Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis

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Summary

Background **Country-specific patients' registries are rarely used to make international comparisons because of protocol discrepancies in data collation. We present data from a European cystic fibrosis registry that is dedicated to collection of demographic data, and assess whether the resources available in countries with and without European Union (EU) membership affects care and survival of patients.**

Methods **Data for demographic indicators—age, age at diagnosis, sex, and genotype—for patients with cystic fibrosis from 35 European countries were combined, and used to establish the differences in demographic indicators between EU and non-EU countries. EU membership status in 2003 was used to divide countries. We modelled demographic indicators of EU countries on non-EU countries to estimate the size of the cystic fibrosis population if non-EU countries had had the same resources available for patients as did EU countries.**

Findings **Data were gathered for 29 025 patients, who had a median age of 16·3 years (IQR 8·9–24·8), with a difference of 4·9 years (95% CI 4·4–5·1; p<0·0001) between EU (median 17·0 years, IQR 9·5–25·6) and non-EU countries (12·1 years, 6·0–19·2). The proportion of patients older than 40 years was higher in EU countries (1205 [5%]) than in non-EU countries (76 [2%]), with an odds ratio of 2·4 (95% CI 1·9–3·0, p<0·0001). We estimated that the cystic fibrosis population in non-EU countries would increase by 84% if patients had a demographic profile comparable to that of patients in EU countries.**

Interpretation **Future studies need to establish the reasons for the lower proportion of patients with cystic fibrosis in non-EU countries than in EU countries, such as underdiagnosis and premature childhood mortality.**

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Introduction

Cystic fibrosis occurs in babies of parents who are apparently healthy carriers of the defective cystic fibrosis transmembrane-conductance regulator gene (*CFTR*), and is one of the most common inherited disorders in populations of European descent. However, at a population level, cystic fibrosis is quite rare. Since individual hospitals do not have sufficient numbers of patients with the disorder, patients' data submitted to registries are necessary to gain an overview of the epidemiological complexities. Such registries have been running in the USA and Canada for many decades, and have been used to inform several features of cystic fibrosis, including demographic indicators,[1,2] the use of genotype to predict mortality,[3] and the effect of socioeconomic status on specific outcomes.[4,5] Similar efforts have taken place worldwide—for example, country-specific databases have been used for benchmarking in Germany,[6] to measure survival improvement in France,[7] and to offset screening costs through a reduced treatment burden in the UK.[8–10]

With recognition of the limits of any national registry, we tried to begin an international comparison of disease outcomes.[11] However, the conflicting evolution of national registries led to a scarcity of standardised data collection, which hampered insightful comparisons. This variance in protocol was unfortunate in view of the substantial financial and human resources that have been used for national registry data collection. For some time, geneticists have instead used *CFTR* mutations reported by cystic fibrosis centres to make worldwide comparisons. Such research has been published but source data were derived from several published reports rather than de novo.[12]

To overcome limitations with data standardisation, a new registry project was proposed in the mid-1990s, and the Epidemiologic Registry of Cystic Fibrosis was developed with sponsorship from the pharmaceutical industry until funding stopped in 2003. Around this time, the European Cystic Fibrosis Society developed a new European registry of cystic fibrosis that concentrated mainly on countries with membership of the European Union (EU) that had available cystic fibrosis registries; the registry has since yielded comparative data for 14 101 patients from ten countries.[13] In 2005, funding was obtained under the European Community's Sixth Framework Programme for Research for a dedicated registry component within the European Coordination Action for Research in Cystic Fibrosis (EuroCareCF). The European Cystic Fibrosis Demographics Registry (ECFDR) now contains data from 35 EU and non-EU countries, and more than 29 000 patients.

EU and non-EU countries have populations of similar sizes (341 million *vs* 378 million) and similar distributions of severe genotypes of mutations causing cystic fibrosis.[12]

Thus, a priori, outcomes should differ little, and recorded differences would be expected to have arisen from causes primarily unrelated to *CFTR*. We present data from ECFDR, with specific comparison of demographic indicators in patients with cystic fibrosis, by membership of the EU in 2003—ie, preceding the expansions of EU membership in central and eastern Europe in 2004. In 2003, median gross domestic product (GDP) per person, a surrogate for health-care spending, was nine times higher in EU countries (US$30 209, IQR $28 239–33 429) than in non-EU countries ($3372, $2138–$7710).[14] With the hypothesis that increased health-care spending in EU countries would correspond to improved care of patients and better survival, we sought to estimate differences in demographic indicators between populations with cystic fibrosis in EU and non-EU countries.

