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Original Article

Cystic fibrosis across Europe: EuroCareCF analysis of demographic data from 35 countries☆

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on behalf of the European Registry Working Group

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(continued on next page)

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Abstract

Background: A 35 country European cystic fibrosis (CF) demographic registry was developed to compare outcomes (EuroCareCF EC-FP6).
Methods: We applied methods that had successfully created country-specific registries inviting wide participation to obtain consent and collate demographic and *CFTR* genotype data.
Results: Among 29,095 patients, a widely different country-specific prevalence of childhood CF exists that cannot be explained by differential population frequency of mutant-*CFTR* or case under-ascertainment with a significant paucity of the homozygous p.Phe508del genotype that presents in childhood in >90% of cases.
Conclusions: Excess premature childhood CF mortality may still occur. The better resourced Western Europe now has a ~5% mortality for childhood CF, which is not apparent in many of the European countries reported here. In addition, a female survival disadvantage exists. The reasons require further investigation. We showcase the value of simple data collection in one rare disease, which might interest those managing rare diseases across the globe.

Keywords: Database; Rare disease; Geography; Chronic disease; Genetics; p.Phe508del; *CFTR*

1. Introduction

Cystic fibrosis (CF) is one of the most common life-shortening, recessively inherited rare diseases; it is most prevalent in Europe, North America and Australasia [1,2]. The vast majority of CF-affected children present to health care services within the first two years of life, many with severe life-threatening disease affecting multiple organs (principally, lung, bowel and the pancreas). CF occurs mainly in children of European descent, while it is much rarer in the Eastern Asia and in most of Africa, except in the European-derived populations of Southern Africa [3]. Less frequently, CF occurs in Arabian populations and throughout South East Asia where it is now sufficiently common to necessitate the formation of specialist CF Centre care. For example, such specialist CF clinics are now found in parts of the Indian Subcontinent [4]. In urban settings, as non-European population admixture increases across Europe and North America, the underlying genetics of CF inheritance is fast becoming a complex issue since the types of CF-causing mutations differ from those found in original European populations [5]. This is especially problematic for "two tier" neonatal screening programmes, which are increasingly being implemented worldwide [6].

1.1. Survival

Historically, and irrespective of geography or a country's economic wealth, most CF-affected babies born in the mid last century would have had very little chance of surviving into adulthood since there were no effective therapies [1]. For example, fifty years ago, around 90% of such infants died from persistent diarrhoea and chronic malnutrition, typically before their second birthday due to pancreatic failure [1]. Survival into early childhood changed dramatically in the middle of the 1980s [7] initially as a result of the development of potent and relatively affordable acid-resistant pancreatic enzyme replacement therapies that aided digestion of foodstuffs to compensate for the pancreatic insufficiency that takes place during *in utero* development. As a result of the development of paediatric CF centres and their care teams, in subsequent decades, CF prevalence among young adults began to accelerate such that a CF patient born in the last two decades of the twentieth century (in an economically developed nation) is now expected to have a greater than 50% chance of living until they are about 40 years of age [8].

1.1.1. Survival from childhood onset

This transition has necessitated the development of adult-oriented CF centres, no longer run by paediatricians for the most part, but this practice varies across nations depending on the availability of specialised adult CF care. Consequently, in some countries paediatricians continue to look after CF adults. Although survival of CF patients diagnosed in early childhood is improving all the time, CF "survivors" into adulthood (rather than those who often present in adulthood with a relatively milder form of the disease without pancreatic failure), remain in a small minority when compared to the entire demographic profile of all CF cases in a given population [9]. We recognised that adult survivors of childhood CF do vary in prevalence across CF centres with some well resourced and long standing adult CF centres in Western Europe reporting a much higher prevalence of such survivors of childhood onset disease [10]. At the outset of the work reported here, we considered that in some countries without the resources available to economically advanced nations, a relative paucity of adult survivors from a CF diagnosis in infancy could be reflective of an underlying higher mortality from an earlier era in such 'child-diagnosed' cohorts. Hence, in this paper we investigated the underlying CF demography focussing on country-specific CF prevalence. Typically, CF survival improves relatively slowly by approximately five years in each successive ten year cohort [7,11,12] and it remains to be seen whether this incremental trend will eventually flatten. It is estimated that the annual mortality in current cohorts aged over 40 years is around 3–4% [9]. Such epidemiological predictions are generally robust since they are largely based on data that meet stringent quality criteria [13]. However, such accurate predictions result from considerable and long-term investment, mainly by CF patient support groups, that set up accurate, verified longitudinal repositories of clinical and demographic data (i.e. CF Registries).

1.2. Registries

Currently, most CF Registries that report data are located in Western Europe, North America and Australia. Their analyses of the underlying demographic trends suggest that substantial progress is being made in improving survival for almost all CF-affected babies, with the caveat that this advance is only reported from socio-economically developed nations who have the necessary reporting structures in place. Investigators examining the UK socialised medicine programme (National Health Service, NHS) pioneered a critical example of such a robust epidemiological approach [7]. The authors provided evidence that multiple case ascertainment from the subset of NHS hospitals caring for CF patients coupled to data from Primary (Family) Care, the UK CF Trust (the CF patient support organisation) and a comprehensive analysis of Government recorded CF deaths (UK Registrars General) confidently ascertains ~90% of the CF cases of all types and severity referenced against the expected genetic incidence. This comprehensive 'UK Survey' is no longer operational and such highly accurate methodology cannot easily be replicated in the vast majority of European countries that do not have such an overarching government led infrastructure in health care [5]. Mostly with respect to CF registries, the fragmented nature of country-specific reporting leads to a substantially lower coverage with typical estimates being between 40% and 80%. Such coverage estimates mainly rely on CF centre based aggregates of patient data composed into a national or regional picture as described in detail elsewhere [5,14,15]. In summary, registry evolution shows that there is always a delicate balancing act between collecting purely demographic information (small numbers of highly accurate quantitative data fields, with a large population coverage) versus the clinical imperative to be comprehensive

(i.e. to collect as many clinically relevant fields as possible of high quality) both of which can, however, only be gathered from CF centres with the necessary resources.

1.3. European expansion in 2004

At the outset, we recognised that it might be difficult to apply CF centre-based methods across the whole of Europe given the different country-specific trajectories of underlying economic and health care infrastructure development. Such disparities in development of care are highly relevant to CF since over the last four decades its therapy has changed the most. In parallel with the rapid positive socio-economic changes in Central and Eastern Europe (since 1990) and following the expansion of the European Union (EU) (May 2004) with "New Member States", the current paper reports cross-sectional CF demography, by focussing on recent country-specific population profiles aggregated from CF referral centres across 35 European countries. Such was the demand from nations across Europe to join our project that our original plan to collect data from 22 countries was soon surpassed and in the final event, we had to turn away some countries because they arrived too late to meet the tight deadlines of this time-limited European Commission (EC) "Coordination Action" project which closed in June 2009.

1.4. EuroCareCF remit

This three year project was funded by the Sixth Framework Programme under the eponymous name of EuroCareCF (www.eurocarecf.eu; Project coordinator: D.N. Sheppard, University of Bristol, Bristol, UK). The project was divided into 'Workpackages' each dedicated to different tasks. The hypothesis tested in our Workpackage 2 (relying on the coordinating efforts of the Dundee and Prague groups) was contingent on the notion that provision of simple oral therapeutic measures, such as acid-resistant pancreatic enzyme replacement therapy from the middle of the nineteen eighties, which had previously been shown to correlate with a substantially improved survival towards the end of the last century, would have a measurable effect on disease outcome. Thus, we hypothesised that a current cross-sectional snapshot of CF population profiles could indicate how a given country's health care system was able to deliver 'at the bed side' for this particularly vulnerable group of CF children, who would otherwise suffer high mortality within a few years after birth without appropriately targeted and relatively affordable CF therapy. Our initial remit was to create the conditions for legal consent. Using these procedures, which took two years to develop and implement, we were contracted to produce a report on country-specific CF demographics based on the above consent that was compatible with the laws of each country. Other Workpackages of the EuroCareCF project such as Workpackage 1 focussed on care issues, care teams and their underlying support structures. These issues are excluded from the current report as they lay outside our remit. Here, we report substantial variability in CF demography in some, but not all countries that requires follow up from respective Health Authorities both at EU and/or Member State levels. Our findings, when considered with those of other EuroCareCF Workpackages might also be of interest to developing nations where CF is increasingly being recognised as a clinical entity as childhood mortality from infectious disease wanes and health care resources increase.

