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Cystic Fibrosis mortality and survival in the United Kingdom, 1947 to 2003.

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ABSTRACT

Data up to 1995 have previously been published on the survival of three year cohorts of people with cystic fibrosis (CF) in the UK born between 1968 and 1992. This paper reports survival data up to the end of 2003 together with a 2003 population estimate.

All persons with CF born in the UK between 1968 and 1992 were identified by active enquiry, up to 1997, through recognised CF clinics and other hospital consultants..

We have added information from the death certification authorities up to end 2003. Death certificates which could not be matched with UKCFS records were investigated and the data reconciled.

The observed survival to 2003 of CF subjects born in 1978 is males 55%, females 49%. For 1988 and 1992 the data are 91% and 88% and 97% and 96% respectively.

The estimated 2003 mid-year CF population is 8284.

The continuing improvement in survival of CF subjects in successive cohorts means that the previous prediction of median survival exceeding 50 years for those born in 2000 continues to look realistic, even in the absence of proven effective therapy aimed at correcting the basic CF defect.

INTRODUCTION

Standard methods for the collection and analysis of data on national mortality have long been available from the World Health Organisation (WHO) [1]. There are two separate parts to the data collection. The first is the total population census and the second is the recording of deaths in that population. An electronic literature search in July 2005 (Science Citation, Medline, Embase, search terms cystic fibrosis, mortality, survival, incidence) showed four national censuses of a cystic fibrosis population for the purpose of calculating disease incidence. They were: one for Sweden for the period 1950-57 [2], one for The Netherlands 1961-65 [3], one for Czechoslovakia 1960-67 [4] and one for the United Kingdom (UK) 1968 to 1993 [5,6,7].

The UK census data, which was collected by the UK Cystic Fibrosis Survey (UKCFS) until 1997, has been linked with subsequent national death registration data, thus attempting to adhere to the WHO criteria for mortality statistics. Death certification data for children for England and Wales showed a striking decline in post-neonatal mortality from CF between 1968 and 2000, and also a steady but less marked decline among 1-5 year olds [8]. The present report expands this information to include adults, and compares data from successive cohorts.

The sources of the data have been described in detail in earlier papers, particularly in the first of the series.[5] Briefly, they were obtained by regular surveys initially sent to all paediatricians and chest physicians in the United Kingdom, among others. Later, the number of respondents was reduced by eliminating those who stated that they did not look after CF patients, usually naming colleagues who did. Clinicians who did not respond by the due date were reminded, usually by telephone calls to them or their secretaries, and each survey was not concluded until the coordinator was satisfied that all the data up to the end of an agreed calendar year had been obtained. This meant

that published reports were irregular, and not annual as originally hoped. The UKCFS is unique in its coverage of the CF population, being clinician-based and not clinic-based, and previous surveys indicated that it included more than 95% of patients. Although there is a wide variety of CF phenotypes (CFP), which may to some extent modify clinical presentation and apparent incidence in different populations [9] the common approach to patient management in many countries suggests that, in the absence of other data, the UK mortality data can be taken as illustrative of a general trend.

As a further report in the series based on UKCFS data, we present here updated cohort survival data and current survival data for the UK and, for the first time, life tables including the (tentative) expectation of life for people with CF.

METHODS

Data

Active surveillance of the CF population ran from 1982 to 1997 under the auspices of the (then) British Paediatric Association and the British Thoracic Society, and was funded by the Cystic Fibrosis Trust. The present study is essentially a follow-up of the previous report nearly a decade ago [6]. It used the subset of the 1997 data, used in previous mortality calculations, and personal identification data were removed before being passed to the statisticians. It included all known persons resident in the UK with a diagnosis of CF who were either born since 1968 or born before 1968 and alive in 1977. Death certification data up to the end of 1995 were used. It was accepted that ascertainment would be incomplete for the cohorts from 1990 either because some patients had not yet been diagnosed or because of delays inherent in the data collection methods [6]. Strict confidentiality was maintained, and the identity of

individuals was known only to the corresponding consultant paediatrician or adult physician and the non-medical co-ordinator of UKCFS. All data released from UKCFS were aggregated and anonymised.

