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Growing old with cystic fibrosis – The characteristics of long-term survivors of cystic fibrosis

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Received 14 September 2007; accepted 8 October 2008
Available online 20 November 2008

KEYWORDS

Ageing;
Cystic fibrosis;
Longevity;
Survival

Summary

Background: The proportion of patients with cystic fibrosis (CF) who are middle-aged is increasing – and is likely to continue to do so. We surveyed a population of long-term CF survivors to assess their burden of illness and profile their disease characteristics.

Methods: A case series ($n = 112$) of patients from one specialist centre who had reached their 40th birthday without transplantation. Hospital records and annual review data were examined.

Results: The median age of the group was 43.1 years (range 40–71.1); 57% were men. 68% were diagnosed before 16 years of age. 30% were $\Delta F508/\Delta F508$, 76% having at least one $\Delta F508$ allele. When compared with the total adult CF population, the older patients were significantly less likely to have a $\Delta F508$ mutation or colonisation with *Stenotrophomonas maltophilia* and MRSA; but more likely to have pancreatic sufficiency, colonisation with *Pseudomonas aeruginosa* or allergic bronchopulmonary aspergillosis. On average they required less than one hospital admission a year; lung function and body mass index were relatively well preserved. Many were married and working.

Conclusions: We describe one of the largest surveys to date of CF patients aged more than 40 years. The full spectrum of disease is represented in this population and, importantly, 30% are $\Delta F508$ homozygous. Provision needs to be made for the healthcare needs of this increasing population of older patients.

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Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; BMI, body mass index; CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; MRSA, methicillin resistant *Staphylococcus aureus*; RBH, Royal Brompton Hospital.

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Introduction

Cystic fibrosis (CF) causes premature death, usually as a result of recurrent pulmonary infections progressing to respiratory failure. Despite the lack of any cure, survival rates have progressively increased since CF was first identified as a specific disease entity in 1938 - when over 70% patients died in their first year of life.¹ The current median survival is 36.8 years² and children born in the 2000s are now predicted to have a median survival into their 50s.³ Importantly, in many countries there are now more adults with CF than children.⁴ Consequently, increasing numbers of CF adults reaching middle age or older are predicted for the future.

The explanations for improved survival are complex and likely to be influenced by clinical characteristics (genetic and non-genetic), healthcare provision, the environment and socioeconomic factors.⁵ The term 'CF' covers a spectrum of disease, now sub-classified into classic (or typical) and non-classic (or atypical) disease.⁶ The diagnosis of classic CF is usually straightforward, whereas non-classic CF can be a diagnostic dilemma, characterised by an equivocal (or normal) sweat chloride and, in the absence of confirmatory genotyping, requiring further quantification of CF transmembrane conductance regulatory (CFTR) function. Patients with non-classic CF often have milder symptoms, are predominantly pancreatic sufficient, usually have a better prognosis - and may be diagnosed relatively late in life.⁷⁻⁹ Consequently, they may represent a significant proportion of long-term survivors, especially as there is now increased awareness of atypical disease amongst both CF and non-CF specialists.

Some hold that survival rates are being significantly skewed by patients with non-classic disease. Experience in our centre suggested that this was not necessarily the case since we had observed that many patients with classic disease were surviving into their 40s. There are few descriptions of patients who are approaching and surpassing this age; most are case reports^{10,11} but one study of 55 patients concluded that late diagnosis is a characteristic of many long-term survivors of CF.¹²

In light of the paucity of information on this CF population, we surveyed the older patients registered with our specialist centre, the largest survey of such patients to date. We hypothesised that this group would predominantly have rare (and mild) genotypes, have been diagnosed in adulthood and be in relatively good health with few complications.

Materials and methods

Subjects

Since 1965 details of all patients referred to the Royal Brompton Hospital (RBH) and confirmed to have CF have been entered onto a database. The diagnosis is based on clinical features and a positive sweat sodium (>70 mmol/L) or chloride (>60 mmol/L) or, in cases with a borderline sweat test result, the presence of a known disease-causing mutation on each CFTR gene or of an abnormal nasal

potential difference measurement. Data are updated each year at annual review.