2. Methods

2.1. Data collection

The methodological approach was based on pilot experience as detailed elsewhere [14]. As explained above, there always exists a delicate balancing act between obtaining data of high accuracy (i.e. only collecting limited data fields) versus a justified desire to be as comprehensive as possible by collecting additional clinical outcome data. In our earlier pilot studies, we had already published on the possibility of comparing clinical outcomes across continents from existing data sets that had been already collated in developed nations in their own CF Registries [5]. However, we found that this was not a simple task because of the difficulties associated with the separate country-specific development of standards and definitions of disease complications. The principal problem was in the lack of agreed international standards, even for 'core' clinical CF data, which would inevitably fail normative criteria for clinical data quality [13] within any eventual report that we might produce. For example, should we record best or worst lung function and if we chose one or other option, could we agree a 'best' reference equation? These standards were not available and had not been internationally agreed upon. Therefore, we chose the only other path available to us and collected a focussed, quantitative data set containing a few, high quality, verifiable fields mainly of a demographic nature and related to the underlying CF genetics.

Our study design was underpinned by the fact that the variation in CF prevalence between European populations had already been previously assessed by a variety of methods [3,16] providing evidence that the mean prevalence of CF in Europe is 0.737/10,000, close to the value in the United States (0.797/10,000), with the only outlier being the Republic of Ireland where as many as 1 in 17 carry a defective *CFTR*. Moreover, the random nature of CF incidence in the offspring of apparently healthy ("obligate carrier") parents of this autosomal recessive "rare disease" from all social strata provided additional confidence that the above approach was justified. We had the further advantage that the background data on the distribution of the most common CF-causing mutations have been collected for many years from a representative set of European molecular genetic diagnostic laboratories which are traditionally affiliated to their respective CF centres. The size and quality of such data sets relies on the stability of the Hardy–Weinberg equilibrium to estimate the population prevalence of the defective *CFTR* gene [3]. Although the commonest p.Phe508del (synonymous with ΔF508, Phe508del and F508del in "legacy nomenclature") mutation frequency decreases in Europe along the Northwest-to-Southwest gradient, this mutation is "complemented" by

non-p.Phe508del mutations most of which also induce pancreatic insufficiency (PI) in a similar manner to p. Phe508del. Therefore, the distribution of PI-inducing genotypes of CF-causing mutations is not generally different in various European populations since historically carriers of these alleles were positively selected for, as has been the case for p.Phe508del. Moreover, CF carrier and/or neonatal screening programmes are gradually providing updated and more accurate CF incidence estimates in various European countries, which will correct previous inaccurate epidemiological estimates of CF incidence that were confounded by variation in the ability of primary health care to clinically diagnose new cases of the disease [17].

Finally, we had previous estimates of death data and earlier demographic analyses with which we could compare our results [18–21]. The data reported here represent the most up to date demographic data set and therefore differ numerically from our earlier work focussing on Europe as a whole rather than country-specific analyses [21]. In that analysis, we focussed on the relative paucity of CF adults in countries whose gross national product was very low relative to the old member states of the EU. We also observed that the childhood demography of CF in these countries was suggestive of under diagnosis and premature childhood mortality given that the underlying CF gene frequency was not different between the compared regions of Europe [21].

To determine the demographics of CF across countries in Europe, anonymised patient data from participating countries were collected using Microsoft® Office Excel™. Initially, a spreadsheet containing basic demographic data fields (compatible with the US Cystic Fibrosis Foundation PortCF programme definitions — www.portcf.org) was designed to aid international comparison and research. Some countries used this form of reporting. This initial requested data set was subsequently modified by colleagues from the European CF Society (ECFS) (www.ecfs.eu), whereby additional clinical data were added. This updated spreadsheet was completed by other countries. A few countries with existing CF Registries preferred to use their own spreadsheet for providing the necessary demographic data. Finally, some of the existing CF Registries had earlier provided data to the ECFS and for four such countries, these were obtained directly from the ECFS. Importantly, all of the utilised spreadsheets used identical definitions for the demographic data reported here.

2.1.1. Data validation

The data definitions for the demographic variables were similar for all countries and all data were verified by one data manager (M. Fraser; Dundee, UK) who has over 30 years experience in clinical data handling in the UK NHS. Each country's data were inspected and the very small minority of records where either month/year of birth or gender were missing were discarded. Likewise, duplicate records were disregarded. This did not affect the overall results as shown later. The protocols used to validate the obtained data are detailed elsewhere [14].

2.1.2. Data definitions and nomenclature

The year of data collection was taken as the year in which the youngest reported patient was born for each country. We justify this on the basis that CF care improves relatively slowly by incremental steps taking several decades so that differences in the time of data collection between various countries were unlikely to significantly impact the interpretation of data. As shown in Table 1, this year varied between 2003 and 2008. In our analyses, adjustments were made for the different years of data collection where age-related information was being reported. Thus, in the figures showing patients under 18 or over 18 years old and in the 5-year age distributions the relevant number of patients per country was calculated before aggregating data into "European totals".

Importantly, it should be borne in mind that where numbers are small for an individual country, the percentages reported in

Table 1
Data include those patients who have died. Where fewer than 70 patients were reported, the exact number has not been shown in order to maintain patient anonymity as specified in the consents and ensure compliance with the Data Protection Directive 95/46/EC of the European Parliament and country-specific national legislation (data not shown).

Country	Youngest patient born	Patients reported
Armenia	2006	<70
Austria	2006	94
Belarus	2007	153
Belgium	2005	912
Bosnia	2007	<70
Bulgaria	2007	75
Croatia	2007	106
Cyprus	2006	<70
Czech Republic	2007	490
Denmark	2005	441
Estonia	2004	<70
France	2004	4533
Georgia	2008	73
Germany	2005	4758
Greece	2007	177
Hungary	2006	113
Iceland	2005	<70
Ireland	2006	675
Israel	2005	498
Italy	2003	4138
Latvia	2006	<70
Lithuania	2004	95
Macedonia	2007	90
Moldova	2008	72
The Netherlands	2007	888
Portugal	2006	233
Romania	2006	197
Russia	2007	535
Serbia	2007	70
Slovakia	2006	491
Slovenia	2007	107
Sweden	2003	362
Turkey	2007	481
Ukraine	2006	96
United Kingdom	2005	8027
Europe	2003–8	29,095

the data bins within the graphs can vary slightly when patients are allocated arbitrarily to one or other 'bin category' such as a given age band in the age distribution or age at diagnosis. In such cases, a different allocation of even a few patients can alter the percentages reported. Thus, all country graphs should be considered as estimates to the nearest 2% and the somewhat artificial 'bin boundaries' should be viewed with this cautionary note in mind. The convention applied here is that the age of a patient is calculated from the date of birth, but adjusted to the 1st of January of the year after the 'year of data collection' shown in Table 1. Where an age range is shown, this is called a 'data bin' and the upper 'bin' boundary should be read as less than the numerical age value shown and the lower boundary should read 'equal to or greater than' the numerical value. For example: 0–5 years actually refers to children of 0–<5 years who lie within a bin, and 5–10 years means 5 or more years old etc. In the adult children split ratios (pie charts), any person eighteen years or older is reported as an adult. In the case of age at diagnosis, data are rounded to the nearest whole month. Thus, a patient diagnosed at 1 week of age until day 15 was reported as diagnosed at 0 months, while a patient diagnosed at 3–4 weeks was reported as diagnosed at 1 month of age.

2.2. Deaths

29,095 patient records were included for their demographic data, including 1128 (3.9%) patients (from 27 countries) who had died. Some, but not all, countries provided information on patients who had died. The graphs presented for Europe include all patients. However, the age related graphs for each individual country have had records for these patients removed to ensure accuracy of comparison at a country level. At a European level, no significant difference was observed in the 5-year age distribution when the small numbers of deceased patients were excluded compared with when these were included (see Discussion). For one country the inclusion of deaths in their data created a falsely high unknown value data bin. For example, when the *CFTR* genotype of a dead patient was unknown, it would appear that the percentage of unknown genotypes was high. In fact, *CFTR* genotype data would have been more useful if only living patients were used as the denominator. Thus, the unknown columns reported need to be treated with some caution, but we are confident that reporting will improve in the future.

2.3. Exclusions and caveats

Only 66 (0.2%) of records (from 15 countries) were excluded because either month/year of birth or gender data were missing. The age at diagnosis was not provided for 210 patients (0.7%) and was estimated from the date of *CFTR* genotyping. In addition, a further 6 countries in Europe expressed their willingness to participate, but due to delays in obtaining the necessary local legal and ethical permissions or due to severe local resource limitations, they have been unable to provide data in time for this publication. Some countries outside Europe also expressed an interest, but we were unable to include their data due to a lack of resources. Simple clinical data were requested, but on closer inspection had to be excluded from the analysis as they were not comparable across countries. For example, percent predicted lung function could not be used as different countries used different reference equations to perform their calculations. As the date at which lung function was recorded was not requested, it was not possible to recalculate all raw lung function values using a common equation. Likewise, it was not known whether a country had provided the 'best' lung function value in the year, the 'average', or simply the 'reading on the day'.

