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Case report

# The prevalence of cystic fibrosis in the European Union

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**Abstract**

This study combined a variety of methods to determine the prevalence of cystic fibrosis in the European Union. The results of literature reviews, surveys, and registry analyses revealed a mean prevalence of 0.737/10,000 in the 27 EU countries, which is similar to the value of 0.797 in the United States, and only one outlier, namely the Republic of Ireland at 2.98.


*Keywords:* Cystic fibrosis; Prevalence; Incidence; Europe; European Union

Although the incidence of cystic fibrosis (CF) has been generally well defined throughout Europe in recent years from newborn screening programs [1], its prevalence is more difficult to ascertain for a number of reasons, including the fact that the medical/scientific literature and patient registries vary in quality. Thus, the prevalence of CF in the European Union (EU) has not been determined with sufficient accuracy in its 27 constituent countries. During the past two decades, care for European patients with CF has been increasingly organized in specialized centers and diagnoses generally reported to regional or national registries. This facilitates determination of the prevalence of CF for most European countries. The available data, however, show substantial variations, although all of the information suggests a prevalence that is much lower than 5 per 10,000 population, the limit for "orphan disease" designation. [2]

A quantitatively and geographically comprehensive assessment of CF in Europe was performed and published by Farrell's research team in collaboration with Milan Macek [3]. Their project was designed to determine the worldwide distribution of CFTR mutations and the number of patients so assessed in each country. This article [3] was published after an exhaustive literature search that included 33 European countries and 115 references which are available online. Subsequently, only a limited number of other articles have appeared, but the CF patient registries of European countries have improved significantly during the past few years. Furthermore, many European countries now require patients to be registered at CF centers in order to receive reimbursed care. These developments made it possible to determine the prevalence of CF throughout the EU with estimation required in one country with only limited information. This brief report describes the multiple methods used to determine CF prevalence among Europeans and data from the 27 EU countries, as well as incidence data where available.

## 1. Methods

For this evaluation of CF prevalence in the 27 EU countries, after an uninformative EMBASE.com search, a combination of three methods was used: 1) a PubMed literature search from 1990 through 2006; 2) a review of CF patient registry data available from the European Cystic Fibrosis Society and individual countries, generally for the year 2004; and 3) a survey of CF leaders in 18 European countries accomplished by exchanging e-mail communications. In addition, where no reliable CF patient information could be found for the country (i.e., Malta), the number of CF patients was estimated/predicted by multiplying the average prevalence determined in other European countries times the population reported in 2004. The population values for each country were obtained from the U.S. Census Bureau website for the last complete year available at

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the time of this analysis, namely 2004 [4]. This corresponds closely to the period that most of the information on reported CF patients was obtained. To ensure accuracy, these population values were compared with data published by Eurostat, which is the Statistical Office of the European Communities [5]. The average difference in the population values listed by the U.S. Census Bureau and the values published by Eurostat was 1.43% for the 27 countries. Thus, the U.S. Census Bureau figures were considered sufficiently accurate for the purposes of this study.

In addition to identifying data on CF patient numbers reported and/or registered in EU countries, the literature review included a survey of reported CF incidence values. Whenever possible, birth incidence values based on newborn screening experience were obtained as the likely most accurate data [1].

The validity of the prevalence data was established by examining survey results for potential biases and demonstrating comparability when several sources were available. Instead of merging such data or calculating a weighted average, it was decided to accept and report the highest number of patients because of the probability of under-reporting [6].

## 2. Results

The accompanying table provides a summary of available information for EU countries during 2004 and includes population, the number of reported CF patients, calculated prevalence, estimated prevalence, incidence reported in the literature (birth incidence, whenever available), and source of the data. All CF prevalence values were data-driven determinations from the literature and/or registries, and generally from multiple sources, except for Malta where the prevalence was estimated from the population and mean EU prevalence; because the population of Malta at 397,000 is only 0.8 % of the EU total, this estimation has a negligible effect on overall precision (Table 1).

The CF incidence data of the table were derived from the most accurate sources that could be found in the literature and are expressed in the conventional fashion as CF cases diagnosed in relationship to livebirths. Whenever there was information derived from nationwide newborn screening, those values were selected as presumably the most accurate. This explains why the incidence data listed for some countries such as France (1:4700) vary from the older values reported by Bobadilla et al. [3]. For other countries such as the Czech Republic more analysis of birth incidence based on newborn screening outcome data will be needed to insure accuracy.

Combining all EU countries, there were 35,806 CF patients identified in a total population during 2004 of 486,114,000, resulting in a mean prevalence of 0.737 per 10,000 in the 27 EU countries. A similar calculation for the United States indicates 0.797 CF patients per 10,000 people using the very accurate data of 2005 from the U.S. Cystic Fibrosis Patient Registry which reports 23,347 patients registered for care in a population of 293,028,000 [7]. This relatively close agreement, which is not altogether surprising, helps validate the accuracy of the EU prevalence value reported herein.