For this survey, we identified all patients who had, by October 31st 2004, reached 40 years of age (the 95th age centile^{4,13}) without organ transplantation. From a total of 885 patients on the database 112 were thus eligible for this survey. Six had received lung transplants after the age of 40; information for them was used only up to the date of transplant.

Study design and methods

We collected, from clinical notes and annual review records, the following information: age by October 31st 2004 or of death if earlier, genotype (where available), age and clinical presentation at diagnosis. Sputum microbiologies were based on the most recent pathogen present in sputum on a continuous basis (>75% cultures over the last year of records). CF associated complications were recorded (pancreatic status, history of pneumothorax or major haemoptysis, CF related diabetes (CFRD), allergic bronchopulmonary aspergillosis (ABPA), distal intestinal obstruction syndrome (DIOS) and CF liver disease) as were other important medical conditions.

The weight, height, body mass index (BMI, kg/m²), forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were recorded at 5-year intervals from the age of 35 years until death or the end of the study period. FEV₁ and FVC were recorded on a Vitalograph spirometer and expressed as percentages of predicted normal values for age, sex and height.¹⁴ The total number of courses of intravenous antibiotics and hospital admissions was recorded from the age of 35 years until death or the end of the study period. Yearly averages were calculated for each five-year period.

These data were compared with the entire UK adult CF population⁴ or, where comparative figures were not available, with information from the US Cystic Fibrosis Foundation (CFF) patient registry.¹³ The reference populations were added to give readers better insight to the overall profile of adult CF on a national level along with the in depth profile we describe in our centre population. In some categories data were not available on all cases or for every five-year period. Differences between our group and the reference populations were tested by Fisher's exact test. Informed written consent was obtained from all patients for their anonymised data to be included in the database for research purposes.

Results

The entire adult (16+ years) UK CF population in 2003 comprised 3989 patients; the majority (54%) was 16-25 years of age and 17% were older than 35 years.⁴ In the present study we describe the characteristics of 112 patients over 40 years of age. Sixty four (57%) were male, a proportion no different from that in the entire adult UK CF population (56.2%, $p = 0.92$). The median age at death or at the end of the study period was 43.1 years (range 40.0-71.1) - a figure very similar to the median age of death (42.8 years). Twenty eight percent were diagnosed in

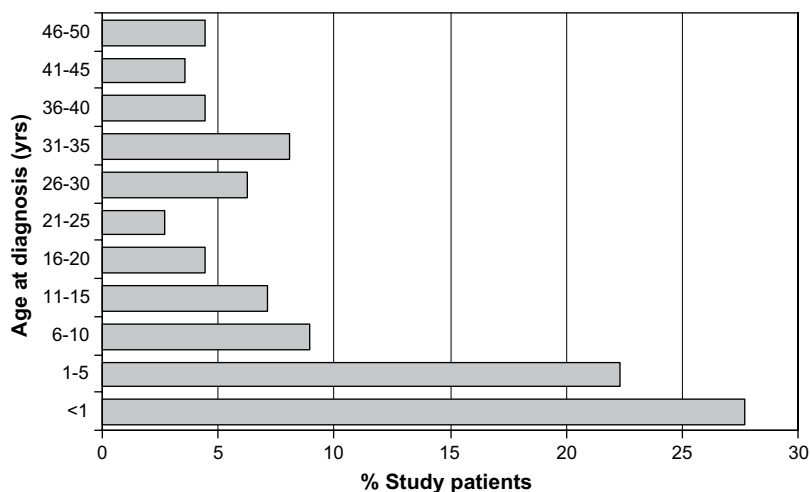


Figure 1 Age at diagnosis.

their first year of life and 32% after 16 years of age (Fig. 1). In the UK CF population, 12% of new CF diagnoses in 2003 were made after age 16, a proportion significantly lower than in our group ($p < 0.001$).

The most common clinical presentations leading to diagnosis were respiratory disease (46%), followed by malabsorption (28%) and failure to thrive (24%). Fifteen percent were initially investigated following diagnosis in a relative. Less common presentations included rectal prolapse (4%), meconium ileus (4%), DIOS (2%), recurrent sinusitis (1%) and polyarthropathy (1%).