2.4. Anonymisation and analyses

For the merged European data set, all patients were further anonymised in Dundee by creating a country and clinic code in order to avoid the possibility of a patient being identified in the European data set from a combination of factors. This was particularly the case for countries with small numbers of patients reflective of a more limited *CFTR* genotype distribution, the presence of a frequent founder mutation(-s) specific for a given population or the failure to recognise most patients with the disease in their health care setting. All analyses were carried out using Microsoft® Office Excel and Microsoft® Office Access.

2.5. Ethical and legal issues

Prior to requesting data from any of the participating countries, compliance requirements were checked with the Data Protection Directive 95/46/EC (http://ec.europa.eu/justice_home/fsj/privacy/law/index_en.htm) and relevant Member State Data Protection laws and ethics rules (data not shown). Following advice from the UK Data Protection Officer (Europe), a sample Patient Information Sheet and sample Consent Form were drafted and approval obtained from the EuroCareCF legal and ethical experts (Workpackage 8, H. Nys, K.U. Leuven, Leuven, Belgium). Next, a set of procedures was circulated for each country to ensure compliance with their own national laws and ethical requirements. Both sets of documents are also available on line [21] as web appendices, but are reproduced here with permission from the *Lancet* for convenience. These procedures took into account the design of any ultimate software package and its associated protocols. These protocol issues were discussed at meetings of users set up during the course of the project. In order to protect the anonymity of patients in some of the countries with small numbers of patients reported and to comply with local laws and ethics procedures, all countries in the country-specific sections of this report are identified only by a randomly allocated confidential country code, which is known only to each country representative. However, each country coordinator was asked for their permission to declare their total patient numbers as shown in Table 1. These ethical, legal and consent procedures have been adopted by the ECFS and will serve as a basis for procedures within the new

European Clinical CF Registry (ECFR) that is currently under development (http://qa.ecfs.eu/projects/ecfs-patient-registry/introduction).

3. Results

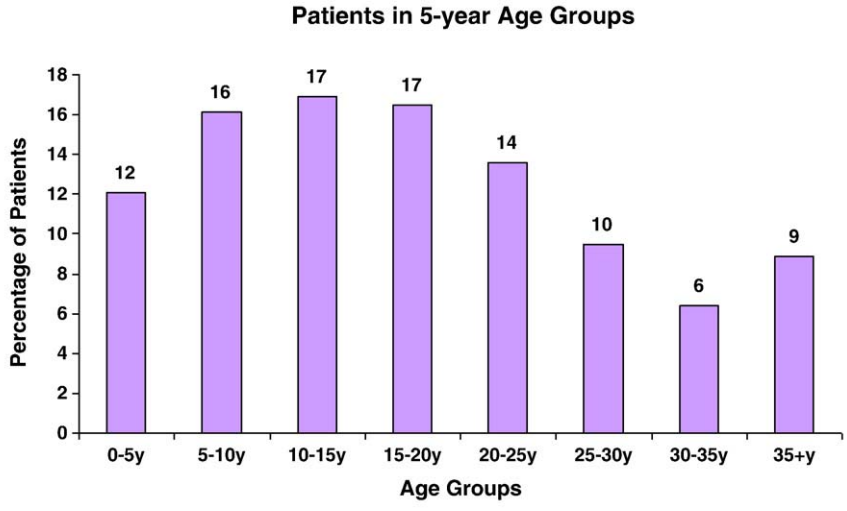
The participating countries and their patient numbers are shown in Table 1. While every effort has been made to include information from as many patients as possible, the data reported here do not necessarily include all patients in each country. In less than 5 countries, for example, only data from one large centre were available, but generally coverage exceeds 50%. At the time of writing this paper in late 2009, many of these countries have updated their patient numbers for inclusion in the newly developed ECFR.

We began our analysis by focussing on the sex and age distributions where and adult is defined as being 18 or greater years of age. We recognised that the age at which a child legally becomes an adult varies across Europe. For example, in some countries, such as the UK, CF 'adults' transfer from children's clinics at earlier ages (around 16 years), but we did not collect these data and figures for adults should be considered as minimum values (see Methods).

3.1. Demographic profile

The data demonstrate that CF adults (12,616 patients) and CF children (16,479 patients) have not yet reached parity across Europe as a whole and there are approximately 4 CF children for every 3 CF adults (57% versus 43%, respectively) in our aggregated CF centres (29,095 total patients). While it is recognised that, at birth, there exists a slight excess of male over female births in the non-CF population (around 1.1 males for every female), that male excess in non-CF babies is offset by a higher male mortality in childhood thus restoring the balance by reproductive age. However, for CF children a clear male preponderance persists and this is even reflected at all ages such that 53% (15,302) are male from 29,095 patients. In summary, in CF, males outnumber females and children outnumber adults in Europe.

We were also interested to examine the age profile of CF patients while recognising that only a small minority of countries were screening for CF at birth at the time the data were collected. Hence (Fig. 1), childhood and adult cases were divided into five year age bands (see Methods for age boundary definitions). We were expecting our observed relative paucity of diagnoses in very young children (since they would not yet have been clinically ascertained) in the absence of Europe-wide neonatal CF screening when compared to those found to be already at school age at the time of data collection. Thus, Fig. 1 shows the expected pattern of patients by age in five year age bands. To a first approximation 1500 CF pre-school children were 'missing' since only 3524 children were of pre-school age compared to the expected number of about 5000. Thus, there remain many undiagnosed young CF children in Europe, some of whom may well have already died because the height of the first bar of pre-school age children is lower than that for older children. In early adult life there is also the expected sharp decrease of the 25–30 year old group, which more than halves in number between 30 and 35 years of age. This rate of change per decade for Europe as a whole is analysed elsewhere in detail [21]. That analysis showed a significantly greater decline in patient numbers with each succeeding decade in patients reported from the Eastern parts of Europe relative to the more



0-5y	5-10y	10-15y	15-20y	20-25y	25-30y	30-35y	>35y	Total
3524	4672	4920	4806	3959	2774	1856	2584	29,095

Fig. 1. Age distribution of CF patients: the bar graph shows patients in 5-year age groups as a percentage of total patients (29,095) in the data set. All patients greater than 35 years old at the year of reporting are aggregated in the last column. The percentages are rounded hereafter unless otherwise stated. The table shows actual numbers of patients in these 5-year age groups, the percentages of which are shown in the bar graph ordinate. For the allocation of patient ages into each bin, see Methods.

affluent Western European countries studied. The fate of these 'missing' adult patients is unknown, but the pattern of decline fits with the expected age of maximum mortality [7]. This older group size disparity most likely reflects differential outcome consequences of inadequate childhood nutrition from an earlier era of unavailability of acid-resistant pancreatic enzyme substitution in the early part of the nineteen eighties in some countries.

3.2. Gender issues

Having observed a "female disadvantage", we focussed on the percentage of males and females by age (Fig. 2) and found that overall, males significantly outnumber females and that this trend further increases in adults. In order to determine the age of onset of the "adult increase", we plotted the age/gender distribution data in five year bands as before to reveal the underlying trend (Fig. 3). The post pubertal onset of the male female ratio imbalance is clear whereby the boys outnumber the girls by one percent point per 5-year age bin and this disparity persists after puberty consistent with the known decreased survival of females in some countries. However, we also note that the excess number of young CF males is consistent across age bins, but becomes even more pronounced as the analysed age increases. The gap between young boys and girls is less than one percentage point per age bin, but the cumulative difference is a full 4 percentage points and is highly significant using a test of proportions ($p<0.001$). Thus, even in childhood there exists a relative paucity of girls (see Discussion).

3.3. Genotypes

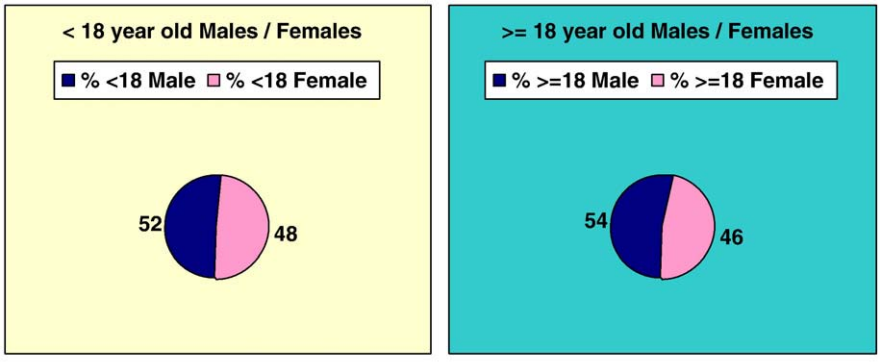
Next, we determined the spread of *CFTR* genotypes across Europe (Fig. 4) using the most common CF mutation as a general indicator for 'PI-inducing mutations' genotype distributions: 46% of all cases were homozygous for the widely prevalent PI phenotype p.Phe508del mutation, p.Phe508del in compound heterozygosity with another non-p.Phe508del CF-causing mutation accounted for 39% and the minority with no p.Phe508del on either allele comprised the remaining 14%. It is important to note that this distribution is drawn from only ~26,000 patients and not from the entire 29,095 patient data set. The missing genetic data are highlighted in the legend Fig. 4.