Panel: Countries included in the study, by European Union (EU) membership status as per 2003, cystic fibrosis population size, and year of most recent data provision

EU countries

- 3–30%: France (2004), Germany (2005), Italy (2003), UK (2005)
- 1·5–3%: Belgium (2004), Ireland (2006), Netherlands (2007)
- <1·5%: Austria (2006), Denmark (2005), Greece (2007), Portugal (2006), Sweden (2003)

Non-EU countries

- 1·5–3%: Czech Republic (2007), Israel (2005), Russia (2007)
- <1·5%: Armenia (2006), Belarus (2007), Bosnia and Herzegovina (2007), Bulgaria (2007), Croatia (2007), Cyprus (2006), Estonia (2004), Georgia (2007), Hungary (2006), Iceland (2005), Latvia (2006), Lithuania (2004), Macedonia (2007), Moldova (2006), Romania (2006), Serbia (2007), Slovakia (2006), Slovenia (2007), Turkey (2007), Ukraine (2006)

Methods

The European Cystic Fibrosis Demographics Registry

The partnership between EuroCareCF and the European Cystic Fibrosis Society aimed to obtain comprehensive demographic data, with optional clinical data, for patients with cystic fibrosis in countries across Europe. ECFDR has provided a foundation to further the cystic fibrosis registry in Europe with the support of the European Cystic Fibrosis Society. To ensure uniformity of data collection, and to account for the independent evolution of national registries, we gathered data with spreadsheets that were standardised across countries, as agreed by EuroCareCF and the European Cystic Fibrosis Society, and were compatible, where possible, with data definitions used by the US Cystic Fibrosis Foundation's registry.[15] With the partnership of EuroCareCF, the European Cystic Fibrosis Society, and the US Cystic Fibrosis Foundation, this global initiative could provide meaningful international comparisons in the future, and parallel efforts to standardise data definitions are under way.[15]

Study design

35 countries were studied; for those without a functioning national registry before this study, diagnoses of cystic fibrosis were recorded by centres and reported by a nominated national representative (European Registry Working Group). We judged that core registration details—age, age at diagnosis, sex, and genotype—would form the highest quality data on the basis of previous experience from the UK Cystic Fibrosis Database,[16] keep missing data to a minimum, and circumvent the challenges of different reference equations, units, and methods that are presently in use across Europe. We complied fully with data protection requirements (EU Data Protection Directive 95/46/EC), and a common consent form was created that could be modified according to national data protection legislation in the various countries (webappendix pp 1–3).

See Online for webappendix

Demographic data were sought from patients with cystic fibrosis reporting to a national registry or seen at a hospital or clinic between January, 2003, and December, 2007. Age, age at diagnosis, and homozygous Phe508del status were selected for analyses. We calculated patients' ages from the date of birth to Jan 1 of the year after registration of the youngest patient in that country. These calculations assumed that no deaths occurred, since mortality data were largely incomplete and not externally validated; furthermore, deaths in childhood are uncommon in countries where treatment is well funded.[17] For 148 patients with no age at diagnosis recorded, age at sweat test was used as a surrogate marker. Europe was subdivided into EU and non-EU countries as per membership status in 2003 to represent the circumstances present for the majority of patients' lives. To ensure that we studied disease cases of similar severity across countries, patients' age was compared for genetically homogeneous patients between EU and non-EU countries with use of the severe Phe508del homozygous genotype as a reference, since across Europe, this mutation is the most common and severe defect causing cystic fibrosis.[12]

