Effects of social class, sex, and region of residence on age at death from cystic fibrosis

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Abstract

To determine the time trend in age at death from cystic fibrosis and the independent effects of social class, sex, and region of residence mortality data for England and Wales from 1959 to 1986 were analysed. Median age at death increased from 6 months in 1959 to 17 years in 1986 and was higher in most years from 1970 in male patients (by one to six years) and in social classes with non-manual occupations (by one to 12 years). Independent odds ratios for death above the median age for the year of death (calculated for years from 1974, when regions of residence were coded by regional health authority area) were 1.47 (95% confidence interval 1.16 to 1.87) in male compared with female patients and 2.75 (2.16 to 3.52) in non-manual compared with manual social classes. The independent odds of death at above the median age also varied significantly among regions of residence by a ratio of up to 2.67.

Social class, sex, and region of residence are all potential determinants of survival of patients with cystic fibrosis. Social class is particularly likely to confound the effect of management in specialist centres on survival.

Introduction

Thirty years ago most patients with cystic fibrosis were expected to die in infancy or childhood.^{1,2} Now most can expect to survive into adulthood.³⁻¹³ This dramatic change, attributed to developments in diagnosis and management of cystic fibrosis,¹⁴ has been particularly noticeable among patients attending centres specialising in caring for those with cystic fibrosis.^{7-12, 15-17} Consequently, many doctors support the expansion of the role of specialist centres.^{7, 9, 15}

Concentration of resources into specialist centres may be one means of providing the skill and support required in managing cystic fibrosis, but a disadvantage is that the clinics tend to be less accessible than more localised forms of health care. As a result the patients who attend specialist clinics may tend to be fairly affluent or more motivated to comply with treatment. One recent description of the characteristics of patients attending such a clinic in England clearly showed a social class bias, with 56% of patients coming from social classes I and II against an expected proportion of 20%.¹⁸ If social class is related to survival with cystic fibrosis then part of the apparently better performance of specialist clinics may be due to confounding by social class. The effect of social class has not, however, been controlled in comparisons of survival between clinic populations, and the extent of the effect of social class on survival with cystic fibrosis is not known.

The present study used data on mortality from cystic fibrosis in England and Wales to establish whether

social class is an independent determinant of age at death from cystic fibrosis and therefore a potential confounder of the effect of management in specialist clinics on survival. The study also documented time trends in age at death in England and Wales after 1959 and estimated the independent effects of patients' sex and the regional health authority in which they lived.

Methods

Mortality data for cystic fibrosis were obtained for England and Wales for 1959 to 1986 from the Office of Population Censuses and Surveys. Underlying cause of death, age at death, and sex had been coded throughout this period; social class from 1970; and regional health authority of usual residence from 1974.

Underlying cause of death was coded by the International Classification of Diseases (ICD) category applying to cystic fibrosis. From 1959 to 1967 this was category 587.2, which also included other diseases of the pancreas.¹⁹ In 1968 the diseases of the pancreas were assigned to category 577.9 and a code exclusive to cystic fibrosis was created, being 273.0 between 1968 and 1978 and 277.0 thereafter.^{20, 21} The distribution of ages at death from cystic fibrosis and from other diseases of the pancreas in categories 273.0 and 577.9 for the three years after the change in coding showed a clear age distinction between the categories, with only one death from cystic fibrosis occurring above and five deaths not from cystic fibrosis occurring below the age of 50.²²⁻²⁴ Deaths recorded before 1968 were therefore adjusted for the inclusion of deaths from other pancreatic diseases coded in the same ICD category by excluding deaths at or over age 50.

Age at death for people surviving beyond their first birthday was coded as age in years at the last birthday, and for those dying before 1 year in days for the first week, weeks for the first month, and months thereafter. Social class of those who died aged <16 was coded by the mother's occupation or, if the mother had no paid occupation, that of the father; for those who died aged ≥16 it was coded by their own occupation or that of the spouse. People in the armed forces were coded separately by codes that did not distinguish manual from non-manual occupations.