3.4. Age at diagnosis

Next, we determined the age at diagnosis and tested the hypothesis that the *CFTR* genotype would affect the age at diagnosis (Fig. 5). These data show that many patients continue to be diagnosed beyond infancy as expected consistent with the fact that neonatal screening was not widespread across Europe at the time of data collection. Additionally, Fig. 5 shows that few patients (less than 1%) who are homozygous for the p.Phe508del mutation are diagnosed in early adulthood. The remainder are diagnosed throughout childhood and later in adult life (Fig. 6) reflecting the heterogeneity of the underlying *CFTR* mutation distribution and the severity of pancreatic disease. Thus, the key advantage of studying the homozygous "p.Phe508del disease" is that outcome reflects childhood care in more than 95% of cases.

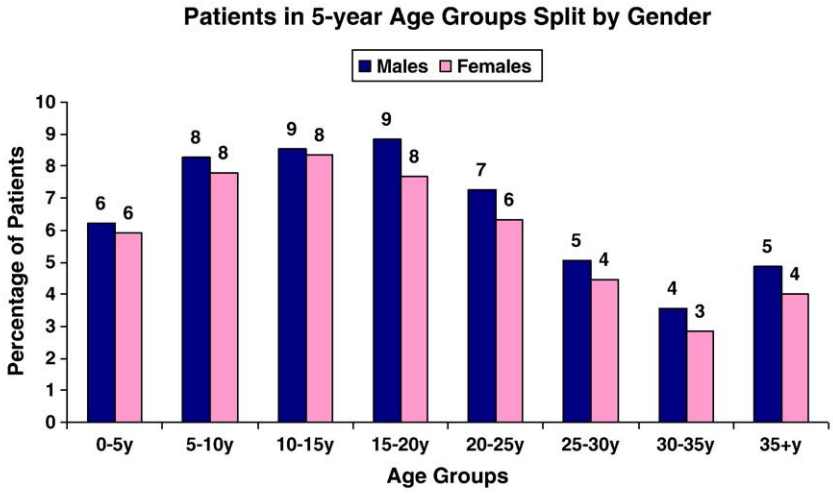
3.5. Relevance to European CF outcomes

A key 'Governmental' objective of the EuroCareCF project was to empower each country representative (who might not be medically trained) with the tools to compare their own data with those of Europe as a whole in a simple format easily understood by non medical staff and/or policy makers. However, it was agreed at the outset that countries should not be identified without their consent in order to protect their anonymity. The latter problem was acute in those countries with a handful of patients (such as Iceland) who could potentially be identified by



<18 year old Males	<18 year old Females	>=18 year old Males	>=18 year old Females	Total Patients
8497	7982	6805	5811	29,095
Total <18 year olds: 16,479		Total >=18 year olds: 12,616		

Fig. 2. Males outnumber females at all ages. Gender split as a percentage (rounded up) of all patients who are less than 18 years old (16,479, left chart) or as a percentage of all patients who are more than or equal to 18 years old (12,616, right). The table shows actual numbers of patients in these categories. Using a test of proportions the differences are highly significant ($p<0.003$) with an estimate of the true value for females residing between 47 and 49%.

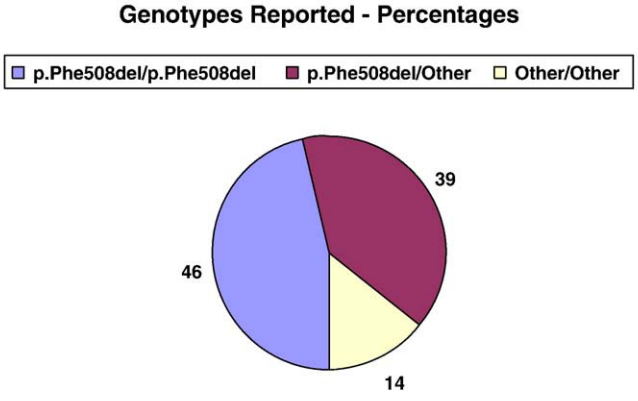


0-5y		5-10y		10-15y		15-20y	
Male	Female	Male	Female	Male	Female	Male	Female
1803	1721	2406	2266	2485	2435	2569	2237
20-25y		25-30y		30-35y		>35y	
Male	Female	Male	Female	Male	Female	Male	Female
2119	1840	1476	1298	1030	826	1414	1170
Total		Total		Total			
Male		Female		All Patients			
15,302		13,793		29,095			

Fig. 3. Onset of male excess: the bar graph shows males and females in 5-year age groups as a (rounded up) percentage of total patients (29,095) in the data set. All patients greater than 35 years old at the year of reporting are aggregated in the last column. The table shows actual numbers of males and females in these 5-year age groups, the percentages of which are shown in the bar graph rounded to the nearest integer which explains the apparent differences in bar height.

a combination of various key factors. As shown in Table 1, we chose 70 patients as an arbitrary cut-off below which numbers of patients would not be specified per country to avoid any potential breach of anonymity.

Nevertheless, in order to maintain data utility for a given country, we allocated a secret country code which remains confidential to that country and on that basis, in Appendices 4 and 5 we reproduce key comparative Figures for Europe as a whole, but now reformatted to facilitate easy cross comparison at an individual country level (Appendix 5). Comparison of these two Appendices illustrates the substantial diversity of country-specific demographics with the caveat that these should



p.Phe508del/p.Phe 508del	p.Phe508del/Other	Other/Other	Total Reported
12,129	10,205	3784	26,118

Fig. 4. Genotypes: the pie chart shows patients in the genotype categories “p.Phe508del/p.Phe508del”, “p.Phe508del/other” and “other/other” as a (rounded up) percentage of all patients where genotype was reported (26,118). The table shows actual numbers of patients in these categories which differ from the totals in earlier figures. The pie chart does not show patients where genotype was not reported (2977), 10% percent of total number of patients in the data set (29,095).

be read with caution should the patient numbers not be large enough to exclude random errors arising from small data set variations.

The power of our simple demographic and gender based approach is reflected by an example (Fig. 7) which at first glance (upper graph) looks very similar to Europe as a whole, but upon further inspection of its underlying gender ratio reveals a marked difference in prevalence for young males versus females (lower graph). Other disparities between countries are presented in the Appendices, referenced against Europe as a whole and are intended for use by participants of the project to illustrate to their respective funding bodies and/or policy makers how a comparison of their own country data might provide evidence to improve their resource allocation for CF care.

4. Discussion

EuroCareCF was a comprehensive pan-European effort running from 2006 to 2009 consisting of a number of projects (Workpackages described on the web site www.eurocarecf.eu) aimed at enhancing complex CF research and care across the EU. Our second Workpackage focussed on registry issues and its main outcomes are reported here. Our primary purpose was to measure CF demography across European countries. This ambition required a legal framework based on sound ethical principles that did not violate data protection laws that are applied differently in each country (see Appendices 1–3 for the forms used for consent as examples, reproduced from *Lancet* with permission). In this way, we could take the initial, but critical data survey step using a restricted, but high quality, data set. Our hypothesis was that only then could we contemplate making the necessary incremental advances in the depth of comparative data coverage based on our earlier experience that identified the key problems associated with an international comparison using clinical data [5,19]. Our secondary purpose was to present our results in an easy to digest format for a non-medical audience where an individual country could compare how well they were performing against Europe as a whole. Hence, the comparative data set in Appendices 4 and 5 coupled to the subset of archetypal graphs reported in the main results section can be combined to illustrate the key differences in demographic profile for 29,095 patients in Europe against which each participating country can easily compare their own profile. Thus, we believe we have set a standard against which future improvements can be measured, thereby meeting our major objective within Workpackage 2 of the EuroCareCF project. We have excluded any reference to the aims of other Workpackages as these will be covered in later reports published in a separate supplement to the Journal of Cystic Fibrosis.