Genotype was available for 93 (83%) patients. Thirty percent ($n = 34$) were homozygous for the $\Delta F508$ mutation, a figure significantly lower than that for the total UK adult CF population of 50% ($p < 0.001$) (Table 1). Although 12 different mutant allele combinations were present, the majority (76%) carried at least one $\Delta F508$ mutation, a proportion a little lower than in the UK CF population (85%, $p = 0.03$). Of the known $\Delta F508$ compound heterozygotes (ie. $\Delta F508$ /other; $n = 16$), the second mutation was mild in four patients – R117H ($n = 3$) and R347P. The remaining second mutations were G551D ($n = 4$), G542X ($n = 3$), N1303K ($n = 2$), G85E ($n = 1$), 1717 – 1G → A ($n = 1$) and 621 + 1G → T ($n = 1$). Among those diagnosed after 16 years of age, 8% ($n = 3$) were homozygous for $\Delta F508$ and 67% were heterozygous ($n = 24$).

Table 1 The genotype of the study group compared with the entire UK adult (16+ years) CF population.

Genotype	Number of patients	Study group (%) ($n = 112$)	UK reference population (%) ($n = 3989$)	p value
$\Delta F508/508$	34	30	50	<0.001
$\Delta F508/N$	36	32	13	<0.001
$\Delta F508/other$	16	14	22	0.062
Other/N	5	4	2	0.095
N/N	1	1	3	0.378
Other/Other	1	1	4	0.095

N = unidentified gene, other = any identified CF allele that is not $\Delta F508$.

Sputum cultures were varied with a large number of different pathogens; often more than one pathogen was present (Table 2). *Pseudomonas aeruginosa* was the most

Table 2 The disease characteristics of the study group.

Disease characteristics	Study group (%)	Reference population - % (35+)	p value ^a (35+)
Organism in sputum			
<i>P. aeruginosa</i>	76	63 (51)	0.005 (<0.001)
<i>S. aureus</i>	48	24 (25)	<0.001 (<0.001)
<i>H. influenzae</i>	17	6 (4)	<0.001 (<0.001)
<i>B. cepacia</i>	9	6 (6)	0.675 (1.0)
<i>S. maltophilia</i>	2	11 - US	0.008
MRSA	3	11 - US	0.024
<i>Aspergillus fumigatus</i>	3	6	0.29
Complication			
Pancreatic insufficiency	82	90 - US	0.01
DIOS	36	28	0.105
CFRD	27	21 (33)	0.197 (0.238)
Significant haemoptysis	14	9 - US	<0.001
CF Liver disease	14	20	0.147
Pneumothorax	11	7 - US	0.195
Nasal polyps	14	4	<0.001
ABPA	10	3	0.002
Osteoporosis	8	10 - US	0.632
CF arthropathy	3	5	0.361

^a Study group was compared with the entire UK adult CF population (16+ years and 35+ years of age where stated) unless stated as US which was taken from the CFF registry (adults, 18+ years) and published pneumothorax²⁹ and haemoptysis data.³⁰ Definition of complications: pancreatic insufficiency - taking pancreatic enzymes, CFRD - taking hypoglycaemic agent (insulin or oral agent), DIOS and ABPA - clinical diagnoses, CF liver disease - abnormal liver enzymes with no other precipitating cause, significant haemoptysis - >100 mls blood in one episode and pneumothorax - all types.

Table 3 Period prevalence of other medical conditions present in the study population.

n (%)	8 (7)	6 (5)	4 (4)	3 (3)	2 (2)	1 (1)
Medical condition (ever)	Depression	GORD	Malignancy ^a Epilepsy	Cataracts	Retinopathy CVA Renal stones Hypertension	IHD Renal impairment Hyperparathyroidism Rheumatoid arthritis Crohns disease OSA

^a Malignancies were pancreatic, breast, colonic and chronic lymphocytic leukaemia. GORD = gastro-oesophageal reflux, CVA = cerebrovascular accident, IHD = ischaemic heart disease and OSA = obstructive sleep apnoea.

common pathogen (isolated in 75% of men and 83% of women), followed by *Staphylococcus aureus* and *Haemophilus influenzae*. Three percent ($n = 3$) cultured non-tuberculous mycobacteria.

The most common complication after respiratory infection was pancreatic insufficiency, followed by DIOS and CFRD (Table 2). Of the patients diagnosed after 16 years of age, 56% were pancreatic insufficient. The median age of diagnosis of diabetes was 35 years (range 10–57). Other medical conditions were not common (Table 3).