Further calculations from the EU data reveal a variance $[P\times(1-P)=0.737\times0.263]$ of 0.194 and a SD of 0.44. The range of CF prevalence is from 0.104 in Latvia to 2.98 in the Republic of Ireland (per 10,000). Using the 95% confidence interval (0→1.5994) for evaluating individual countries indicates that only the Republic of Ireland is an outlier. As the table shows, Ireland also appears to have the highest incidence at 1:1353 based on registry and survey data [8]. The UK with the

Table 1
Population and prevalence of patients with CF in E.U. countries

| | Population in 2004 (thousands) | # CF patients | CF prevalence (per 10,000) | Estimated CF incidence | Source(s) |
|---|---|---|---|---|---|
| Austria | 8,175 | 686 | 0.839 | 1:3500 | Ia, [1] |
| Belgium | 10,348 | 1065 | 1.03 | 1:2850 | Ib, IIa, [13,14] |
| Bulgaria | 7,518 | 170 | 0.226 | 1:2500 | [13] |
| Cyprus | 776 | 26 | 0.335 | 1:7914 | [15] |
| Czech Republic | 10,246 | 570 | 0.556 | 1:2833 | Ic, IIa, [14,16] |
| Denmark | 5,413 | 412 | 0.761 | 1:4700 | IIa, [14,17,18] |
| Estonia | 1,342 | 83 | 0.618 | 1:4500 | [17] |
| Finland | 5,215 | 64 | 0.123 | 1:25000 | Id, [17,19] |
| France | 60,424 | 4533 | 0.750 | 1:4700 | Ie, IIa, IIe, [1] |
| Germany | 82,425 | 6835 [a] | 0.829 [a] | 1:3300 | If, IIa, [14,16,20] |
| Greece | 10,648 | 555 | 0.521 | 1:3500 | Ig, [14] |
| Hungary | 10,032 | 410 | 0.409 | | Ih |
| Ireland | 3,970 | 1182 | 2.98 | 1:1353 | Ii, IIb, [8] |
| Italy | 58,057 | 5064 | 0.872 | 1:4238 | IIc, [21] |
| Latvia | 2,306 | 24 | 0.104 | | [7] |
| Lithuania | 3,608 | 47 | 0.130 | | [7] |
| Luxembourg | 463 | 20 | 0.431 | | [7] |
| Malta | 397 | 23 | 0.579 | | IV |
| Netherlands | 16,318 | 1275 | 0.781 | 1:4750 | IIa, [22] |
| Poland | 38,580 | 987 | 0.256 | 1:5000 | Ij, [1] |
| Portugal | 10,524 | 285 [a] | 0.271 [a] | 1:6000 | Ik,[7] |
| Romania | 22,356 | 238 | 0.106 | 1:2056 | [23] |
| Slovakia | 5,424 | 340 | 0.627 | 1:1800 | IIa, [24] |
| Slovenia | 2,011 | 66 | 0.328 | 1:3000 | [7,25] |
| Spain | 40,281 | 2200 [a] | 0.546 [a] | 1:3750 | Il, [13,14] |
| Sweden | 8,986 | 362 | 0.403 | 1:5600 | IIa, [26] |
| United Kingdom | 60,271 | 8284 | 1.37 | 1:2381 | Im, IIa, IId, [9] |

I = survey data.
a. Austria (Manfred Götz).
b. Belgium (Jean-Jacques Cassiman).
c. Czech Republic (Milan Macek).
d. Finland (Leena Jokinen).
e. France (Virginie Scotet).
f. Germany (Gerd Döring and Andreas Reimann).
g. Greece (Maria Tzetis).
h. Hungary (Klara Holics).
i. Ireland (Linda Foley).
j. Poland (Dorota Sands).
k. Portugal (Maria Celeste Barreto and Margarida Amaral).
l. Spain (Silvia Gartner and Manuel Sanchez-Solis de Querol).
m. United Kingdom (Anil Mehta).
II = registry information.
a. European CF Registry (provided by Karleen De Rijcke).
b. The CF Registry of Ireland (provided by Linda Foley).
c. Registro Italiano Fibrosi Cistica (provided and translated by Carlo Castellani).
d. UKCF Database (provided by Anil Mehta).
e. Observatoire National de la Mucoviscidose (provided by Virginie Scotet).
III = extrapolation (see text).
–Arabic numerals correspond to references in bibliography.
[a] Revised from EU submission to COMP.

next highest prevalence at 1.37 per 10,000 also has one of the highest incidence values at 1:2381 [9]. With this in mind, it was of interest to compare using regression analysis the determined prevalence and reported incidence figures. In this analysis, we found that the Pearson correlation coefficient between the prevalence and incidence data presented in the table is 0.5688 ($p$=.0057). Also, using regression analysis in an attempt to predict incidence from prevalence, we found the following formula — incidence = 0.00019 + 0.00016 × prevalence per 10,000 — and a $p$-value for this model of 0.0015. This significant relationship reflects the correlation between prevalence and incidence and the relative clustering of CF in EU countries.

## 3. Discussion

In general, the agreement of calculated prevalence values for a variety of large European countries strongly suggests that the data are consistent, valid, and as accurate as possible. Also, in the relatively large European countries that have performed multiple determinations of the total number of registered CF patients, the agreement among prevalence values found is generally satisfactory. For instance, comparing values in the UK reveals 7046, 7500, 6861 and 8284 patients with CF from a variety of recent observation periods, while France reported 4140 and 4533, and Belgium registered 859, 860, and 1065 patients in three different tallies.

Although the larger European countries were found to have data available from a variety of different studies, rather than combining and averaging these prevalence values, it seems preferable to use the highest number available, as was done in the table. This decision was based in part on the fact that not all CF patients receiving care in some European countries are registered with cystic fibrosis centers. In fact, information available from the UK provides an opportunity to adjust the calculated prevalence data for potential under-reporting to registries. The adjustment amounts to 14%, i.e., there may be up to 14% more CF patients in other European countries. However even with such an adjustment, the calculated prevalence value is 0.840 per 10,000, which is well below the requirement of less than 5 per 10,000 for orphan designation in the EU. In addition, the extent of precision is more than satisfactory. Furthermore, it seems likely that the determined EU prevalence of CF is not going to change significantly during the next decade because although CF patients may be living longer [9], smaller families [10] and prenatal screening will tend to lower the prevalence [11,12]; however, further research with actuarial modeling will be necessary to address this issue.

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