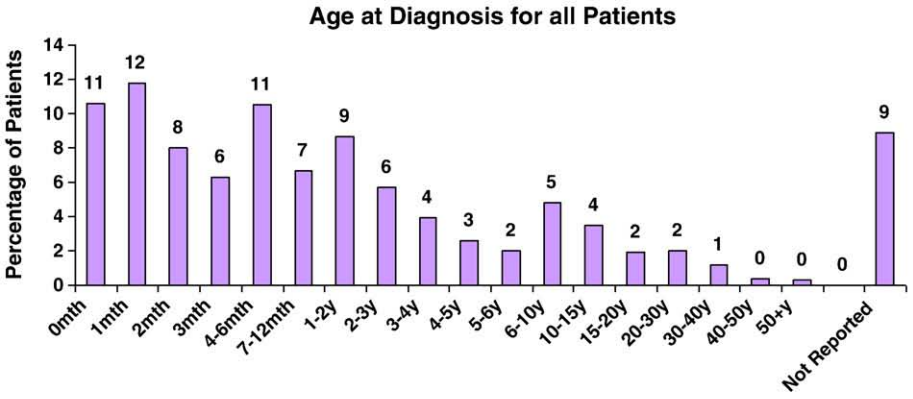
4.1. How should these demographic CF data be interpreted?

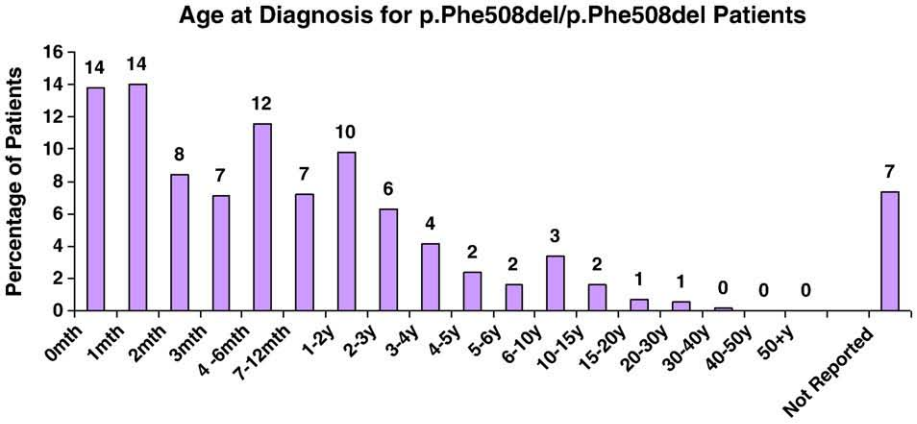
The relative paucity CF patients in some countries reported here cannot be attributed to a lower population prevalence of the defective *CFTR* alleles when referenced against the known geographic distribution of *CFTR* mutations in Europe [17] and/or when assessed by thorough analysis of CF prevalence in Europe [20]. In a separate paper [21], we have highlighted related issues of context by analysing a less complete version of this data set (from 2008) but there, we used the gross national product of groups of countries as a divisor. In that study, we found significantly poorer demographic outcomes in aggregates of those countries who were not members of the EU in 2003 and suggested that resource allocation may be a key issue for early clinical diagnosis, treatment and hence, CF outcomes for a given health care system [21]. As in this study, to keep within our consent, we did not identify any particular country. However, for the current paper, we additionally wrote to each country to ask them for permission to report the raw numbers in Table 1. Crucially, from our new analysis reported here, it is apparent that some countries' demographics are demonstrably failing to reach the European average, which is admittedly skewed by an overrepresentation of patient numbers from economically advantaged nations in the west of Europe (~75% of the total). As might be expected, this enhanced ability to collect data from most CF patients in wealthy countries reflects better coverage based on the maturity of their CF registries, their earlier establishment of nation-wide CF centres and the consequent better survival of CF patients into adulthood. We suggest that the country-specific data outputs shown in Appendix 5, particularly focussing on children under the age of 15, when combined with our Europe wide analysis [21] and comparisons in Appendix 4, show that much could be done to help improve the health status of CF patients in certain European countries relative to their more affluent neighbours.

We have exercised considerable caution in data presentation because we were anxious to avoid any simplistic 'league table' format as we and others have previously found this to stifle progress in interpretation unless due care be taken to counter the effects of random variation [22]. In EuroCareCF, because each country knows their own secret country code, but each is unaware of the coded data from their peers, they can in the first instance, discuss, update and add to the depth of their data internally (which many have already done, not shown) before

Fig. 5. p.Phe508del/p.Phe508del genotype is largely of childhood presentation: the upper bar graph shows all patients grouped by age at diagnosis as a percentage of total patients (29,095). Patients diagnosed later than 50 years old are aggregated into one column. The last column shows patients where age at diagnosis was not reported. The percentages are rounded (e.g. 0% indicates less than 0.5%). The upper table shows actual numbers of patients in the age at diagnosis groups, the percentages of which are shown in the bar graph. Many diagnoses occur after the new proposed gold standard at 2 months (see Discussion). Only 5% of cases present above the age of 15 years which is consistent with the recognised natural history of CF as a childhood disease. The lower bar graph shows the equivalent p.Phe508del/p.Phe508del patients grouped by age at diagnosis as rounded percentages of all p.Phe508del/p.Phe508del patients (12,129). The lower table shows actual numbers of p.Phe508del/p.Phe508del patients in the groups. This form of CF hardly ever presents in adult life. The next figure shows that the reverse is the case for patients without this p.Phe508del on either chromosome who, in direct contrast to the common genotype, form the majority of adult diagnoses.

public scrutiny. While to some readers, our confidential approach may seem to be needlessly restrictive, whenever data are presented for the first time at a country level, our experience in the UK and elsewhere shows that it is an important confidence building measure for such countries to be able to discuss their own data frankly with their own health care



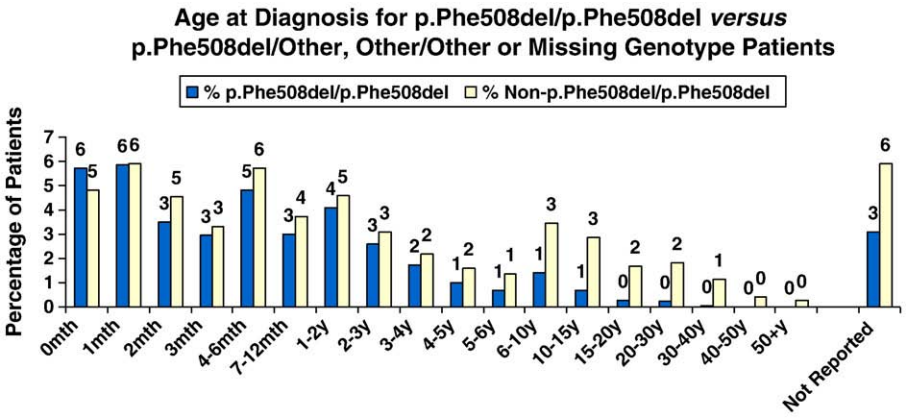


All Patients

0 months	1 month	2 months	3 months
3076	3421	2337	1826
4-6 months	**7-12 months**	**1-2y**	**2-3y**
3068	1958	2525	1657
3-4y	**4-5y**	**5-6y**	**6-10y**
1138	743	586	1407
10-15y	**15-20y**	**20-30y**	**30-40y**
1031	567	592	349
40-50y	**Over 50y**	**Not Reported**	**Total Patients**
125	73	2616	29,095

p.Phe508del/ p.Phe508del

0 months	1 month	2 months	3 months
1672	1702	1017	864
4-6 months	**7-12 months**	**1-2y**	**2-3y**
1405	877	1193	758
3-4y	**4-5y**	**5-6y**	**6-10y**
500	286	193	406
10-15y	**15-20y**	**20-30y**	**30-40y**
195	79	64	19
40-50y	**Over 50y**	**Not Reported**	**Total Patients**
4	0	895	12,129



	0 months	1 month	2 months	3 months
p.Phe508del homozygote	1672	1702	1017	864
Rest	1404	1719	1320	962
	4-6 months	7-12 months	1-2y	2-3y
p.Phe508del homozygote	1405	877	1193	758
Rest	1663	1081	1332	899
	3-4y	4-5y	5-6y	6-10y
p.Phe508del homozygote	500	286	193	406
Rest	638	457	393	1001
	10-15y	15-20y	20-30y	30-40y
p.Phe508del homozygote	195	79	64	19
Rest	836	488	528	330
	40-50y	Over 50y	Not Reported	Total Patients
p.Phe508del homozygote	4	0	895	12,129
Rest	121	73	1721	16,966

Fig. 6. Non-p.Phe508del on either chromosome and adult diagnoses: the bar graph shows patients in the two genotype categories, p.Phe508del/p.Phe508del versus the rest comprising the sum of heterozygotes for p.Phe508del with another disease allele, other/other and unknown genotypes. Patients are grouped by age at diagnosis, split into the two groups, as a percentage of all patients (29,095). Patients diagnosed later than 50 years old are aggregated into one column. The last column shows patients where age at diagnosis was not reported. The percentages are rounded (e.g. 0% indicates less than 0.5%). The table shows actual numbers of p.Phe508del/p.Phe508del and non-p.Phe508del/p.Phe508del (other/other) patients. Adult CF diagnoses almost never bear a p.Phe508del allele in a homozygote state.

providers in the first instance before subjecting their outcomes to public analysis at a European and/or national "governmental" level. This caveat does not apply to those countries with mature registry data sets spanning decades with their attendant coverage of about 70–80% of CF cases. They have already begun these discussions in recent years in an effort to improve resource allocation or quality management as is the case in Germany, for example. Earlier, we applied a similar confidential approach across CF centres in the UK [14,15,19] and recently, in Scotland, CF Centre Directors have agreed to share their local secret codes to internally audit their outcomes.

