an
association between smoking status and height
for cases (p=0.3) or controls (p=0.8). We were
able to calculate a body mass index for 568
cases (64%) and 3649 controls (62%) and
found evidence of a positive association be-
tween quintile of body mass index and cryp-
togenic fibrosing alveolitis (odds ratio (OR) per
increase in quintile of body mass index 1.08,
95% CI 1.01 to 1.16). Before the first recorded
diagnosis of cryptogenic fibrosing alveolitis sig-
nificantly more cases had been prescribed an
oral corticosteroid than controls (325 (37%)
versus 436 (7%), p<0.001). There was some
evidence of an inverse association between
height and exposure to oral corticosteroids for
controls (p=0.001) but not for cases (p=0.2).

An inverse association was found between
quintile of adult height and cryptogenic fibros-
ing alveolitis (OR per increase in height
quintile 0.93, 95% CI 0.86 to 0.99). This odds
ratio was not altered by the addition of either
the smoking variable (OR 0.93, 95% CI 0.87 to
1.00) to the model, but some minor attenuation
did occur after adjust-
ment for oral corticosteroid exposure (OR
0.94, 95% CI 0.88 to 1.02) (table 2). There
was no significant interaction with age (p=0.3).
Evidence of significant effect modification by
sex was observed (p=0.048; table 2) such that
the effect of height was strong in women (OR
0.85, 95% CI 0.75 to 0.97) and absent in men
(OR 1.00, 95% CI 0.91 to 1.09) (table 2). In
women the odds ratio for the shortest quintile
compared with the tallest was 0.50 (95% CI
0.27 to 0.90) (table 2). When height was mod-
eled as a continuous variable for women the
odds ratio per 10 cm increase in height was
0.74 (95% CI 0.57 to 0.97).

Discussion
The results of our study provide the first
evidence that there may be an inverse associa-
tion between adult height and the risk of
cryptogenic fibrosing alveolitis. This effect was
strongest in women in whom there was a dou-
bled in risk in the shortest quintile compared
with the tallest, and a 50% increase in risk with
each 10 cm decrease in height.

The GPRD is the largest primary care data-
base in the world12 and its size means that it is
able to yield large numbers of cases even for
uncommon conditions. However, since the
data are not collected as part of a research
study, the accuracy of recorded diagnoses
requires confirmation and, for this reason, we
have previously tested the validity of a diagno-
sis of cryptogenic fibrosing alveolitis in the
GPRD and found it to be high.13 We did not
attempt to validate height measurements but,
since the error associated with these data is
likely to be random, its effect will tend to dilute
any association between height and disease.

The roles of bias and confounding need con-
dereration. The main potential biases in this
study are ascertainment bias and reverse
causation. An ascertainment bias may explain
the positive association between body mass
index and cryptogenic fibrosing alveolitis, since
obesity may precipitate presentation either by
reducing lung volumes13 or increasing respira-
tory symptoms.14 It is also possible that an
ascertainment bias explains the independent
inverse association between height and cryp-
togenic fibrosing alveolitis. For example, if the
symptoms associated with cryptogenic fibros-
ing alveolitis are more closely correlated with
absolute rather than relative lung volumes, then
shorter people will be more likely to present
than taller people because they have smaller
lungs in the first place. Reverse causation
would occur if cryptogenic fibrosing alveolitis
cal caused loss of height rather than the other way
round. It has previously been suggested that

**Table 2** Association between quintile of height and cryptogenic fibrosing alveolitis overall and separately for men and women