There was wide variation in the patients' BMI (Fig. 2) although median values were generally within normal limits (20–25 kg/m²). FEV₁ was affected more severely than FVC but both were also relatively constant across the period of measurement (Fig. 3). The BMI and FEV₁ for the entire adult UK CF population in 2003 were very variable but the majority ($n = 1562$; 64%) had a BMI between 19 and 25 kg/m² and 1247 (52%) had an FEV₁ between 50 and 89% predicted.⁴

Hospital admissions and courses of intravenous antibiotics closely correlated with each other; the average annual rate of admission to hospital and of intravenous antibiotic courses was less than one per year (Fig. 4). At 40 years of age, those patients who were homozygous for $\Delta F508$ had a median BMI of 20.9 kg/m² (range 17.4–28.7) and a median FEV₁ of 53.2% predicted (range 16–100%). In the five years leading up to their 40th birthday they required on average 0.7 (range 0–2.6) courses of intravenous antibiotics and 0.4 (range 0–1.6) admissions per year.

Fifty eight percent ($n = 65$) of the patients were married, 39% ($n = 44$) were in full time employment and 11% ($n = 12$) were working part time. 23 (21%) patients (17

women) had biological children. A further nine (8%) patients had adopted or fostered a child.

Of the 112 patients surveyed 28 (25%) had died. Causes of death included respiratory failure ($n = 16$), massive haemoptysis ($n = 2$), metastatic pancreatic carcinoma ($n = 1$), gastrointestinal bleeding ($n = 1$) and suicide ($n = 1$).

Discussion

We describe here the largest survey of older patients with CF, assessing some of their clinical characteristics and the burden of their illness. A high proportion had features suggestive of classic disease with 82% of them pancreatic insufficient, 30% homozygous for $\Delta F508$ and 68% diagnosed before their 16th birthday. Lung function and BMI were relatively well preserved across the group and the average number of hospital admissions and intravenous antibiotics courses was low, suggesting that disease burden was perhaps not as high as initially thought.

These findings raise a number of important issues, including the recognition of significant disease heterogeneity in long-term survivors. This is important as many of the factors present in this study population are thought to be indicators of poor prognosis; it must be presumed that other, more important factors have influenced long-term outcome. It is also noteworthy that the patients represented in this study had to be born before November 1964 to fulfil our age criterion; of those diagnosed as babies or children, the reported prognosis would have been grave

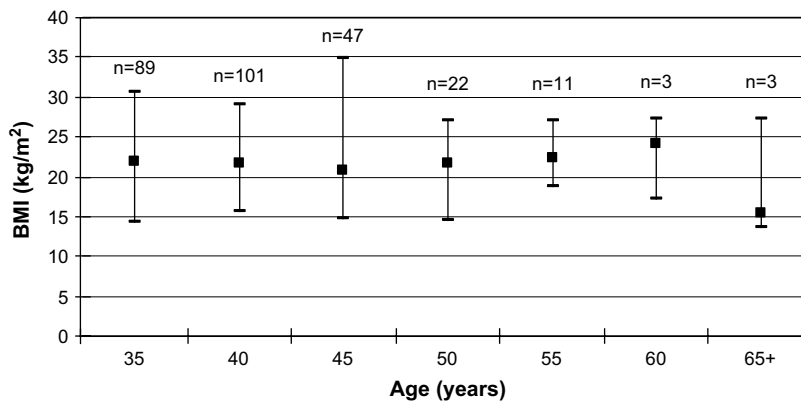


Figure 2 Median BMI values (range) at 35 years onwards.

