Short papers

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 relation 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

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The registered mortality from cryptogenic fibrosing alveolitis has increased markedly during the second half of the 20th century[1 2] and the reasons for this are not clear. There is evidence from epidemiological studies that occupational dust exposures,[3–6] cigarette smoking,[4 7] and antidepressant use[8] 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.[9 10] 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.[11] Briefly, cases were identified using the GPRD, which is the largest primary care population database in the UK[12] 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.[11] 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[11]), body mass index, and oral corticosteroid use before the first recorded diagnosis of cryptogenic fibrosing alveolitis. Multiplicative terms were added as appropriate

Table 1 Distribution of men and women by quintile of height

Height quintile	*Height range for women (cm)*	*Female cases (n=214)*	*Female controls (n=1438)*	*Height range for men (cm)*	*Male cases (n=355)*	*Male controls (n=2231)*
1 (shortest)	122–154	58 (27%)	273 (19%)	125–167	101 (28%)	563 (25%)
2	155–157	62 (29%)	361 (25%)	168–171	49 (14%)	335 (15%)
3	158–161	32 (15%)	221 (15%)	172–175	79 (22%)	584 (26%)
4	162–165	37 (17%)	344 (14%)	175–179	58 (16%)	328 (16%)
5 (tallest)	165–188	25 (12%)	239 (17%)	180–201	68 (19%)	421 (19%)

to test for possible interactions with age (in tertiles) 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 between quintile of body mass index and cryptogenic 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 significantly 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 fibrosing 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) or the body mass index variable (OR 0.93, 95% CI 0.87 to 1.00) to the model, but some minor attenuation did occur after adjustment 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 modelled 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).

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

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

*Odds ratio adjusted for oral corticosteroid exposure.

Discussion

The results of our study provide the first evidence that there may be an inverse association between adult height and the risk of cryptogenic fibrosing alveolitis. This effect was strongest in women in whom there was a doubling 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 database in the world[12] 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 diagnosis of cryptogenic fibrosing alveolitis in the GPRD and found it to be high.[11] 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 consideration. 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 volumes[13] or increasing respiratory symptoms.[14] It is also possible that an ascertainment bias explains the independent inverse association between height and cryptogenic fibrosing alveolitis. For example, if the symptoms associated with cryptogenic fibrosing 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 caused loss of height rather than the other way round. It has previously been suggested that

the kyphosis caused by severe chronic obstructive pulmonary disease (COPD) may explain in part the strong inverse relation between COPD mortality and adult height.[10] 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 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,[9 10] 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,[15] 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.[10 16 17]

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[3–6] and cigarette smoking,[4 7] 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.[18] 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,[19] 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[20] 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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