Data were entered into and analysed on mainframe computers at Nottingham University. Descriptive statistics were produced with the statistical package for the social sciences (SPSS X)²⁵ and logistic analyses with generalised linear interactive modelling (GLIM).²⁶ Social class was classified into non-manual and manual categories in all analyses. As the distributions of ages at death were not normal in any year and no single transformation achieved normality the data were described in terms of median age at death by year, sex, and social class. The independent effects of sex, social class, and region of residence on the odds of death at

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above the median age for the year of death were analysed in a multiple logistic regression analysis of the deaths that occurred after the introduction of the new regional health authority areas in 1974 with male sex, non-manual social class, and residence in the Northern Regional Health Authority as the reference point.

The median and 25th centile of the distribution of age at death were estimated for birth cohorts from 1959 from published numbers of live births in England and Wales by year,^{27,28} with the assumptions that one in 2500 liveborn infants would have cystic fibrosis,²⁹ that cystic fibrosis would be registered as the underlying cause of death in all of these cases, and that no deaths from other causes were misclassified in the registrations of death from cystic fibrosis.

Results

After the effect of including deaths from causes other than cystic fibrosis in ICD category 587.2 from 1959 to 1967 had been allowed for 4107 people (2069 boys or men and 2038 girls or women) in England and Wales were estimated to have died from cystic fibrosis from 1959 to 1986. The total number of deaths each year declined over the period (table I) and ranged from an estimated maximum of 185 in 1963 to a minimum of 94 in 1982. The distribution of age at death from cystic fibrosis changed with time, deaths before 1 year of age decreasing from 106 in 1959 to four in 1986. Median age at death increased from 6 months in 1959 to 17 years in 1986 (fig 1), and the range of age at death between the 25th and 75th centiles increased from 2 to 14 years. Median age at death was similar in the sexes until the 1970s but thereafter was higher in male patients in most years by one to six years (fig 2). From 1970 median age at death was higher in non-manual social classes than in manual classes in most years (fig 3) by one to 12 years.

After the introduction of coding of region of residence by regional health authority area in 1974 there were 1734 deaths from cystic fibrosis, for 160 of which no information on social class was known; a

TABLE I—Number of deaths by age and International Classification of Diseases (ICD) category 1959-86

	Age (years)												Total	Adjusted total*
	<1	1-	5-	10-	15-	20-	25-	30-	35-	40-	45-	≥50		
ICD category 587.2														
1959	106	44	18	4	2				2		2	17	195	178
1960	122	30	19	7	2				2		3	28	213	185
1961	97	30	10	8	2	1			1			18	167	149
1962	107	35	19	7	2	2					1	24	197	173
1963	102	50	19	9	1						1	15	197	185
1964	86	40	22	13	4	1	2		1			16	185	170
1965	73	31	20	10	8	2	2		1		1	13	161	148
1966	78	34	27	14	6	3	1				1	24	188	165
1967	63	28	28	15	8	3			1			11	157	147
ICD category 273.0														
1968	74	31	31	11	11			1					159	
1969	46	29	31	22	7	3	1						139	
1970	50	29	31	22	6	2	1					1	142	
1971	58	24	31	18	10	2	2	1				3	149	
1972	41	27	38	20	9	3	1	1				4	144	
1973	40	14	32	29	11	7	3	1				3	140	
1974	29	21	33	27	8	7	4				1		130	
1975	24	19	35	33	19	10	2					2	144	
1976	23	17	34	34	20	5	12						145	
1977	24	13	26	26	22	12	4	1					128	
ICD category 277.0														
1978	20	14	22	40	25	12	5					1	139	
1979	21	20	36	29	30	15	3	1	2			4	161	
1980	10	9	28	33	32	14	7	1				1	135	
1981	12	11	23	38	23	20	5	1				3	136	
1982	10	8	20	20	11	18	6					1	94	
1983	10	12	24	35	35	19	9	3					147	
1984	7	6	12	28	22	27	9	3	3			2	119	
1985	12	10	11	32	41	17	11		2		1	2	139	
1986	4	7	21	16	25	23	14		1		2		113	

*Excluding deaths of people aged ≥50.