In the present study, the data held in 1997 were supplemented by data from all death certificates for UK residents from 1996 up to the end of 2003 in which cystic fibrosis or any of its synonyms were mentioned (ICD9 codes 2270, 7770 and 7484 and ICD10 codes E84.0, E84.1, E84.8 and E84.9). Prior to version 6 (introduced in 1968) ICD did not separate CF from other diseases of the pancreas, so death certification data would be unreliable. The legal definition of the minimum term for a stillbirth/neonatal death changed in 1996 from 28 weeks to 24 weeks. We used the legal definition of a neonatal death which was relevant for one case.

Death certification data were linked to the UKCFS database only using date of birth and sex. For the purposes of mortality calculation it is only necessary to record one of any duplicate matches. Where there was no match for death certificate data, checks were made by contacting the certifying physician, and the data corrected if necessary. Dead persons not previously known to UKCFS were included as new cases unless positive evidence was found of their ineligibility, such as foreign residents who died while temporarily in the UK, perhaps visiting relatives or requesting a transplant.

The age/sex structure of the 2003 mid year CF population aged 12 years and over is known directly. To estimate the numbers in the 2003 population aged less than 12 years first the total UK live births for each year were found. For these data the CF births could be estimated using an incidence of 1 in 2381 (as reported here). The survival of each of these cohorts to 2003 was presumed to follow the survival of the 1992-94 which leads directly to the estimated numbers surviving.

Incidence was only calculated for the period 1968 to 1987 due to concerns about later under-ascertainment.

Cohort survival was calculated using the life table method and current survival was calculated by applying the age/sex specific mortality rates for one year successively to a hypothetical birth cohort [10]. For the left truncated survival the total UK live births are known for each period and thus the total CF births may be inferred using the incidence. The survey data gives the size of the CF population that survives to a specific age, and the proportion surviving follows. The remaining years survival is calculated using the life table method. The data for the two sexes were pooled due to small numbers in the older age groups. The calculations were performed in SPSS.11

RESULTS

Deaths

There were 1066 deaths from1996 to 2003, average 133 per year, range 120 to 148. In the cohorts born since 1968 there were 872 deaths, 432 (49%) males in the same time period.

Population

Table 1 gives an estimate of the mid 2003 UK cystic fibrosis population, years 0 to 9 based on extrapolations from the UK live births and years 10 onwards from data held. These data form the denominator in the current survival calculations. The 1992 population is now given as 6740.

Table 1. Mid-year 2003 cystic fibrosis population by age and sex. Ages 0 to 9 years were estimated from population births and survival data. Ages 10 years and older were based on data held by UKCFS.

	0-<1	1-<5	5-<10	10-<15	15	16	17-<25	25-<35	35-<45	45-55	55+	
Male	140	550	700	725	152	143	992	672	318	40	7	4439
Female	140	550	700	634	128	140	802	479	221	39	12	3845
Total	280	1100	1400	1359	280	283	1794	1151	539	79	19	8284
%	3.4	13.3	16.9	16.4	3.4	3.4	21.7	13.9	6.5	1.0	0.2	100.0

Incidence

The extra cases found through this study have led to a 1.4% increase in the previous incidence estimate for 1968-87 from 1 in 2416 [6] to 1 in 2381 live births ($6474/15.4 \times 10^6$).

Table 2. Cohort survival of UK cystic fibrosis population: number born, hazard rate (instantaneous mortality rate) per thousand and number of deaths (numbers in parentheses) by sex based on data held to end 2003

	Year of birth															
	1968-70		1971-73		1974-76		1977-79		1980-82		1983-85		1986-88		1989-91		1992-94	
Males																		
Cystic fibrosis births	592		545		482		469		534		472		467		482		396	
Age (years)																		
0-<1	213.1	(114)	182.2	(91)	111.7	(51)	77.5	(35)	47.9	(25)	54.5	(25)	23.8	(11)	18.8	(9)	22.9	(9)
1-<5	18.4	(34)	15.3	(27)	10.7	(18)	11.2	(19)	8.5	(17)	5.7	(10)	2.8	(5)	3.2	(6)	0.6	(1)
5-<10	19.4	(41)	23.8	(48)	18.8	(37)	10.9	(22)	8.3	(20)	4.6	(10)	3.1	(7)	2.6	(6)	0	(0)
10-<15	33.9	(63)	25.8	(46)	19.5	(35)	11.5	(22)	9.1	(21)	7.6	(16)	5.9	(13)	4.3*	(5)	1.5*	(1)
15-<20	33.8	(53)	36.7	(56)	29.6	(47)	24.6	(43)	19.5	(42)	12.8*	(17)	2.7*	(3)				
20-<25	39.8	(52)	42.3	(53)	30.0	(41)	41.7*	(52)	26.4*	(27)								
25-<30	42.4	(45)	45.3	(40)	50.6*	(32)												
30-<35	54.1*	(31)	15.3*	(7)														
Females																		

