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Low socioeconomic status is associated with worse lung function in the Danish cystic fibrosis population

To the Editor:

Low socioeconomic status is associated with worse lung function and greater risk of death in people with cystic fibrosis (CF) in the UK and USA, but there are no population level studies from other countries [1–4]. A feature of previous analyses of inequalities in lung function in CF by socioeconomic status has been the identification of a lung function deficit in more disadvantaged children, which is evident as soon as spirometry can be routinely undertaken at ~5–6 years of age [1, 3]. The finding of a fixed lung function deficit in the most deprived children in the early years of life has important policy implications, and suggests that deprivation has a detrimental effect on lung health in the early years of a child's life [5].

We questioned whether similar patterns were evident in other CF populations, so assessed the effect of socioeconomic status on lung function trajectory measured by forced expiratory volume in 1 s (FEV_1) % predicted in the Danish population. Therefore, we undertook a retrospective, longitudinal, cohort study of all children and adults with CF who had contributed lung function measures to the Danish CF registry between 1969 and 2010 who could be linked to the national level administrative registers.

Patients attending the two Danish CF centres (Copenhagen and Aarhus) were routinely seen every month in the outpatient clinic for evaluation of clinical status, pulmonary function and microbiology of lower respiratory tract secretions. It is estimated that coverage of CF patients resident in Denmark is almost complete from 1990, when CF care was centralised. This coverage and the unparalleled frequency of measurement make this a unique dataset for epidemiological research [6].

The primary outcome for the analysis was FEV_1 % predicted. Pulmonary function tests were performed according to international recommendations [7], measuring FEV_1 expressed as % predicted for sex and height using reference equations from WANG *et al.* [8] or HANKINSON *et al.* [9].

The primary exposure of interest was an individual measure of parental socioeconomic status. Data linkage facilitated collection of data on highest parental education level at birth for each child born with CF, measured using the International Standard Classification of Education (ISCED) score. Individuals were coded as having low socioeconomic status if their highest educated parent had basic school level education up to grade 10 (ISCED 1).

We first assessed the association between this binary socioeconomic status measure and the mean FEV_1 % predicted profile over time, fitted as a linear time trend with a change point, whilst adjusting for birth cohort, sex and genotype (distribution of ΔF508 alleles) (baseline model). We then added clinical characteristics in the final adjusted model (*Pseudomonas aeruginosa* status, pancreatic status and CF-related diabetes). We used a mixed effects model with longitudinally structured correlation, previously developed to analyse this dataset [6]. This approach provides a more realistic estimate of the FEV_1 % predicted trajectory of people with chronic lung disease by acknowledging the imprecision in individual measurements and the correlation structure of repeated measurements on the same individual over time. We estimated model parameters by maximum likelihood, using generalised likelihood ratio statistics to compare nested models, and Wald statistics to test hypotheses about model parameters [10]. The study was approved by the Danish Data inspectorate (Datatilsynet).

The linked dataset contains 65 729 lung function measures (22% low parental education *versus* 78% high education) on 442 patients (21% low *versus* 79% high education) seen between 1969 and 2010 in Denmark. The follow-up rates were similar in the two groups. In terms of the characteristics of the population stratified by level of parental education, the distribution of ΔF508 alleles was similar in each group, as was the median age at diagnosis. However, the low parental education group contained a greater proportion of females (42% in the low parental education group *versus* 51% in the high parental education group), more patients who died during follow-up (24% *versus* 17%), and more patients who developed chronic *P. aeruginosa* infection (50% *versus* 42%) and CF-related diabetes (35% *versus* 23%).

There was no evidence to suggest a non-linear age effect in the longitudinal model; therefore, we modelled the population average as a straight line. The difference in average annual rate of decline FEV_1 (% per year) was -0.32 (95% CI -0.57– -0.07)% predicted in the baseline model and -0.30 (95% CI -0.38– -0.22)% predicted comparing low *versus* high educational status groups. In contrast, the onset of *Pseudomonas* acquisition was associated with an independent effect size of -0.50 (95% CI -0.57– -0.42) percentage points per year.

There was no statistically significant difference in the level of FEV_1 % predicted at 6 years of age between different socioeconomic status groups. Overall the low parental educational level was associated with a change in FEV_1 % predicted of -0.5 (95% CI -0.58– -0.39) percentage points per year after adjustment for demographic, genetic and clinical factors (fig. 1).

This analysis confirms that people with CF from more disadvantaged backgrounds have worse lung function, even in the context of a well-developed Danish health and welfare system. A key strength is the use of a precisely recorded individual level measure of socioeconomic status, facilitated by data linkage systems in Denmark, and the long period of follow-up.