However, not every country representative agreed with our approach and one CF parent representative expressed deep reservations. She informed us that her own government would 'take no notice of this paper' unless they were 'named and shamed' into action in the full glare of the EU Commission. It might be that some country representatives will place their own data in the public domain in order to help persuade their own authorities that something must be done to improve their demographic profile. However, this is not a matter for us as it lies outside of our remit and consent. The main concern on our side is the uncertainty about the depth of coverage for a given country with an apparently 'poorer' outcome. However, there are some findings that cannot easily be dismissed as either bias due to lower national or regional rate/proportionality of case ascertainment or an artefact due to population-based variations in CF carrier frequency, as discussed elsewhere [21].

4.2. Is there a wider message for EU Health expenditure in rare diseases?

4.2.1. Setting demographic standards for CF outcomes

Even if the outcome data reported here are indeed biased in some countries, today's CF patients should nevertheless have a mortality of less than 5% by the time they reach 15 years of age when cared for in a relatively affluent country

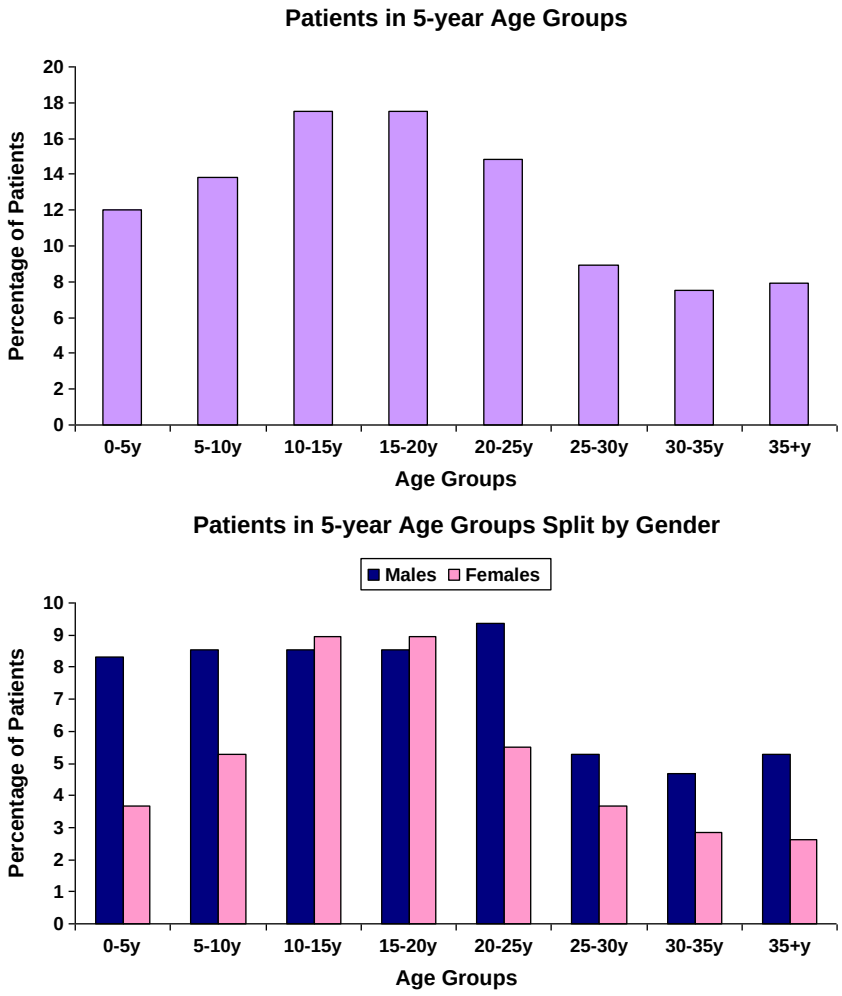


Fig. 7. Gender and outcome: comparison of the overall age profile in the upper graph with the data in Fig. 1 suggests that this country has no difference when compared to Europe as a whole but the sex ratios tell a different story with an unexplained paucity of pre-pubertal girls that requires further explanation (see text in Discussion section about delayed diagnosis in females).

such as the UK [7,11,12]. Because UK demographic data are as complete as possible in terms of avoiding ascertainment bias, this sets an international benchmark for completeness and we can be confident in using them as a target measure. The critical pioneering vision of Professor John Dodge (UK) is acknowledged in this respect in setting up the underlying methodology from the 1960s. Thus, with respect to CF outcome, we should observe a stable (i.e. within 5%) number of children in 5-year age bins between 5–10 years and 10–15 years. In our view, this is a measurable standard for all countries to aspire to in the next phase of this work under the auspices of the ECFS.

These emergent ideas relate to a third EuroCareCF 'aim' which only became apparent from repeated questions posed to us by many different organisations (outside of CF care) responsible for other rare diseases (e.g. Eurordis; www.eurordis.org or Orphanet; www.orpha.net), including representatives of the secretariats of different European governments during the process which led to the adoption of the "EU Council Recommendation on an action in the field of rare diseases (2009/C151/02)" (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF) in June 2009. Their frustration lies in developing robust methods to remotely assess disparities in diagnosis and care for rare diseases across Europe without the confounding factor of poor coverage in rare diseases casting doubt on the conclusions. Their interest lies in measuring the degree to which taxpayer spend translates into better health in the area of rare diseases at Member State and/or EU levels. Furthermore, at the EU level, knowledge of measurable demographic variables, with CF being a useful example because of its random occurrence, various EC directorates (such as DG Sanco) could foster a critical evaluative process by Community level programmes, albeit respecting the principle of national subsidiarity with regard to health care provision. Moreover, since the USA currently is also embarking on Universal Health Care, similar considerations may well apply to health disparities in the wealthiest country in the world. In our CF presentation at the EU parliament in 2009 (at the invitation of the patient organisation, CF Europe — http://www.cfww.org/cfe/), we pointed out to twenty members of Parliament or their representatives, that our CF "registry paradigm" could provide an answer of broader applicability to rare disease in general by

focussing on disease demographics. For example, one EU country may wish to "officially" compare their data with their neighbours and report differences to their respective members of the EU Parliament. These issues received substantial attention at the 5th European Conference on Rare Disease in Krakow — Poland (http://www.rare-diseases.eu/2010/) and it has been acknowledged that CF serves as a model for other rare diseases in this regard.

4.2.2. What should be done across Europe?

A CF outcome measure based on cross-sectional demographics could enable the EU Commission to compare health care across Europe thus measuring multiple modalities in one step should the numbers of CF patients decline across 5-year age bins as children age. We therefore propose a self-referencing simple measure (well within the compass of any CF Centre or the simplest CF disease registry) that aggregates the ability of a country's health care system to firstly diagnose pancreatic insufficient CF (ascertainment of failure to thrive), and secondly demonstrate an ability to treat it effectively in childhood (delivery). We put forward this simple demographic measure because CF arises both randomly and unexpectedly with a high enough population frequency of its carriers coupled to a potential lethality in CF-affected babies if missed. Thus, we consider such CF outcome as part of a broader reality — namely, a measure of the ability of any given health care system to cope with an unexpectedly ill child presenting with multiple organ failures in a targeted and effective manner, see outcomes after CF-related diabetes (CFRD) as a critical example [23]. Hence, we consider survival into late childhood in CF to be a marker of the degree of fitness for purpose of any health care system that claims to care for unexpectedly sick children with a chronic multi-system disease; in this instance a disease that is among the commonest of inherited rare diseases. Our country-specific data demonstrate that many countries in Europe are not apparently matching their CF outcomes against the 'best', defined here as outcomes in well resourced and long standing members of the EU who have published their own outcomes through their own CF patient organisations with robust external validation in one instance [7], i.e. in order to ensure that the data reported are reliable. Such outcomes from relatively economically advanced nations are generally in line with the European pattern as a whole. Recently, Mastella and colleagues [24] compared CF outcomes across the globe and they make a key observation. They comment that properly targeted and CF-specific high calorie nutrition, which is relatively inexpensive for any EU member state, should be the first step towards improving CF outcome. They cite the recent dramatic effects of improving caloric intake in Quebec with corresponding enhanced survival within two decades of introduction. In our view, this should be a critical early step in the next phase of CF data gathering across Europe to try and determine whether poor childhood nutrition can explain why the demographic patterns are so different in some countries. When this idea is coupled to newborn screening for CF (which was not generally prevalent in Europe at the time we undertook this work and may not be affordable in some countries), which permits an early introduction of a suitable high calorie diet and replacement pancreatic enzyme therapy, then it might be expected that CF survival will dramatically accelerate using relatively simple measures whose effects are easily measurable, as discussed elsewhere [21].