FIG 1—Ages at death from cystic fibrosis in England and Wales 1959-86. ---=25th Centile, —=median,=75th centile

FIG 2—Median age at death from cystic fibrosis by sex in England and Wales 1959-86. $\triangle$ =Boys and men, $\blacktriangle$ =girls and women

FIG 3—Median age at death from cystic fibrosis by social class in England and Wales 1970-86. $\square$ =Non-manual occupations, $\bullet$ =manual occupations

further 290 subjects were coded as having no paid occupation and 20 as being in the armed forces; six had no area code. Thus there were complete data for 1258 deaths (605 boys or men and 653 girls or women). Occupation was coded as non-manual for 463 and manual for 763. For deaths coded by the occupation of the father or spouse the 25th, 50th, and 75th centiles of the distribution of ages at death in pooled data for 1974 to 1986 were all higher in non-manual than in manual categories (table II). For deaths coded by own class the 75th centile was higher for manual occupations. All 15 deaths coded by the occupation of the mother were in the non-manual category.

Independent odds ratios for death at age above the median for the year of death were 1.47 (95% confidence interval 1.16 to 1.87, $p<0.005$) for male compared with female patients and 2.75 (2.16 to 3.52, $p<0.0001$) for non-manual compared with manual social class.

After the effects of sex and social class had been allowed for there were significant differences ($p < 0.005$) in the odds of death at above the median age for the year among the areas of England and Wales, the maximum difference being a ratio of 2.67 between the Northern region and Wales (table III).

Estimated median survival based on estimates of the numbers of children affected by cystic fibrosis born each year increased from five years for the 1959 cohort to 15 years for children born in 1971. From 1972 less

than half of the estimated birth cohort for each year died from cystic fibrosis. The estimated 25th centile of the age at death in these cohorts increased from 5 months in 1959 to 10 years in 1976 (table IV).

Discussion

This study was conducted primarily to determine whether the effect of social class is likely to confound differences in survival between patients with cystic fibrosis cared for in a specialist clinic and those receiving care locally. Mortality data from the Office of Population Censuses and Surveys were chosen as they are the only population based data available for cystic fibrosis in England and Wales that include details of social class. Data on social class were available for a high proportion of deaths after coding began in 1970; an occupation code was present for 86% and non-manual or manual occupation could be identified for over 70%.

As cystic fibrosis was coded with other diseases of the pancreas before 1968 the numbers of deaths from cystic fibrosis each year from 1959 to 1967 were estimated by excluding deaths at age 50 or over. In the three years immediately after the segregation of deaths from cystic fibrosis into an exclusive code in 1968 the proportion of deaths misclassified by this process would have been less than 2% of the total; thus it is unlikely that the estimates of numbers and median age at death before 1968 were seriously distorted.

The extent to which the data comprise a complete record of mortality from cystic fibrosis is determined by the degree of misclassification, under-reporting and underdiagnosis of the disease. Misclassification of reported deaths from cystic fibrosis into other disease categories is unlikely to have been a major influence,¹⁶ but the degree of misclassification of deaths from other causes into the category for cystic fibrosis or of under-reporting or underdiagnosis of cystic fibrosis is less clearly established. In the present study the discrepancy between the expected number of children born with cystic fibrosis each year from 1959 to 1962 and the observed number of deaths from cystic fibrosis in the birth cohorts registered by the end of 1986 was about 20%, suggesting that unless these people are still alive, contrary to estimates of life expectancy at the time of birth,^{1,2} up to 20% in the early cohorts may have died with unrecognised or unreported disease.

The data were analysed by median age at death so that all information on social class of people who died after 1970 could be used. The alternative approach would be to use birth cohort analysis; the disadvantages of this method in the present study are that the analysis would be restricted to mortality at relatively early ages in the small numbers of deaths in people born after 1970; inclusion of the effects of region of residence would further restrict the analysis to those born after 1974; differences in existing methods of collecting data would mean that data for deaths and for the population at risk would not be reliably linked for social class; and cohort analysis requires an unsubstantiated assumption that the incidence of cystic fibrosis is the same in all social classes. A shortcoming of the approach used, however, was that the data did not include information on current survivors with cystic fibrosis, so that generalisation of the effects of social class, sex, and region of residence from the present study assumes that effects among those who died also apply to current and future survivors.