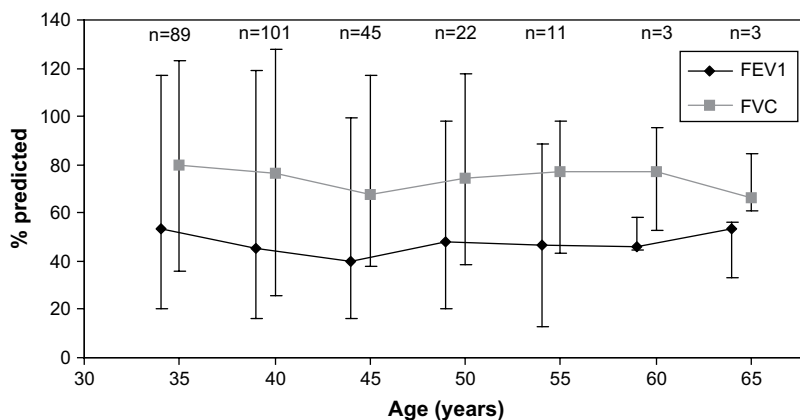


Figure 3 Median lung function (range) at 35 years onwards.

(median survival <20 years before 1970s¹⁵). The proportion of patients who were homozygous ΔF508 was 30% which is lower than in the entire adult CF population but a demonstration that even patients with the most common ‘severe’ mutation can achieve long-term survival.¹⁶ Additionally, of the ΔF508 compound heterozygote patients, only 25% of those had a ‘mild’ second mutation. This serves to highlight the complexity of CF with its lack of genotype–phenotype correlation and considerable variability in outcome.

P. aeruginosa in sputum is reported to be associated with a worse prognosis¹⁷ but was not uncommon in this group. This apparent paradox may have been due to proportionally less mucoid strain¹⁸ and other factors associated with a worse outcome such as earlier acquisition.¹⁹ Female sex is also considered a worse prognostic factor in the context of *P. aeruginosa* infection²⁰ but we found that rates of this infection were higher in women. High rates of *S. aureus* and *H. influenzae* were found in our study group relative to the general adult CF population. These organisms are usually acquired in childhood and *H. influenzae* often disappears after this period. The impact of these

bacteria on disease progression in the older patient group is therefore not clear, although their pathogenicity is debatable in CF.²¹ We found, in comparison to the general adult CF population, low rates of MRSA and *Stenotrophomonas maltophilia*, which may relate to local infection control measures and/or lower antibiotic availability in their former years, although the clinical significance of MRSA and *S. maltophilia* in CF is not clear.^{22–24} The prevalence of non-tuberculous mycobacteria was very low in the study group. This contrasts with a previous study which reported a high rate of isolation of non-tuberculous mycobacteria in patients aged over 40 years.¹² The reason for this difference is not clear, although, in part, may be explained by ascertainment bias.

The prevalence of CFRD is known to increase with age²⁵ and has been reported to be as high as 32% in patients aged >25 years.^{26,27} It is usually associated with a worse prognosis, especially in female patients.^{28,29} 27% of our population had CFRD. This was not significantly higher than in the entire UK adult CF population (21%) which, in part, may be explained by the lower rate of pancreatic insufficiency

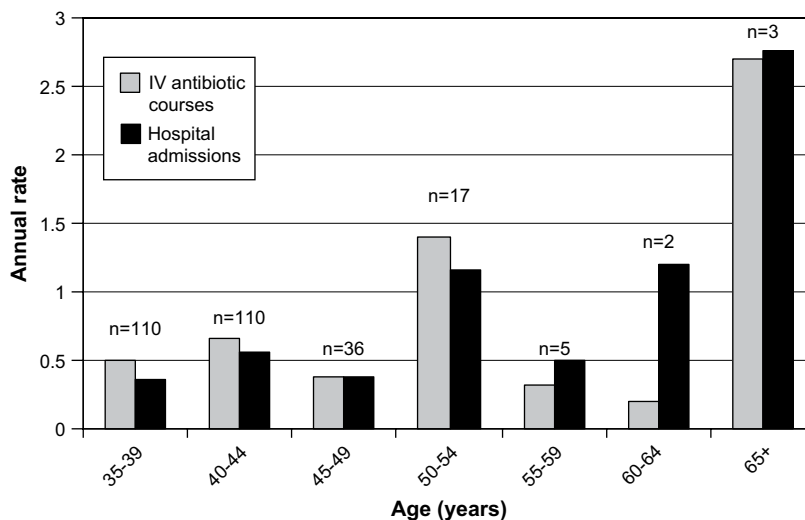


Figure 4 Average annual rate of intravenous antibiotic courses and hospital admissions for each 5-year period from 35 years onwards.