Statistical analysis

We compared EU and non-EU countries by use of the Mann-Whitney *U* test. Odds ratios (ORs) were calculated to establish the odds of patients older than 40 years being inhabitants of EU or non-EU countries. To assess the potential benefits of growing up with cystic fibrosis in an EU country, we modelled demographic indicators (age profile) of patients with cystic fibrosis in EU countries—as an indication of the net effect of population health, treatment, and economic status—on non-EU countries in 5-year age-groups, to estimate the size of the cystic fibrosis population in non-EU countries. First, we estimated the age structure of the population in EU countries by calculating the ratios between the number

of patients in each age-group (EU_i) and those in the age-group of 0–5 years ($EU_{0–5}$). The number of patients in non-EU countries in the age-group of 0–5 years ($non\text{-}EU_{0–5}$) was then multiplied by the ratios from EU countries to estimate the number of patients in each age-group in non-EU countries ($non\text{-}EU_i$), according to the equation:

$$Non\text{-}EU_i = Non\text{-}EU_{0–5} \times \frac{EU_i}{EU_{0–5}}$$

From the difference between the population size recorded in the countries from data registries and the population size estimated from the model, we could gauge the expected change in the size of the cystic fibrosis population in non-EU countries if patients had been subject to the population health, treatments, and economic status of EU countries.

Role of the funding source

None of the funding sources had a role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

29 025 patients with cystic fibrosis were registered in 35 European countries, with 25 216 in EU countries and 3809 in non-EU countries (panel). Full data for patients' age at diagnosis and sex are presented in webappendix pp 4–7. Analysis of the age distribution of patients with cystic fibrosis showed that the population increased to a peak in the age-group of 10–14 years, with less than 2% of the population older than 45 years (figure 1). The cystic fibrosis population size increased in the first decade as new diagnoses entered the pool before numbers stabilised during the teenage years. By the fourth decade onwards, the population size was more than 50% smaller than in the previous decade.

Overall, median age was 16·3 years (IQR 8·9–24·8) and mean age was 17·9 years (SD 11·4), with an age range of 15·7–20·5 years in EU countries versus 6·1–23·0 years in non-EU countries (table). The median age in EU countries was older than in non-EU countries, with a difference of 4·9 years (95% CI 4·4–5·1). The proportions of patients in the older age-groups were smaller in non-EU than in EU countries even before the age of 20 years, with striking differences in the proportions of patients aged 35–44 years (figure 2A). In EU countries, between the age-groups of 0–9 years and 10–19 years, the number of patients with cystic fibrosis increased by 24%, whereas the number of patients decreased by more than 10% in non-EU countries (figure 2B). Population size decreased at a younger age and more sharply in non-EU countries than in EU countries, with the change in population size differing by 20–30% between EU and non-EU countries for patients aged 0–40 years. Additionally, only 21 (60%) of the 35 countries had patients older than 40 years (one in 21 patients in EU countries *vs* one in 50 in non-EU countries), and such patients were more likely to live in EU than in non-EU countries (OR 2·4, 95% CI 1·9–3·0, p<0·0001).

To establish whether the improved odds of patients reaching ages older than 40 years in EU countries was caused by poor case ascertainment in non-EU countries, or by increased ascertainment of mild phenotypes in EU countries, we restricted our comparison to cases of cystic