The most striking observation from the data is the increase in median age at death, from 6 months in 1959 to 17 years in 1986 (fig 1). The increase was apparently linear from the late 1960s. The estimates of survival in successive birth cohorts (table IV) show a similar trend, though these figures may be overestimates

TABLE II—Number of deaths among people with cystic fibrosis and 25th, 50th, and 75th centiles of distribution of ages at death in non-manual and manual social classes. Data are for 1974-86

	Social class	No of deaths	Age at death (years)		
			25th Centile	50th Centile	75th Centile
No who died aged < 16:					
Coded by father's occupation	{ Non-manual	327	4	9	12
	{ Manual	682	3	7	11
Coded by mother's occupation	{ Non-manual	15	15	15	15
	{ Manual	0			
No who died aged ≥ 16:					
Coded by own occupation	{ Non-manual	138	20	22	25
	{ Manual	64	19	22	28
Coded by spouse's occupation	{ Non-manual	16	24	26	43
	{ Manual	16	20	25.5	35

TABLE III—Odds of death from cystic fibrosis in England and Wales at above median age in any year 1974-86

	Estimate	Standard error	Odds ratio	χ^2	df
Intercept (male sex, non-manual social class, residence in Northern Regional Health Authority)	0.84	0.24			
Female sex	-0.39	0.12	0.68	9.9	1
Manual social class	-1.01	0.12	0.36	67.2	1
Region of residence				34.8	14
South East Thames	-0.13	0.30	0.88		
North East Thames	-0.20	0.29	0.82		
South Western	-0.21	0.33	0.81		
South West Thames	-0.37	0.36	0.69		
East Anglian	-0.39	0.39	0.67		
Wessex	-0.40	0.34	0.67		
West Midlands	-0.69	0.29	0.50		
Mersey	-0.89	0.34	0.41		
Oxford	-0.91	0.36	0.40		
Yorkshire	-0.92	0.32	0.40		
North Western	-0.93	0.30	0.39		
Trent	-0.93	0.31	0.39		
North West Thames	-0.96	0.32	0.38		
Wales	-0.98	0.34	0.38		

TABLE IV—Estimated number of births of infants with cystic fibrosis each year in England and Wales, number (percentage) of deaths from cystic fibrosis in each birth cohort, and estimated 25th and 50th centiles of ages at death by year of birth 1959-85

Year	Estimated No of births affected by cystic fibrosis*	No of deaths in cohort with cystic fibrosis (%)	Estimated age at death (years)	
			25th Centile	50th Centile
1959	300	216 (72)	0.4	5.0
1960	314	260 (82)	0.3	4.0
1961	325	256 (79)	0.6	8.0
1962	336	266 (79)	0.4	7.0
1963	342	244 (71)	0.5	9.0
1964	351	242 (69)	1.0	12.0
1965	346	195 (56)	2.0	16.0
1966	340	200 (59)	1.0	14.0
1967	333	184 (55)	3.0	17.0
1968	328	203 (62)	1.0	13.0
1969	320	141 (44)	6.0	>17.0
1970	314	136 (43)	5.0	>16.0
1971	314	157 (50)	5.0	15.0
1972	290	127 (44)	6.0	
1973	271	91 (34)	8.0	
1974	256	83 (32)	8.0	
1975	242	75 (31)	7.0	
1976	234	59 (25)	10.0	
1977	228	56 (25)		
1978	238	43 (18)		
1979	255	41 (16)		
1980	262	21 (8)		
1981	254	27 (11)		
1982	250	18 (7)		
1983	252	15 (6)		
1984	255	10 (4)		
1985	262	12 (5)		

*One birth in 2500.