Cystic fibrosis births	530		514		434		419		439		461		446		418		363	
Age (years)																		
0-<1	190.0	(92)	155.1	(74)	901.6	(38)	87.1	(35)	61.0	(26)	39.8	(18)	24.9	(11)	14.4	(6)	13.9	(5)
1-<5	28.3	(47)	25.6	(43)	20.3	(31)	13.3	(20)	9.9	(16)	5.7	(10)	1.7	(3)	3.0	(5)	2.1	(3)
5-<10	41.8	(74)	27.4	(51)	29.4	(50)	23.8	(41)	16.3	(31)	8.0	(17)	6.5	(1)4	3.5	(7)	5.1	(6)
10-<15	38.7	(56)	27.8	(45)	24.9	(37)	16.7	(26)	16.5	(29)	13.9	(28)	7.8	(1)6	6.0*	(6)	0*	(0)
15-<20	51.9	(60)	38.6	(53)	44.5	(56)	39.1	(53)	27.3	(43)	28.7*	(36)	6.9*	(7)				
20-<25	54.2	(48)	34.1	(40)	51.9	(51)	37.2	(35)	38.0*	(28)								
25-<30	55.0	(37)	50.6	(47)	27.9*	(22)												
30-<35	53.5	(19)	27.2*	(11)														

Notes: (1) Data subject to censoring marked by *. (2) Censored data with fewer than 100 life years of observation and fewer than 10 deaths have been omitted. (3) The standard error of the hazard rate for all the 0-1 year age groups is approximately 10 per thousand, for the 1-5 year group it is approximately 4 per thousand rising to 6 per thousand for the 30-35 year group.

Survival

The survival of three year cohorts 1968 to 1994 for the two sexes is given in figs 1 and 2 with corresponding hazard rates in table 2.

The updated [12] "truncated" survival for 3 year cohorts, 1947-1967 is given in Fig 3.

The current survival for males and females is given in Fig 4.

An abridged expectation of life table is given in Table 3.

Table 3. Abridged expectation of life by sex, 2003

Age	Expected mean Age of death (Males)	Expected mean Age of death (Females)
0	42.62	36.89
1	43.12	37.33
2	43.12	37.33
3	43.25	37.44
4	43.25	37.44
5	43.38	37.55
10	43.63	37.76
15	44.18	38.39
20	45.41	40.43
25	48.66	44.34
30	52.67	49.40

DISCUSSION

The results presented in this paper show that the continued improvement in survival anticipated from previous results is occurring. The median expectation of life for the CF population for 2000-2003 estimated from the current survival calculations averages about 40 years (Fig 4). These calculations assume the current age specific mortality rates will continue. However, their continued improvement, as reflected in table 2, suggests that an estimated median survival for the year 2000 birth cohort of 50 years [13] remains likely.

The small number of death certificates of persons born prior to 1996 who were not known to UKCFS, and previous experience of the active surveillance in uncovering deaths not reported via the certification authority, confirm that these data should not be over-interpreted. During the active surveillance period great care was taken to avoid duplicating cases. The subsequent merging of post 1996 death data is not entirely satisfactory, because patients in the UKCFS database were identified only by their gender and date of birth. There could therefore possibly be some existing cases marked as "deceased" who were new cases and some deceased marked as "new" who were already in the data set, perhaps under another name, although the follow-up enquiries and discussion with the relevant physician about "new" deceased cases should have almost eliminated this risk. The numbers are certainly small, may partially balance out and do not contribute any important errors to these results.