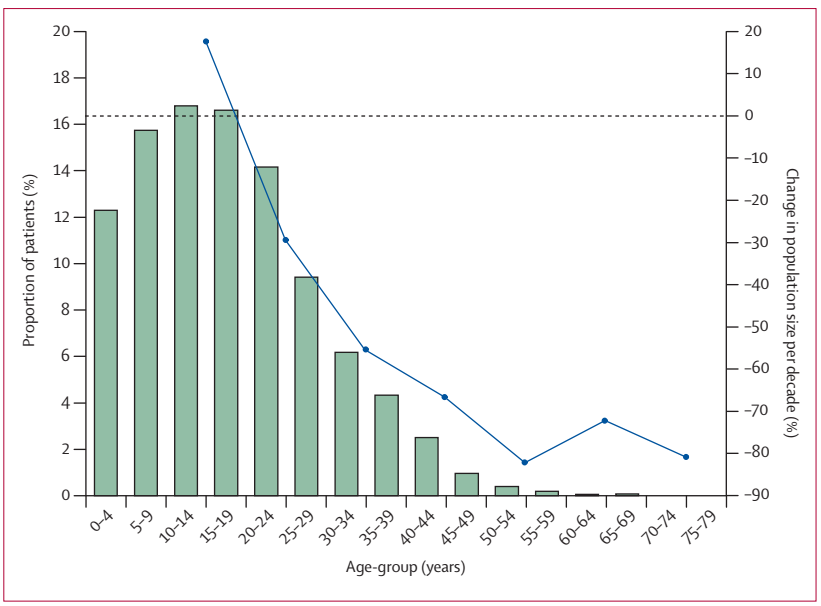

Figure 1: **Age distribution of patients with cystic fibrosis in Europe (green bars) and percentage change in the size of the cystic fibrosis population from the previous 10-year age-group (blue line)**
Black dashed line indicates zero change in population size. Datapoints for percentage change in population size are positioned at the midpoint of the decade that they represent.

	EU countries	Non-EU countries	p value
Age (years)*	17·0 (9·5–25·6); 18·5 (11·5)	12·1 (6·0–19·2); 13·7 (9·9)	<0·0001
<5	2823 (11%)	786 (21%)	..
<18	13 472 (53%)	2732 (72%)	..
18–40	10 539 (42%)	1001 (26%)	..
>40	1205 (5%)	76 (2%)	..
Age at diagnosis (years)†	0·5 (0·1–2·8); 3·4 (7·4)	0·9 (0·3–4·3); 3·9 (7·1)	<0·0001
Age of patients with homozygous Phe508del (years)‡	16·5 (9·4–24·3); 17·7 (10·5)	11·4 (5·5–17·8); 12·4 (8·3)	<0·0001
<5	1197 (11%)	216 (22%)	..
<18	6043 (56%)	735 (76%)	..
18–40	4494 (41%)	230 (24%)	..
>40	341 (3%)	3 (<1%)	..

Data are median (IQR), mean (SD), or number (%). ..=data not calculated. *Recorded for 25 216 patients in countries with and 3809 in countries without EU membership. †Recorded for 22 856 patients in countries with and 3028 in countries without EU membership. ‡Recorded for 10 878 patients in countries with and 968 in countries without EU membership.

Table: **Demographic indicators of cystic fibrosis populations in EU and non-EU countries**