4.3. Why is there a female disadvantage in CF?

When considering survival, female gender and its attendant poor CF outcome is also clearly an issue to consider [23]. Disadvantaged female survival is a complex area with an amalgam of effects causing the disparity between genders (inter alia, worse outcomes after puberty for females with particular reference to CF-related diabetes, the different effects of oestrogens versus androgens on *CFTR*, the unexpected presence of *CFTR* in the hypothalamus and its associated effects on hormone secretion, delayed diagnosis in females in some, but not all parts of the world). These matters, while of great significance to CF research, lie outside the scope of our remit. They combine to create an easily measurable 'gender ratio metric' of relevance to gauge CF outcome because they are amenable to therapy and crucially, might also reflect the response of care teams to gender issues (a critical country example is shown in Fig. 7). Therefore, another future outcome standard for governments might be the relative stability of the numbers of males versus females within less than one percentage point of one another over childhood. These will be matters for the new ECFS European CF Registry, respective national CF patient support groups, their trans-national organisation via activities of CF Europe (www.cfww.org/cfe), and for the ECFS Board.

4.3.1. Is the observed male excess a reflection of distorted gender-related segregation of mutated CF alleles (or "meiotic drive")?

Kitzis et al. [25] refuted the previously suggested preferential transmission of mutated CF alleles through fathers, but intriguingly found a statistically significantly increased number of obligate CF carriers among male siblings, together with a decrease of female carrier siblings, in a large collaborative study analysing European and North-American CF patients with regard to the expected Mendelian pattern expressed by the "2:1" carrier/patient ratio. Although subsequent single sperm-based molecular genetic typing within a sizeable cohort of sperm derived from one p.Phe508del carrier did not find significant differences between the number of p.Phe508del-X chromosome and p.Phe508del-Y chromosome bearing sperm [26], our observation of male excess in childhood in Western European cohorts associated with low early childhood CF mortality rates requires further exploration of this intriguing issue in a larger cohort of p.Phe508del carriers.

4.4. Recognition of sources of bias and their potential impact on the project

4.4.1. Data deficits

In any exercise of this magnitude there are unavoidable limitations. Unlike a highly prevalent, but potentially life-long

disease such as asthma, which can affect 5–10% of otherwise normal children at some time in their lives, the relative paucity of CF suffers for a given hospital or country [20] creates the problem of incomplete case ascertainment. This is made worse by the fact that the clinical diagnosis of CF is not as straight forward as for instance in the case of asthma. Thus, we recognise that the data reported here reflect poor coverage of the CF population for a given country which is only to be expected given differences in history and resources in different parts of Europe. In our previous experience in a well resourced Western European setting, we were only able to improve data capture from 40% to over 70% over the course of ten years and our efforts have been reviewed by others elsewhere [24]. These reviewers note that an incremental approach to data gathering has been adopted by many countries, also over many decades (North America, France, UK, Germany and others). Thus, the data reported here should be viewed only as a first step from which our (currently unknown coverage for many participants) should improve for those countries without a recognised data gathering infrastructure. Setting each individual country a target of around 70% coverage seems a reasonable five year goal.

4.4.2. Country deficits

There was a necessity to make an initial list of established European CF centres aggregated into Table 1 whose identities were ascertained through surveys of national and international CF patient organisations and from members of the ECFS. Importantly, one of us (MM) was able to utlilise his long standing contacts throughout Central and Eastern Europe based on his previous coordination of population genetic studies in CF [17] making us believe we have as broad a coverage as might be reasonably expected. Despite these efforts, some countries could not supply data in time to meet our tight deadlines. Overall, we recognised two sorts of bias affecting the reported prevalence of CF children and adults in our study. Although both biases result from undiagnosed CF cases, given the fact that many of the presenting features of CF are of general nature (diarrhoea, pneumonia, failure to thrive, prolonged jaundice, or heat shock in warm climate being typical examples), they nevertheless operate at different ages within the CF severity spectrum. In some paediatric CF clinics, such patients may not have been identified because as many as 1 in 5 CF-affected babies might have already died unrecognised in the absence of neonatal screening. These missed cases are often labelled as having died from pneumonia or gastroenteritis by those untrained in CF disease [18]. Such under-ascertainment in childhood also pertains at the opposite end of the clinical severity spectrum where the mild CF cases often go unrecognised throughout childhood and are usually only sporadically clinically recognised later in adulthood. This latter factor falsely elevates survival estimates when new adult entrants replace dying childhood cases. In addition, the issue of a delay in the diagnosis of CF in females might explain our failure to find the expected number of females (see above and Fig. 7). Thus, at the outset we recognised that our reported demographic data must be considered as the minimum prevalence.

4.5. Technical issues relating to cohorts

A second caveat to our conclusions is that the year of data collection for the participating countries varied between 2003 and 2008. Although this was not optimal, we felt that as this was the first time that a large number of European countries had collected and pooled their data, this range of years offered the greatest flexibility to participating countries to provide the maximum amount of data that they were realistically able to gather within the limited duration of the EuroCareCF project. Further, even some of the countries with existing registries were able to provide maximum data for a pre-specified year only, often in the earlier part of the period 2003–2008. Because the demographic profile for Europe would not be expected to vary greatly within the 6-year period studied and because CF outcomes such as improved survival evolve only by decades of practice change [7], our chosen range of years was considered the most practical for the demographic analyses reported here. The maximum likely discrepancy in outcomes measured as survival would have been in the range of two years median survival. To determine the magnitude of this effect, we also tested whether deaths might affect our analyses for Europe because we included all patients who had been identified as deceased within the total reported (n=29,095). To confirm that this death inclusion did not significantly affect the final figures if the deceased patients had been omitted, we recalculated the European 5-year age distribution removing deaths (n=27,967). Fig. 8 compares the two sets of figures and substantiates the particularly high robustness of our data.

4.6. Country-specific reports

4.6.1. Matters for national authorities under EU health care-related "subsidiarity" rules

In health care matters, subsidiarity implies that Member States are responsible for their own health outcomes. Many countries reported here manifest delayed 'ages at diagnosis' as shown in the country-specific data to be found in the Appendices. Even if a correct CF diagnosis is made, recent data suggest that an inability to make an early enough diagnosis (enabling prompt and targeted therapy in CF) may adversely influence surrogate markers of a poor prognosis in childhood CF [27]. Such 'diagnosis-delayed' children may well survive into adulthood, but suffer from markedly impaired overall clinical status, thereby increasing treatment and management costs needlessly. Indeed, Phillipp M. Farrell when commenting on the idea that early diagnosis is prognostically important suggests that the new gold standard to improve outcome should be initiation of first line therapy by two months of age (rather than the current three months) following the recent introduction of various CF newborn screening schemes in the majority of US states [28].

We adjusted our 'age at presentation' graphs reported here accordingly and found that many CF patients continue to be diagnosed very late in childhood. This factor could also have introduced a bias into our demographic findings on the profile of CF at different ages because some CF-affected children not

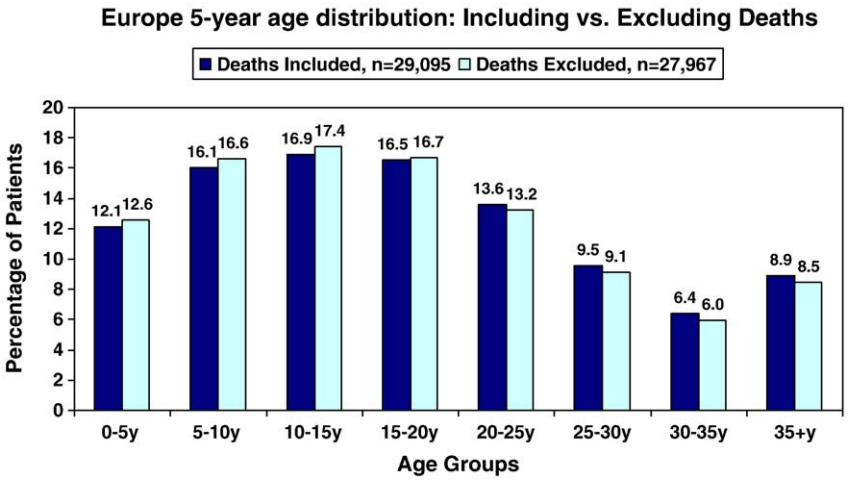


Fig. 8. Accounting for deaths: deaths do not influence the overall demographic profile.

receiving adequate care might not survive into late adult life. Thus, we were expecting a lower number of "older" adults versus children with CF in some countries. However, failure to find enough older CF adults in a given country might not solely be due to earlier childhood death. Another potential source of bias might occur because adult CF centres might not be established in a given country leading to patient dispersal to physicians outside CF after childhood was complete. This is offset by the factor that in some instances, paediatric clinics continue to treat their older patients because no specialist adult care is available. After all, even in a well resourced country like the UK, adult CF care is a relatively recent development as a result of patient pressure on Governments that followed increased childhood survival. In some countries such as Scotland, adult care is funded centrally by top slicing NHS budgets, but this is far from universal. Thus, a failure to find enough CF adults reported from some countries might also reflect gross under-reporting as their care might be dispersed to general pulmologists and/or gastroenterologists with limited CF expertise or indeed, they may be sent back to primary care to manage their own disease. Based on the analyses reported by Britton and co-workers reported above [18], the expected net effect of these potential biases on our expected demography was such that there would likely be a gap of at least 20% between the expected number of CF cases from the known mutated *CFTR* allele prevalence in a given country and the much lower actual number of clinically diagnosed CF cases reported from the specialist clinics within our survey.