The effects of the genuinely "new" cases previously unknown to UKCFS are to increase previous estimates of the population size and to slightly improve the historical survival. The effects may be seen by reference to previous work e.g. the 1992 population is now given as 6740 compared to a previous count of 6499 [6] and an earlier projection of 6000 [7]. After excluding deaths among persons of other nationalities newly or temporarily resident in the UK at the time of death, and misdiagnoses, the remaining cases new to UKCFS suggest that there are still persons with CF born before 1995 who were not identified by the Survey. Nearly all the "new" cases were late diagnoses, either presenting with an atypical history or found by family case studies. Whatever the reasons for their being unknown to UKCFS, the clear implication is that there are still some unreported cases that could affect these data.

In terms of the survival data a proportion, albeit small, of the cohort by cohort increase can be attributed to a greater ascertainment of late-diagnosed, milder, cases. All patients included here have CF. If there is to be any true appreciation of trends in survival it is important that criteria for diagnosis are consistent, and that patients with CFTR-related disorders such as isolated obstructive azoospermia, which do not meet the diagnostic criteria of CF, and are not known to have an impact on life expectancy, are excluded from consideration.

The previously noted pattern of linear descent of the survival curves continues following the addition of the further data (Fig.1). The historical better early survival of males with CF is much less apparent although the survival by gender differs markedly for cohorts born before 1987. It is still not clear whether this is a cohort effect or whether adult females inherently have a worse survival than males. As the age at which the survival curves separate has increased recently, reduction of the adult gender gap may continue.

The truncated survival curves shown in Fig. 3 (truncated because we do not have data for the older cohorts to deduce their shape before 1968) show that a steadily increasing proportion are surviving into their 4th decades and beyond. The characteristics, evolving problems and outlook for these long-surviving patients are the subject of ongoing international studies [19,20].

Specific survival data that may help in informing patients and their carers are given in table 3. Death from CF in the first decade of life is now rare [14]. This is presumably related to steadily improving clinical management. Earlier cohorts show a striking reduction in deaths in the first year of life, which was associated with the (now almost universal) survival of infants with meconium ileus resulting from improved neonatal management [6,7] (figs 1-3). The post-infancy rate of attrition depicted in the cohort survival curves has consistently flattened out, suggesting that with that exception, no single new therapeutic intervention can be identified as a major reason for the improved survival. In 1968 in England and Wales, there were 118 deaths attributable to CF in children aged 28 days to 16 years, compared with 75 in 1985 and 15 in 2000 [8].

This makes the cohort effect the major determinant of survival, and much stronger than sex.

Occasionally, CF patients die from unrelated causes such as road traffic accidents. One such instance

during the period covered here is known to us but unless CF was mentioned on the death certificate this would not be the case. However, such deaths would be few, would have the same background mortality as the general age-matched population, and would not obscure the observation that survival of people with CF continues to improve.

The data for the expectation of life may lead to more realistic life insurance being made available to people with CFP. Conversely, these results should lead to a lower benefit being available for an impaired life annuity.

Comparisons with other studies.

A proper comparison with the results from other published data sets present serious technical and methodological problems. This is because these data sets do not conform to the WHO standard of a total defined population, and thus require non-cohort analysis. The results from these analyses are frequently misinterpreted, as comparisons are made using relative risks (or odds ratios) with insufficient explanation (for further explanation see Bradford Hill [15]). Other examples of problems in interpreting CF survival data are available [16]. However, survival data from large national registries which, unlike UKCFS, are based on information only from specialist clinics and therefore have a selection bias, show broadly comparable and gratifying trends [17,18].

Conclusions.

(1) This total population study shows that survival with Cystic Fibrosis continues to improve in the UK, and by implication in many other countries also.

(2) Continued growth of the adult CF population by about 145 patients per annum has national and local implications for health care provision and training of staff to manage adult CF clinics. The annual population increase would approximate to the size of a moderately large adult clinic.

(3) The expectation of life data should be of value to life insurance companies in calculating risks and returns on life annuities for people with CF

(4) Previously published predictions of a mean survival exceeding 50 years, for infants with CF recently born in the UK, continue to look realistic, even in the absence of proven effective therapy aimed at correcting the basic CF defect.

COMPETING INTERESTS

None declared

JD originated the UKCFS study and followed up unmatched death certificates

PL suggested this paper and calculated the cohort survival.