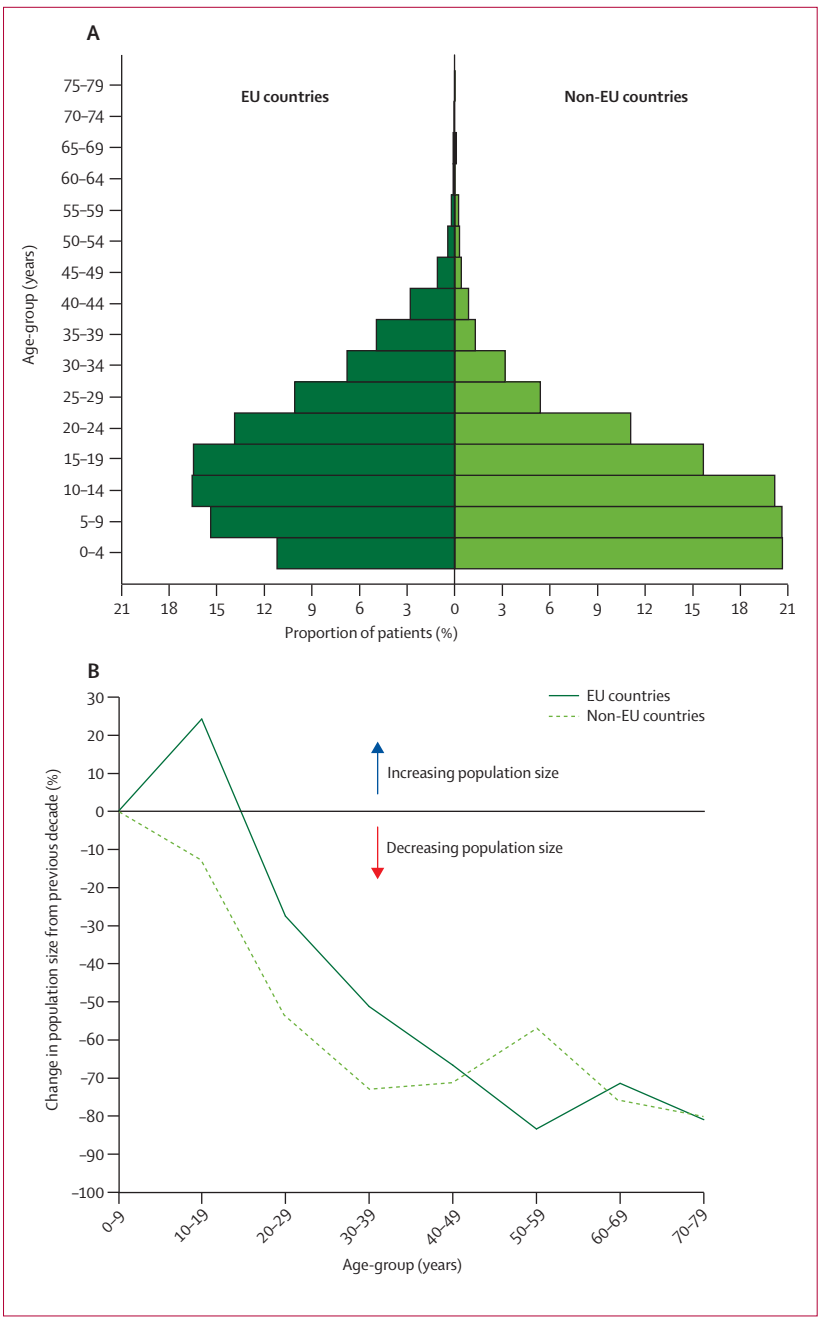

Figure 2: **Population pyramid of mean age of patients with cystic fibrosis in EU and non-EU countries (A), and percentage change in the size of the cystic fibrosis population from the previous 10-year age-group (B)**

fibrosis that were homozygous for the Phe508del mutation. The genotype mostly presents in childhood—UK data showed that 96% of such cases were diagnosed in mid-childhood (GM, unpublished) but the genotype is mostly lethal if untreated. The differences between EU and non-EU countries shown in figure 2A persist even after exclusion of milder genotypes (figure 3A), and, despite a common severe genotype, the population declines at an earlier age and with greater rapidity in non-EU countries than in EU countries (figure 3B). Such findings exclude the possibility that the differences between EU and non-EU countries could be caused by a higher proportion of milder genotypes in EU countries. Patients with homozygous Phe508del had an age range of 0·1–60·8 years in EU countries versus 0·1–49·5 years in non-EU countries. The implications of the finding that median age at diagnosis was 0·4 years younger in EU than in non-EU countries (table) is discussed in webappendix p 4.

We modelled demographic indicators of EU countries on non-EU countries to estimate the size of the cystic fibrosis population, which showed that a further 3212 patients—84% more than we recorded from data registries—would be alive in non-EU countries if the EU demographic conditions had applied (figure 4). Notably, the main driver for this difference is the age profile for patients aged older than 10 years. Conversely, had the cystic fibrosis population in EU countries of 25 216 patients been exposed to the demographic conditions of non-EU countries, we calculated that the population would be 54% of the original size with 13 680 patients (loss of 11 536 patients; data not shown).

Discussion

We have shown that far fewer children and young adults have cysic fibrosis in non-EU countries than we expected. This finding is reinforced by the increased chance of patients surviving to 40 years in EU countries, even if they have the severe Phe508del mutation. This difference does not seem to be caused by an increased proportion of mild phenotypes in EU countries, which suggests that poor survival in non-EU countries could be a contributing factor. Moreover, application of demographic data from EU countries to the cystic fibrosis population in non-EU countries suggests that if non-EU countries had comparable resources to EU countries, the size of the cystic fibrosis population could increase by 84%.