This is the first population level study to clearly demonstrate a difference in the longitudinal rate of decline of lung function in CF on the basis of socioeconomic status, but in contrast to previous studies there was no evidence of a significant social difference at 6 years of age. In the UK people from the most deprived areas have significantly worse lung function (FEV_1 % predicted -4.12 (95% C1 -5.01– -3.19) percentage points) at 5 years of age, but the social gap in FEV_1 % predicted did not increase over time. By contrast, in the analysis

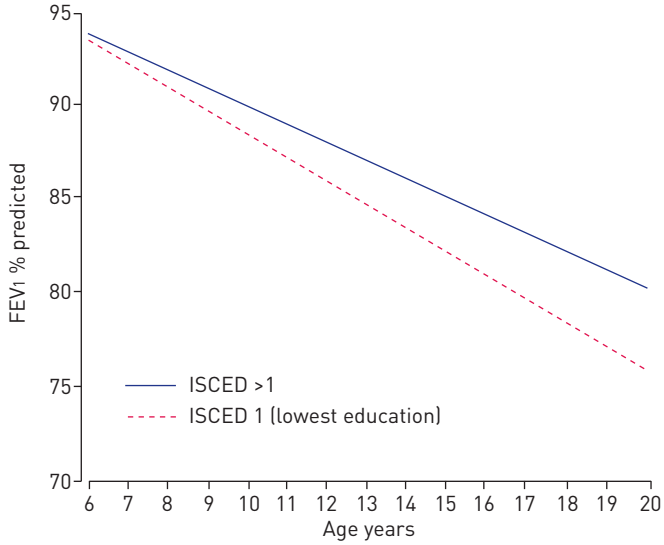

FIGURE 1 The effect of socioeconomic status as measured by parental education level on the mean forced expiratory volume in 1 s (FEV1) trajectory in children with cystic fibrosis in Denmark. Trajectories plotted with other covariates remained constant for a person born in the 1988–1998 cohort. ISCED: International Standard Classification of Education.

presented here, an equivalent gap of four percentage points between the most and least advantaged groups (on the basis of parental education) develops in Denmark at ~17 years of age. In the cross-sectional study of US data by SCHECHTER *et al.* [1], large inequalities in FEV1 % predicted by Medicaid status were evident at 5 years of age (9% difference), and these widened slightly up to 20 years of age. In their longitudinal US study, O'CONNOR *et al.* [2] found a difference of 5.5% between the most and least deprived income quintiles, which did not increase significantly over time.

There are several possible explanations for the differences between the studies. Methodological differences between these studies mean that direct comparison between the UK, USA and Denmark on the magnitude of the deprivation gap in lung function is inappropriate since the socioeconomic exposure measures used are different. The UK and US studies used area-based measures of deprivation or income, whereas this study used a precise individual level measure of maternal educational status. Furthermore, the high frequency follow-up in this unique Danish dataset has allowed us to fit a more sophisticated model, which we believe leads to more efficient estimation of the rate of lung function decline in Denmark [6].

However, the differences may reflect substantive societal level differences between Denmark, the UK and the USA, or differences in CF care. For instance we can speculate that the Danish welfare system, coupled with lower levels of child poverty, and universal access to high quality healthcare may reduce social differences in outcomes in early childhood [11]. Furthermore, the approach to CF care in Denmark, characterised by monthly follow-up and aggressive treatment of infections, may protect the most disadvantaged in the early years. We can further speculate that the emergence of individual level factors, such as disease self-management, may play more of a role in later life, and may account for the deterioration in lung function seen in more disadvantaged children at older ages in Denmark.

Low socioeconomic status can damage lung function in the early years, and can also lead to an increased rate of decline over the longer term. This suggests that environmental and social factors have an important influence on lung function in people with CF, which act across the life course, starting from an early age [3, 12]. Tobacco smoke exposure may be an important mediator of the relationship between socioeconomic status and adverse outcomes in CF, since there are striking and persistent differences in smoking prevalence by socioeconomic status in the general population in Denmark [11] and the UK [5], and environmental tobacco smoke exposure is associated with poorer growth and lung function in CF [13]. Policies should focus on providing additional support to children and adults with CF from more disadvantaged backgrounds over the life course, with a focus on getting things right in the early years [14].

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Low socioeconomic status is associated with worse lung function decline in the Danish CF population http://ow.ly/zUDsH

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The impact of novel tests for tuberculosis depends on the diagnostic cascade

To the Editor:

At least 3 million people with active tuberculosis (TB) are missed by national systems every year. Reaching these individuals is a critical priority [1]. Novel molecular diagnostics, notably Xpert MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) [2, 3], are important tools in this effort. Over 6 million Xpert cartridges have been procured worldwide since late 2010 [4] but two recent randomised trials in southern Africa [5, 6] suggest that Xpert, despite high sensitivity, may not significantly reduce morbidity and mortality. It is therefore useful to demonstrate how TB diagnostics function not in isolation but rather as part of a "diagnostic cascade."

We therefore adapted a transmission model of diagnostic testing among adults with active TB in Southeast Asia [7]. This model categorises a high-burden population into subpopulations characterised by TB status, HIV status and access to TB care. Parameter values, available in the original publication, are consistent with