<table>
<thead>
<tr>
<th>Height quintile</th>
<th>Overall Odds ratio*</th>
<th>95% CI</th>
<th>Men Odds ratio*</th>
<th>95% CI</th>
<th>Women Odds ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (shortest)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.77</td>
<td>0.62 to 1.09</td>
<td>0.80</td>
<td>0.53 to 1.21</td>
<td>0.67</td>
<td>0.42 to 1.07</td>
</tr>
<tr>
<td>3</td>
<td>0.77</td>
<td>0.53 to 0.93</td>
<td>0.83</td>
<td>0.58 to 1.20</td>
<td>0.67</td>
<td>0.39 to 1.14</td>
</tr>
<tr>
<td>4</td>
<td>0.79</td>
<td>0.57 to 1.03</td>
<td>0.98</td>
<td>0.66 to 1.47</td>
<td>0.54</td>
<td>0.32 to 0.92</td>
</tr>
<tr>
<td>5 (tallest)</td>
<td>0.76</td>
<td>0.54 to 0.99</td>
<td>0.92</td>
<td>0.62 to 1.37</td>
<td>0.50</td>
<td>0.27 to 0.90</td>
</tr>
<tr>
<td>Odds ratio per increase in height quintile</td>
<td>0.94</td>
<td>0.88 to 1.02</td>
<td>1.00</td>
<td>0.91 to 1.09</td>
<td>0.85</td>
<td>0.75 to 0.97</td>
</tr>
<tr>
<td>Test for trend</td>
<td>0.12</td>
<td></td>
<td>0.9</td>
<td></td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratio adjusted for oral corticosteroid exposure.
the kyphosis caused by severe chronic obstructive pulmonary disease (COPD) may explain in part the strong inverse relation between COPD mortality and adult height. A direct effect of cryptogenic fibrosing alveolitis on the thoracic skeleton seems unlikely, but our cases were more likely to receive corticosteroids than controls, suggesting that some of our cases were prevalent rather than incident cases. Although exposure to oral corticosteroids is likely to be a prevalent rather than incident cases. Although exposure to oral corticosteroids is likely to be a marker of more severe or aggressive disease, it may also lead to osteoporosis. In the event, adjustment for the effect of oral corticosteroid exposure in the analysis only slightly attenuated the effect of height. Since adult socioeconomic status is associated with adult height, it is a potential confounder for the association between adult height and cryptogenic fibrosing alveolitis. In the GPRD there are no data on adult socioeconomic status so we were unable to exclude this explanation for our findings. However, adjustment for the effect of current smoking habit, which is known to be associated with socioeconomic status in the UK, had no effect on the association between height and cryptogenic fibrosing alveolitis. Furthermore, other studies have found little evidence that adult socioeconomic status explains the relation between height and cardiovascular disease.

The finding of strong effect modification by sex was unexpected. This argues against an important influence of adult socioeconomic status and also reverse causation, but would be in keeping with an ascertainment bias since women have smaller lungs than men. Women develop connective tissue diseases more commonly than men, but it seems unlikely that women with cryptogenic fibrosing alveolitis will have a diagnosis of connective tissue disease missed or not recorded more often than female general population controls. Alternatively, it may be that exposure rates to other important causes of cryptogenic fibrosing alveolitis are higher in men than in women and are masking the effect of height. Although there are few data available on risk factors for cryptogenic fibrosing alveolitis, the main ones identified to date are occupational dust exposure and cigarette smoking, both of which are more common in men than in women.

Socioeconomic disadvantage in childhood has an important influence on growth and has been shown to be a predictor of adult height. Thus, one explanation for the inverse association between adult height and cryptogenic fibrosing alveolitis is that early life exposures such as nutrition, infection, or exposure to passive smoking increase the lifetime risk of developing chronic inflammatory diseases in general, and thereby increase the risk of developing interstitial lung diseases. Since alveoli start to develop in utero at about week 30 but continue to multiply and develop through early childhood, an important influence of early life experience on the subsequent risk of cryptogenic fibrosing alveolitis seems biologically plausible. The finding that lung fibrosis is more common in shorter than in taller chrysotile miners and millers also raises the possibility that early and late environmental exposures may interact in determining the risk of interstitial lung disease.

In summary, the finding of an association between adult height and cryptogenic fibrosing alveolitis raises for the first time the possibility that early life exposures may influence the lifetime risk of developing this chronic inflammatory disease. However, further research is required confidently to exclude confounding by adult socioeconomic status and ascertainment bias and to establish whether this effect is restricted to women.

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