We have presented results from the largest multinational study of demographic indicators in patients with cystic fibrosis. In 1997, the first Epidemiologic Registry of Cystic Fibrosis project reported data for 6800 patients in six countries,[18] and, by 2001, data for 12 447 patients in nine countries were available.[19] Peak published enrolment in the Epidemiologic Registry of Cystic Fibrosis was 15 339, around half the enrolment of ECFDR that we have reported.[20] Moreover, the enrolment in ECFDR has exceeded that reported in the US Cystic Fibrosis Foundation's annual data report, 2007, by 18%.[21]

Importantly, patients' consent was obtained from every participating country and all our registry protocols were compliant with the relevant national data protection laws, creating a legal foundation for all future clinical research with this dataset. Although our ECFDR data are collated on a strictly anonymous basis, the underlying procedures and consent (webappendix pp 1–3) explicitly permit future application to improve care of patients (including

clinical trials) with stringent safeguards to prevent their identification (for example those with rare *CFTR* genotypes).

The difference between the number of patients with cystic fibrosis between EU and non-EU countries is striking in view of the similarity of general population sizes and the expected disease prevalence.[22] This disparity in demographic indicators might be due to reduced availability of specialist drugs, equipment, and trained multidisciplinary staff in non-EU countries, rather than lower gene frequency, greater disease severity, or poorer treatment adherence than in EU countries. Since ECFDR began, 12 non-EU countries have become full EU members, and, with other potential candidate countries about to enter, we need to establish which factors will make the biggest difference to outcome in cystic fibrosis, such as neonatal screening or improved treatment.

Arguably, the greatest health and cost benefits can be delivered by an equitable investment in the basic provision of cystic fibrosis care to new EU and non-EU nations alike, but an early diagnosis coupled to available treatment is crucial.[8,9] Notably, diagnoses of children younger than 1 year are scarce in non-EU countries, which could be caused by bias due to insufficient data on disease incidence, but is probably a result of deaths due to unrecognised cystic fibrosis. In equal measure, screening with no treatment available is worthless. Substantial developments in cystic fibrosis treatment could potentially lead to corrective rather than palliative treatments. However, a large number of treatments are in development for a fairly small cystic fibrosis population, and since patients could derive maximum benefit from early intervention, access to additional cystic fibrosis populations for clinical trials is needed to rapidly test the efficacy of novel approaches.

The disparities in demographic data between patients in EU and non-EU countries might be of interest to governments and cystic fibrosis organisations providing funding for care. Resource allocation needs to account for the prevalence of disease in different countries, but Farrell[22] reports that the incidence in non-EU countries (eg, Bulgaria one in 2500, Cyprus one in 7914, Czech Republic one in 2833, Slovakia one in 1800, Slovenia one in 3000) to be similar to that of EU countries with large cystic fibrosis populations (eg, France one in 4700, Germany one in 3300, Italy one in 4238, UK one in 2381).[22] Across 27 EU countries, the prevalence was 0·737 per 10 000, ranging from 2·98 in Ireland to 0·12 per 10 000 in Finland.[22] We estimate that an extra US$7·8 million per year (£4·9 million) would be needed to care for the additional 3212 patients that we predicted would be alive in non-EU countries if these patients had the demographic indicators of EU countries. This estimate is based on the median cost of care for UK patients with cystic fibrosis aged 1–9 years of $2442 (£1526) at 2002 prices, which was previously calculated for clinically diagnosed patients from birth to age 9 years.[10]