MS calculated the current survival and expectation of life

JW handled the left-truncated survival, and the population estimate and incidence.

All authors contributed to drafting the paper.

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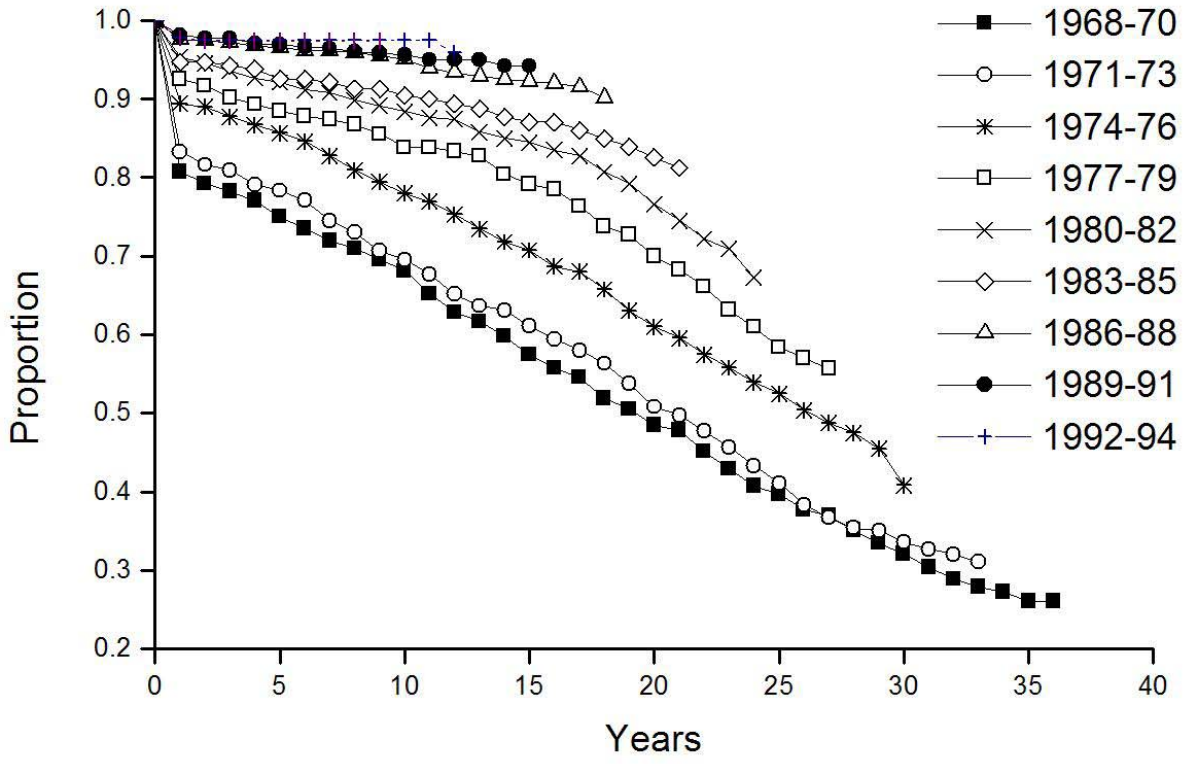

Fig1. UK cystic fibrosis population, proportion of males surviving to 2003 of each three year cohort.