because of underdiagnosis and under-reporting of cystic fibrosis. Several factors are thought to account for the increasing life expectancy, including improvements in the management of meconium ileus,^{5 7 11 30 31} the introduction of effective antibiotics for staphylococcal and pseudomonal infections and of vitamin and pancreatic enzyme supplementation,¹⁴ and the increased ascertainment of milder forms of cystic fibrosis in adults.^{2 3 32-36}

Since the mid-1970s median age at death has tended to be higher in male patients and in patients with non-manual occupations. The odds of death at above the median age for the year of death were independently related from 1974 to sex, social class, and region of residence. Some reports have noted significantly longer survival in male patients^{4 6 15} and others have not,^{4 11 13 31 37 38} perhaps because the difference in age at death (about two years in the present study) is fairly small. The reason for the male advantage is not clear, and confounding of increasing age at death with time makes it uncertain whether the increased survival in male patients is due to a differential effect of treatment or to more rapid deterioration in female patients after late childhood.³⁹

After the effects of sex had been allowed for social class had a strong and independent effect on age at death. The effect of social class in the present study is open to bias by reverse causation (that is, cystic fibrosis determining social class) and by confounding by the method of coding social class. Reverse causation is particularly likely in adults, who represent a success in survival, and may because of respiratory disability tend to select non-manual occupations. This influence will be offset to some extent by the fact that adults in manual occupations are likely to be those with the least disability and the best prognosis. For deaths under age 16 coding of social class by the mother's occupation may be associated with prolonged survival as mothers may be unlikely to take paid work of any category unless their child is old enough and well enough to attend school. Father's social class is likely to be the least biased indicator of family lifestyle but is available in data from the Office of Population Censuses and Surveys only if death occurred below age 16 and in the absence of a working mother.

The social class of most (83%) of those who died was coded by the father's or spouse's occupation; this showed a consistent trend towards a higher age at death in non-manual occupations (table II). In deaths coded for own occupation the age at death represented by the 75th centile was higher in the manual category, supporting the suggestion that adults who choose manual occupations tend to have a better prognosis. The small number of deaths with social class coded by the mother's occupation were all in the non-manual category, and age at death was higher than in groups coded by the father's occupation. This supports the association of working mothers with older children, and although the group was small, the fact that all of the mothers had non-manual occupations suggests that these older children tended to come from families of a higher social class. Thus despite the bias inherent in the methods of recording social class the consistent effect of social class suggests that the observed relation between higher social class and higher age at death is valid. The lower ages at death in the lower social classes may be caused either by a lack of resources to permit visits to hospitals or the local doctor or to provide medicines and dietary supplements, or by factors such as increased parental smoking, poor quality or overcrowded housing, and lower levels of education.⁴⁰

After the effects of sex and social class were allowed for there were appreciable differences in the odds of death at above median age among the regions of England and Wales. The differences had no clear

geographical pattern. Climate, air pollution, the availability and nature of health services, and the differential effects of social class are all potential contributors to these differences.

This study showed that the prognosis of cystic fibrosis improved greatly in England and Wales over the past 30 years and that social class, sex, and region of residence were all independent determinants of age at death. Given the disproportion of non-manual occupations among patients attending at least one specialist clinic in England,¹⁸ social class is particularly likely to confound the association between attendance at specialist clinics and improved survival. The reasons for the effect of social class on survival with cystic fibrosis should be investigated further to determine whether alternative, possibly less centralised, forms of health care might be more effective for patients from lower social classes. Current plans to provide facilities to care for the growing numbers of patients with cystic fibrosis should take particular account of the effect of social class.

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Plasma lipid and coagulation factor concentrations in insulin dependent diabetics with microalbuminuria

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Abstract

Objective—To determine whether insulin dependent diabetics with microalbuminuria have significant abnormalities in concentrations of lipoproteins, apolipoproteins AI and B, fibrinogen, and clotting factor VII which could result in increased cardiovascular risk.

Design—Case-control study.

Setting—Outpatient department of a metabolic ward.

Patients—Group of 20 insulin dependent diabetics with urinary albumin excretion rates greater than 30 µg/min (microalbuminuria) and 20 individually matched insulin dependent diabetics with normal urinary albumin excretion rates (below 30 µg/min) matched for age, sex, and duration of diabetes.