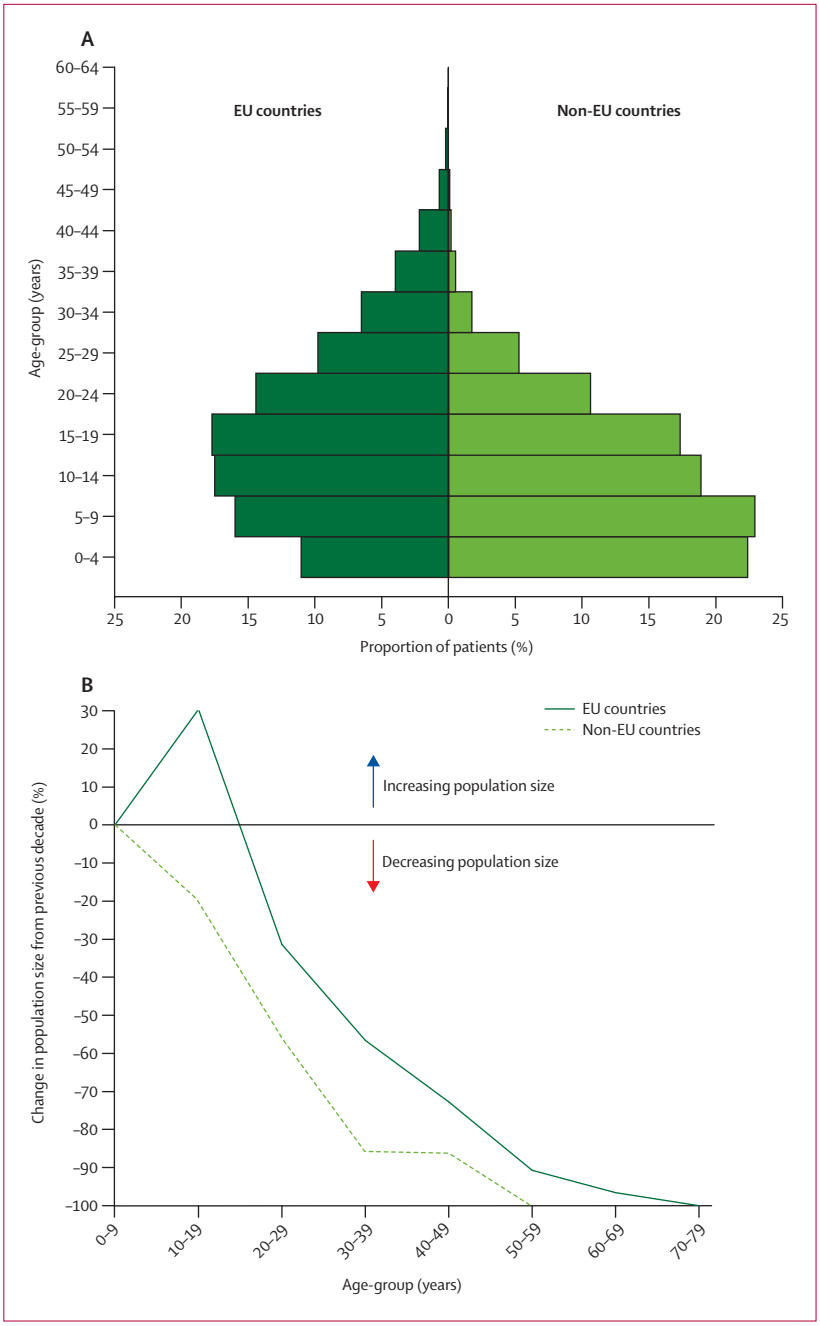

Figure 3: **Population pyramid of mean age of patients with cystic fibrosis and homozygous Phe508del in EU and non-EU countries (A) and percentage change in the size of the cystic fibrosis population with homozygous Phe508del from the previous 10-year age-group (B)**

An international project of this size has several limitations. Four established EU registries contributed three-quarters of the ECFDR data, which is probably caused by a combination of country-specific population size and registry maturity and effectiveness, rather than increased prevalence per se. Consequently, countries with smaller general population sizes seem to have a lower representation in the results. Although data