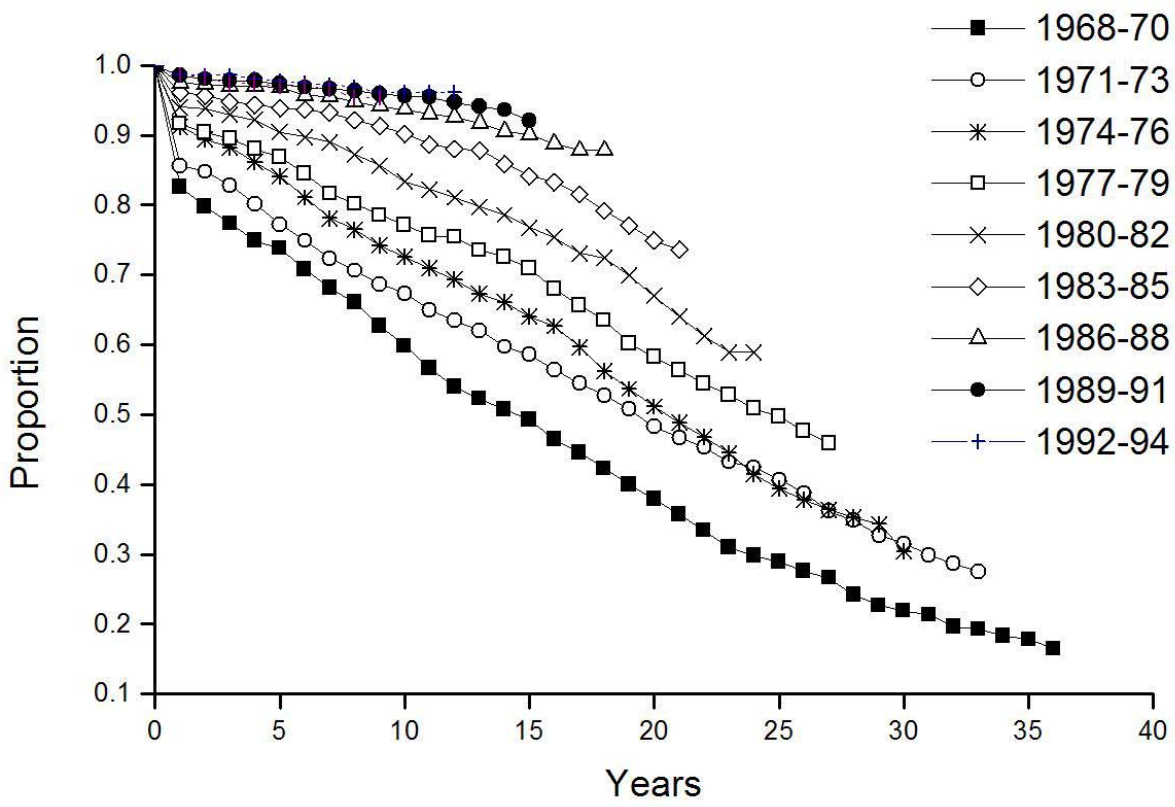

Fig 2. UK cystic fibrosis population, proportion of females surviving to 2003 of each three year cohort