in our population. The high prevalence of ABPA was unexpected as it is usually associated with worse lung function. It is possible that these patients were reviewed more frequently and more closely monitored which may have conferred a more positive outcome; alternatively a diagnostic time bias may have existed as they had a longer period of time available for the diagnosis to be made. Other CF related complications were found at similar rates to the entire adult CF population, including DIOS, CF liver disease, pneumothorax, osteoporosis and CF arthropathy, although numbers in some groups were small. Directly comparing these factors is fraught with difficulty due to differences in definitions between databases. For example, based on the UK database, the prevalence of pneumothoraces is only 1% as it includes only those instances requiring a chest drain. However, a recent review of all types of pneumothoraces³⁰ based on 28,191 patients in the US CFF database confirmed a prevalence of 7.2% in the adult population (18+ years). Based on this value there was not a difference between the two groups.

One of the striking features of this study is that physical parameters were relatively well preserved at each 5-year increment from age 35 years. Courses of IV antibiotics and hospital admission also remained low over the same age range. These figures may be an underestimate since while we know that the majority of patients were solely treated at a single specialist centre, some will have been admitted to other hospitals and received antibiotic courses elsewhere without our knowledge. The prevalence of other medical conditions, including hypertension and malignancy, shows that common age-related illnesses are beginning to emerge in CF but at present these rates are low. As survival increases, they are likely to become more common and require increasing access to more medical services. This study also shows that having CF does not preclude individuals from normal social interactions as many were married, employed and had children.

The only other study to assess a population of patients at this age concluded that patients diagnosed as adults differ distinctly from long-term survivors diagnosed as children, with less $\Delta F508$ homozygosity and less pancreatic insufficiency.¹² Our findings lend this description some support; of the patients diagnosed in adulthood, just 56% of our group were pancreatic insufficient and only 8% were homozygous $\Delta F508$. However our findings indicate also that increasing numbers of patients with features suggestive of classic disease are now reaching 40 years with reasonable lung function and BMI and relatively little use of hospital resources.

We compared our group with all adults with CF on a UK database - or where necessary an equivalent US database. Our study group of older patients is actually contained within the UK database but represents less than 3% of its population. We could not make comparisons with only the remaining 97% so the whole adult population was used, but any consequent error will have been very small. Additionally, we could not compare all our findings with CF patients over 40 years of age from other centres as very limited published data are available. Therefore, it is not possible to say if our findings are applicable to the adult CF population in general or are a centre-specific phenomenon. However, where available, a comparison

was also made with the UK CF population over 35 years of age and the results were unchanged. Further evaluation of older patients across Europe and North America is required to confirm if these findings can be generalised across the CF populations.

Cross-sectional studies of 'surviving' populations need to be interpreted with unusual care. It is wrong, for example, to assume that the characteristics of such a population reflect or are even related to the determinants of their longevity. Indeed the opposite is more likely to be true; that some of these characteristics are the result of such survival since their likelihood of occurrence can only increase with time. We did not set out to identify specific factors that determine longevity but to demonstrate that long-term survival can occur - and increasingly frequently does - even in patients traditionally thought to have a poor prognosis. Our findings confirm the complexity of CF and generate a number of important hypotheses. Is the variable outcome predominantly influenced by genetic factors, including modifier genes and variations in CFTR function, or are clinical factors such as BMI, lung function or CFRD equally, or more, important? Is there an optimal age to reach when the risk of a good outcome can be predicted with greater certainty? How have advances in CF therapies impacted long-term survival and how important are environmental factors? Such questions require very carefully controlled epidemiological studies of large populations of older patients and more precise assessments of CFTR function.

Conflict of interest statement

None of the authors of this manuscript have any potential conflicts of interest to declare, nor do they have any financial or personal disclosures.

Acknowledgements

The authors thank Michael Roughton for his statistical advice and also Marilou Balkin and Jennifer Welch for their assistance with the CF database.