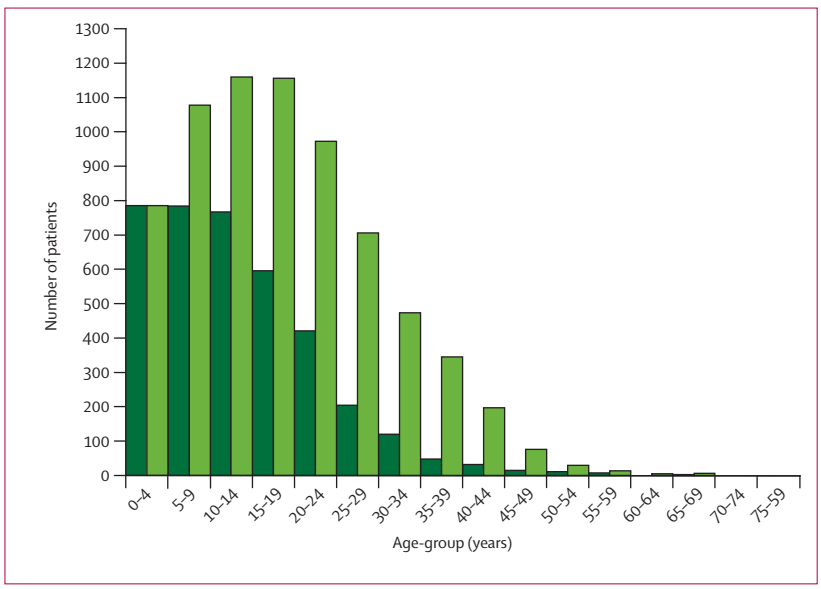

Figure 4: **Size of the cystic fibrosis population in non-EU countries recorded from data registries (dark green bars) and remodelled with demographic indicators from EU countries (light green bars)**

coverage is probably better in established registries, even these registries do not have complete coverage and we acknowledge that non-comprehensive case-reporting will occur in most or all registries. Further, in some non-EU countries, adults with cystic fibrosis might be under-represented because of poor data coverage rather than poor survival, and because low frequency of neonatal screening could lead to undiagnosed children dying from diarrhoea, failure to thrive, and pneumonia.

As a cross-sectional project, calculation of prevalence from registry data is inextricably linked with data coverage, but prevalence, and therefore population size, by individual country has not been reported in our study. Data coverage would also have been affected by genotype. The form used for data collection in each country did not specify the number of mutations (which now exceed 1600) that each country searched for, but if the EU countries that contributed most patients had detected an increased proportion of mild genotypes or late diagnoses than the remaining EU and non-EU countries, the results could have been biased.

With selection of specific high-quality variables, we gathered data from 99·9% of patients for age and sex, and 89·2% for age at diagnosis. Prediction of the potential size of the cystic fibrosis population from non-EU countries if patients had the same demographic indicators as those from EU countries, gives a snapshot of the disparity in survival between EU and non-EU countries. However, this prediction is based on several assumptions since the demographic data will be in a constant state of flux because of newly introduced neonatal screening programmes, new diagnoses, late presentations, immigration, emigration, and deaths; and demographic data are also affected by limitations and assumptions about incomplete data coverage, genotype differences, and incidence. Nevertheless, we do not believe that our data are confounded by an increased proportion of mild phenotypes in the EU since for EU and non-EU countries, the population decline was similar for the whole cystic fibrosis population and for children and young adults with the severe form of cystic fibrosis (homozygous Phe508del).

Cystic fibrosis registries have proved to be highly valuable to estimate the size of the European cystic fibrosis population—and the proportional size of the adult population—for the first decade of the 21st century. Indirectly, these data have provided an indication of where additional resources are needed to improve diagnosis and treatment. With the introduction of a common data collection system across Europe in 2009, combined with contributions from additional countries, about 60 000 patients with cystic fibrosis will be registered in Europe and the USA. During this study, we were unable to accommodate requests from India to join our initiative and we are encouraged that South Africa, Australia, and New Zealand also wish to participate. We believe that our first steps to drive an international collaborative endeavour will continue to provide important findings for patients with cystic fibrosis worldwide and for funding institutions, which is crucial in these financially difficult times. In 2000, Fogarty and colleagues[23] updated their analysis of global mortality in cystic fibrosis, and concluded that misclassification of infant deaths from cystic fibrosis could account for up to 20% of the difference between the number of cases recorded and those expected from genetic predictions, which could partly account for the discrepancy that we noted between the numbers of expected cases in non-EU countries and the actual numbers recorded. Additionally, Fogarty and colleagues[23] suggested that for countries in which underdiagnosis was probably not a major factor, inequality in access to health care could be the major driver for younger median age at death. In our study, both factors are likely to affect new members of the EU, and these matters need urgent attention by governments.

Contributors

JM, GM, and AM participated in the study design. GM, HVO, LV, and MM participated in data collection. JM verified and analysed the data, and wrote the report. JM, GM, and AM participated in data interpretation. All authors participated in editing of the report, and have seen and approved the final version.

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Conflicts of interest

We declare that we have no conflicts of interest.

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