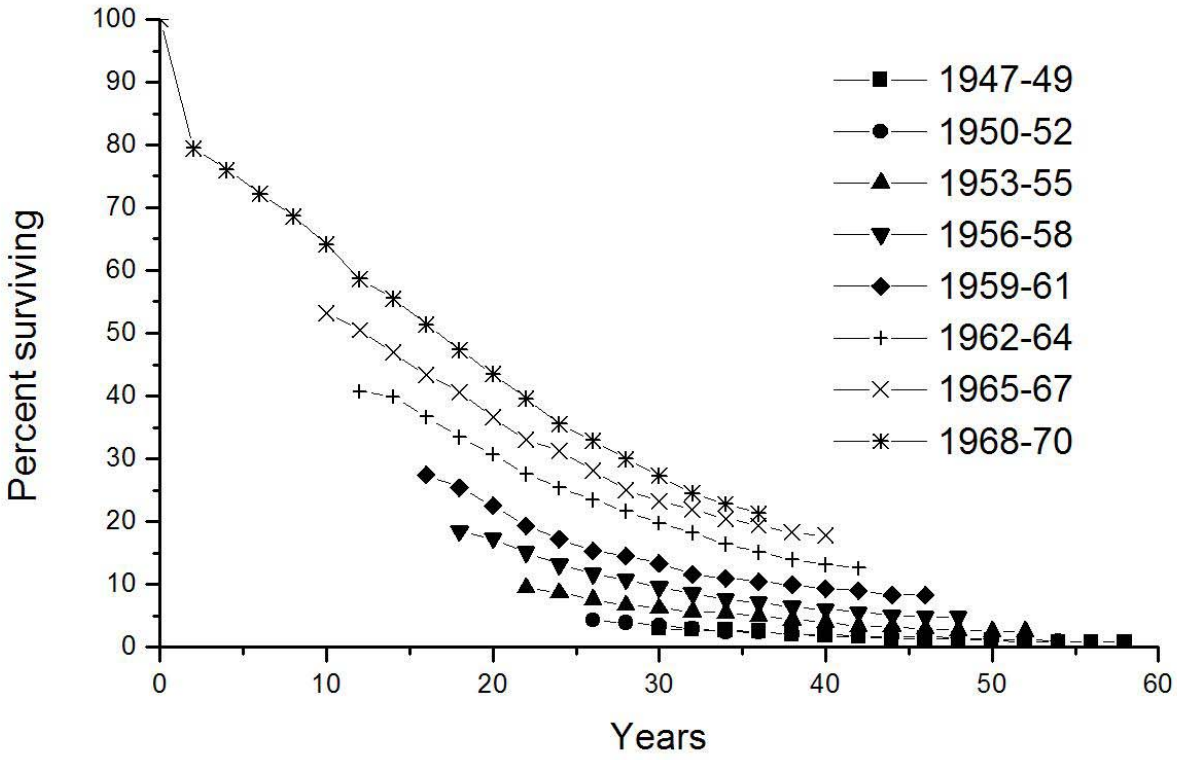

Fig 3 Left truncated survival curves, UK cystic fibrosis population 1947-1967, three year cohorts, to 2003

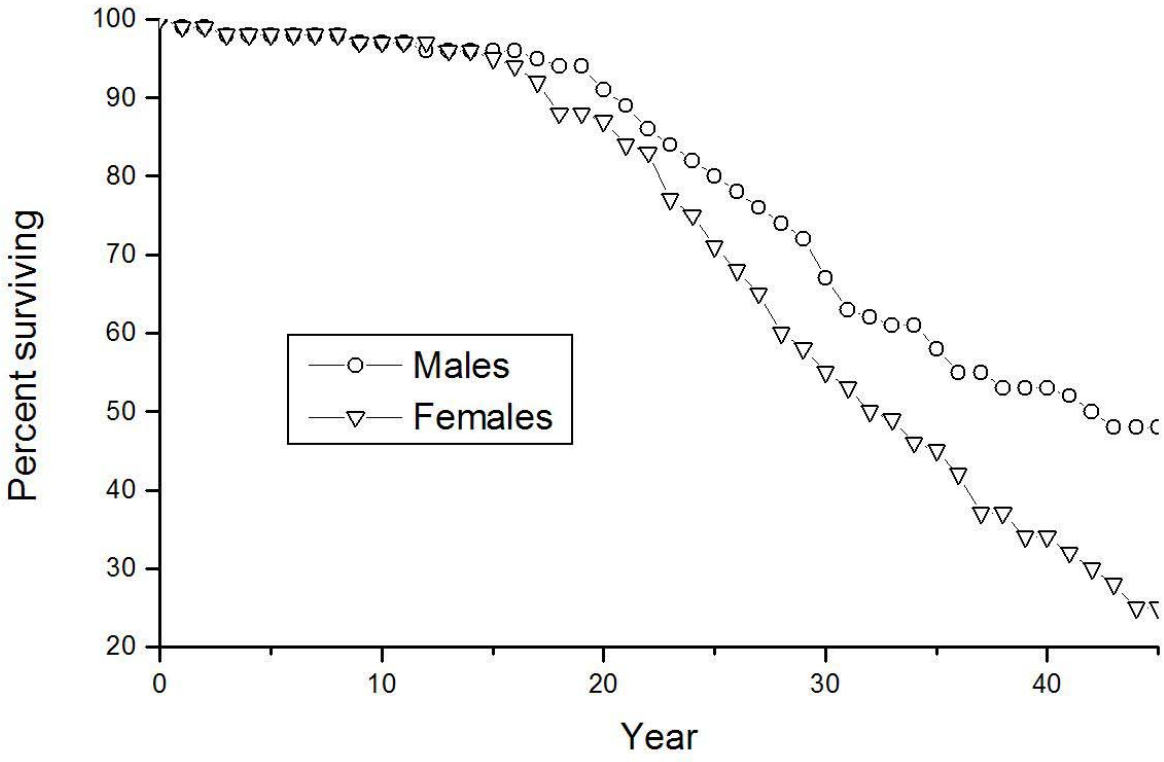

Fig 4. Current survival UK cystic fibrosis population, males and females, 2003.