4.7. Next steps

4.7.1. All data fields are not of equal value for outcome determination

Others have led the way in data field discrimination. For example, Marshall and colleagues published a model [29] that might be predictive of survival in a US setting and comment that not all data items in a registry are prognostic for survival. These authors suggest that a focus be placed on age, sex, FEV_1, weight-for-age as a Z score, pancreatic status, diabetes mellitus (CFRD) and *Staphylococcus* or *Burkholderia* chronic bronchial colonisation status. However, this approach is not the only one available and O'Conner and colleagues from Canada take a slightly different view [30] focussing on age, gender, age at diagnosis, sweat sodium concentrations, ethnic origin, symptoms at diagnosis and the distribution of *CFTR* genotypes. Although the model developed by Marshall and colleagues [29] was developed for the purpose of the Cystic Fibrosis Foundation and the specifics of the US health care, it remains to be properly substantiated how data field discrimination might be applied in Europe with its diverse national and/or regional health care approaches. The most appropriate variables for collection are currently under discussion within the European CF Registry Working Group that succeeded EuroCareCF initiative. In the view of the authors of the current paper, gender, *CFTR* genotype and age at diagnosis are critical issues because their intrinsic variability may also help us to understand CF natural history at a country level.

4.7.2. Exit strategy

The EuroCareCF project was of a fixed duration, ending in June 2009. At the project outset, it was therefore important to have a clear exit approach in mind to ensure continuity. Our report does not address clinical data, which are being handled by the ECFS separately although clinical data were collected where possible on a pilot basis to ascertain likely difficulties (not shown). Once all countries start to use the standard software being implemented for use across Europe by the ECFS, or they are able to standardise their data definitions to a common agreed European basis (underway through activities of M. Stern, Tübingen, Germany), such obstacles will be more easily overcome. The ECFS with whom EuroCareCF has worked closely and who are committed to continuing the European CF Registry after the end of the EuroCareCF project are currently addressing these issues (http://www.ecfs.eu/projects/ecfs-patient-registry/intro).

In conclusion, CF demographics vary greatly across Europe. The reasons need to be examined critically at a country level in order to set standards for improvement. We urge the European Commission and all European Member State Governments whether inside or outside the EU to act

swiftly. We also ask these governments to evaluate the use of outcome in childhood as a surrogate marker for the ability of their own general health care systems to deliver at the citizen level in a life-limiting inherited disease that occurs randomly and crucially, is lethal unless treated promptly.

Conflict of interest statement

The authors have no conflict of interest that could influence the content or processing of this manuscript. The funders had no input into the current paper, which is an output from Workpackage 2 of the EuroCareCF Coordination Action dealing with work for the European Cystic Fibrosis (CF) Patient Registry.

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References

[1] Davis PB. Cystic fibrosis since 1938. Am J Respir Crit Care Med 2006;173 (5):475–82.
[2] Walters S, Mehta A. Epidemiology of cystic fibrosis in cystic fibrosis. In: Hodson M, Geddes D, Bush A, editors. Great Britain: Hodder Arnold; 2007.
[3] Bobadilla JL, Macek Jr M, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations—correlation with incidence data and application to screening. Hum Mutat 2002;19(6):575–606.
[4] Sharma N, Singh M, Kaur G, Thapa BR, Prasad R. Identification and characterization of CFTR gene mutations in Indian CF patients. Ann Hum Genet 2009;73(1):26–33.
[5] McCormick J, Sims EJ, Green MW, Mehta G, Culross F, Mehta A. Comparative analysis of Cystic Fibrosis Registry data from the UK with USA, France and Australasia. J Cyst Fibros 2005;4(2):115–22.
[6] Mehta A. A global perspective on newborn screening for cystic fibrosis. Curr Opin Pulm Med 2007;13(6):510–4.
[7] Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947–2003. Eur Respir J 2007;29(3):522–6.
[8] Wolfenden LL, Schechter MS. Genetic and non-genetic determinants of outcomes in cystic fibrosis. Paediatr Respir Rev 2009;10(1):32–6.
[9] Hodson ME, Simmonds NJ, Warwick WJ, Tullis E, Castellani C, Assael B, et al. An international/multicentre report on patients with cystic fibrosis (CF) over the age of 40 years. J Cyst Fibros 2008;7(6):537–42.
[10] Simmonds NJ, Cullinan P, Hodson ME. Growing old with cystic fibrosis — the characteristics of long-term survivors of cystic fibrosis. Respir Med 2009;103(4):629–35.
[11] Dodge JA, Morrison S, Lewis PA, Coles EC, Geddes D, Russell G, et al. Incidence, population, and survival of cystic fibrosis in the UK, 1968–95. UK Cystic Fibrosis Survey Management Committee. Arch Dis Child 1997;77(6):493–6.
[12] Dodge JA, Morison S, Lewis PA, Coles EC, Geddes D, Russell G, et al. Cystic fibrosis in the United Kingdom, 1968–1988: incidence, population and survival. Paediatr Perinat Epidemiol 1993;7(2):157–66.
[13] Black N. High-quality clinical databases: breaking down barriers. Lancet 1999;353(9160):1205–6.
[14] Mehta G, Sims EJ, Culross F, McCormick JD, Mehta A. Potential benefits of the UK Cystic Fibrosis Database. J R Soc Med 2004;97(Suppl 44):60–71.
[15] Sims EJ, McCormick J, Mehta G, Mehta A. Newborn screening for cystic fibrosis is associated with reduced treatment intensity. J Pediatr 2005;147 (3):306–11.
[16] Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. Stat Med 1996;15(5):449–62.
[17] Bobadilla JL, Farrell MH, Farrell PM. Applying CFTR molecular genetics to facilitate the diagnosis of cystic fibrosis through screening. Adv Pediatr 2002;49:131–90.
[18] Fogarty A, Hubbard R, Britton J. International comparison of median age at death from cystic fibrosis. Chest 2000;117(6):1656–60.
[19] McCormick J, Green MW, Mehta G, Culross F, Mehta A. Demographics of the UK cystic fibrosis population: implications for neonatal screening. Eur J Hum Genet 2002;10(10):583–90.
[20] Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros 2008;7(5):450–3.
[21] McCormick J, Mehta G, Olesen HV, Viviani L, Macek M, Mehta A. Demographics of the European Cystic Fibrosis Population, a cross sectional study. Lancet 2010;375:1007–13.
[22] Spiegelhalter DJ. Funnel plots for comparing institutional performance. Stat Med 2005;24(8):1185–202.
[23] Sims EJ, Green MW, Mehta A. Decreased lung function in female but not male subjects with established cystic fibrosis-related diabetes. Diab Care 2005;28(7):1581–7.
[24] Buzzetti R, Salvatore D, Baldo E, Forneris MP, Lucidi V, Manunza D, et al. An overview of international literature from cystic fibrosis registries: 1. mortality and survival studies in cystic fibrosis. J Cyst Fibros 2009;8(4): 229–37.
[25] Kitzia A, Chomel JC, Kaplan JC, Giraud G, Labbe A, Dastugue B, et al. Unusual segregation of cystic fibrosis allele to males. Nature 1988;333: 215.
[26] Williams C, Davies D, Williamson R. Segregation of ΔF508 and normal CFTR alleles in human sperm. Hum Mol Genet 1993;2:445–8.
[27] Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. Pediatrics 2007;119(1):19–28.
[28] Farrell PM. The meaning of "early" diagnosis in a new era of cystic fibrosis care. Pediatrics 2007;119(1):156–7.
[29] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153(4):345–52.
[30] O'Connor GT, Quinton HB, Kahn R, Robichaud P, Maddock J, Lever T, et al. Case-mix adjustment for evaluation of mortality in cystic fibrosis. Pediatr Pulmonol 2002;33(2):99–105.