Interventions—Fasting venous blood samples were taken for determination of concentrations of glucose, glycated haemoglobin, lipoproteins, apolipoproteins AI and B, fibrinogen, and factor VII. Height, weight, arterial pressure, and usual insulin dose were recorded, and each patient was given a dietary questionnaire to be completed at home.

End point—Comparison of blood pressure and concentrations of lipoproteins, apolipoproteins AI and B, and fibrinogen in the diabetics with microalbuminuria and the controls.

Measurements and main results—Patients with microalbuminuria had significantly higher concentrations of low density lipoprotein cholesterol (mean 3.33 (SE 0.20) v 2.84 (0.12) mmol/l) and very low density lipoprotein cholesterol (0.30 (0.05) v 0.17 (0.03) mmol/l) than controls but significantly lower concentrations of high density lipoprotein 2 subfraction cholesterol (0.32 (0.04) v 0.54 (0.04) mmol/l). Concentrations of total triglyceride (1.11 (0.14) v 0.68 (0.08) mmol/l), very low density lipoprotein triglyceride (0.56 (0.10) v 0.30 (0.05) mmol/l), apolipoprotein B (0.88 (0.06) v 0.67 (0.03) g/l) and fibrinogen (2.2 (0.1) v 1.9 (0.1) g/l), and diastolic arterial pressure (80 (2) v 74 (2) mm Hg), were also higher in patients with microalbuminuria.

Conclusions—Cardiovascular risk factors—namely, disturbances in lipoprotein and apolipoprotein concentrations, increased fibrinogen concentration, and increased arterial pressure—are already present in insulin dependent diabetics with microalbuminuria. The increased risk of coronary heart disease in patients with clinical proteinuria may result from prolonged exposure to these risk factors, which are present before any impairment of renal function.

Introduction

Insulin dependent diabetics who develop clinical proteinuria have a much greater risk of premature death from cardiovascular complications than those without proteinuria.^{1,2} A subclinical increase in urinary excretion of albumin (microalbuminuria) predicts the development of persistent clinical proteinuria and renal failure in insulin dependent diabetics.^{3,4} In both prospective and cross sectional studies of non-insulin dependent diabetics microalbuminuria strongly indicated an increased risk of death from cardiovascular complications,^{7,9} and it may also do so in non-diabetics.^{10,11}

At the stage of clinical proteinuria and progressive renal failure changes in plasma lipoprotein concentrations,¹²⁻¹⁴ an increase in systemic blood pressure,¹² and haemorrhological changes^{15,16} have each been proposed as contributing to the increased cardiovascular risk. The situation is less clear in patients with microalbuminuria, in whom renal function is normal or even supranormal. Several workers have shown a raised arterial blood pressure at this stage,^{4,6,17} and control of blood glucose concentration has also been reported to be worse.¹⁷ Reports have suggested that profiles of lipoprotein concentrations are changed in diabetics with microalbuminuria and lie between those in diabetics with normal albuminuria and diabetics with clinical proteinuria.^{13,14} The differences, however, were not significant and could have been accounted for by the poorer glycaemic control in the diabetics with microalbuminuria.¹³

In this case-control study we compared concentrations of lipoproteins, apolipoproteins, fibrinogen, and factor VII in insulin dependent diabetics with microalbuminuria and diabetics with normal albumin excretion rates with similar control of their blood glucose concentration.

Patients and methods

Twenty insulin dependent diabetics with microalbuminuria were matched individually for age, sex, and duration of diabetes with 20 insulin dependent diabetics shown to have normal rates of albumin excretion. All were less than 65 years old and had had diabetes since before the age of 35. All patients were Europeans and received the standard dietary advice given to diabetics. None were taking drugs other than insulin apart from two patients with microalbuminuria, who were receiving long term thyroxine and cortisol replacement treatment. No patient had a history of renal disease or of drug or alcohol abuse.

As part of a collaborative screening programme¹⁸ we

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