References

1. Anderson DH. Cystic fibrosis of the pancreas and its relation to celiac disease. A clinical and pathological study. *Arch Dis Child* 1938;**56**:344-99.
2. Cystic Fibrosis Foundation. *Patient registry 2005 annual data report*. Bethesda, MD: Cystic Fibrosis Foundation; 2006.
3. Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *Eur Respir J* 2007;**29**:522-6.
4. UK Cystic Fibrosis Database. *Annual Data Report 2003*. University of Dundee; 2005.
5. Schechter MS. Non-genetic influences on cystic fibrosis lung disease: the role of sociodemographic characteristics, environmental exposures, and healthcare interventions. *Semin Respir Crit Care Med* 2003;**24**:639-52.
6. De Boeck K, Wilschanski M, Castellani C, et al. Cystic fibrosis: terminology and diagnostic algorithms. *Thorax* 2006;**61**:627-35.

7. Widerman E, Millner L, Sexauer W, Fiel S. Health status and sociodemographic characteristics of adults receiving a cystic fibrosis diagnosis after age 18 years. *Chest* 2000;**118**:427–33.
8. Gilljam M, Ellis L, Corey M, Zielenski J, Durie P, Tullis DE. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. *Chest* 2004;**126**:1215–24.
9. Gan KH, Geus WP, Bakker W, Lamers CB, Heijerman HG. Genetic and clinical features of patients with cystic fibrosis diagnosed after the age of 16 years. *Thorax* 1995;**50**:1301–4.
10. Hunt B, Geddes DM. Newly diagnosed cystic fibrosis in middle and later life. *Thorax* 1985;**40**:23–6.
11. Sanders JS, Pryor TD, Wedel MK. Prolonged survival in an adult with cystic fibrosis. *Chest* 1980;**77**:226–7.
12. Rodman DM, Polis JM, Heltshe SL, et al. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. *Am J Respir Crit Care Med* 2005;**171**:621–6.
13. Cystic Fibrosis Foundation. *Patient Registry 2003 Annual Data Report*; 2004. Bethesda, Maryland.
14. Gibson GJ. Standardised lung function testing. *Eur Respir J* 1993;**6**:155–7.
15. Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;**46**:881–5.
16. Correlation between genotype and phenotype in patients with cystic fibrosis. The cystic fibrosis genotype-phenotype consortium. *N Engl J Med* 1993;**329**:1308–13.
17. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* 2002;**34**:91–100.
18. Parad RB, Gerard CJ, Zurakowski D, Nichols DP, Pier GB. Pulmonary outcome in cystic fibrosis is influenced primarily by mucoid *Pseudomonas aeruginosa* infection and immune status and only modestly by genotype. *Infect Immun* 1999;**67**:4744–50.
19. Aebi C, Bracher R, Liechti-Gallati S, Tschappeler H, Rudeberg A, Kraemer R. The age at onset of chronic *Pseudomonas aeruginosa* colonization in cystic fibrosis – prognostic significance. *Eur J Pediatr* 1995;**154**:S69–73.
20. Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: *Pseudomonas aeruginosa* infection. *J Clin Epidemiol* 1995;**48**:1041–9.
21. Ericsson-Hollings A. *Serological markers of pulmonary infection in patients with cystic fibrosis*; 1987. Stockholm.
22. Miall LS, McGinley NT, Brownlee KG, Conway SP. Methicillin resistant *Staphylococcus aureus* (MRSA) infection in cystic fibrosis. *Arch Dis Child* 2001;**84**:160–2.
23. Thomas SR, Gyi KM, Gaya H, Hodson ME. Methicillin-resistant *Staphylococcus aureus*: impact at a national cystic fibrosis centre. *J Hosp Infect* 1998;**40**:203–9.
24. Steinkamp G, Wiedemann B, Rietschel E, et al. Prospective evaluation of emerging bacteria in cystic fibrosis. *J Cyst Fibros* 2005;**4**:41–8.
25. Moran A, Doherty L, Wang X, Thomas W. Abnormal glucose metabolism in cystic fibrosis. *J Pediatr* 1998;**133**:10–7.
26. Moran A, Hardin D, Rodman D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. *Diabetes Res Clin Pract* 1999;**45**:61–73.
27. Lannig S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: five year prospective study. *BMJ* 1995;**311**:655–9.
28. Finkelstein SM, Wielinski CL, Elliott GR, et al. Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;**112**:373–7.
29. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. *Diabetes Care* 2005;**28**:2141–4.
30. Flume PA, Strange C, Ye X, Ebeling M, Hulseley T, Clark LL. Pneumothorax in cystic fibrosis. *Chest* 2005;**128**:720–8.