Diabetes as a Determinant of Mortality in Cystic Fibrosis

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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Background: Diabetes is increasingly common in cystic fibrosis (CF), but little exists describing its influence on mortality. Using national UK data, this study documents diabetes-specific mortality rates, estimates the impact of diabetes on survival, and estimates population attributable fractions.

Methods: This retrospective cohort study identified 8,029 individuals aged 0-65 years from the UK CF Registry (1996-2005). 5,892 patients were included in analyses of mortality rates and 4,234 in analyses of risk factors. We calculated age-adjusted mortality rates using Poisson regression, standardized mortality ratios using the population of England and Wales, and relative risks using proportional hazards modeling.

Findings: During 17,672 person-years of follow-up, 393 subjects died. The age-adjusted mortality rate was 1.8 /100 person-years (95% CI 1.6 to 2.0). The age-adjusted mortality rates per 100 person-years were 2.0 (CI 1.8 to 2.4) in women and 1.6 (95% CI 1.4 to 1.9) in males, and 4.2 (95% CI 3.4-5.1) in individuals with diabetes vs 1.5 (95% CI 1.3 to 1.7) in those without diabetes. Independent risk factors for death included diabetes (hazard ratio, 95% confidence interval, 1.31 (1.03 to 1.67), female sex (1.71, 1.36 to 2.14) plus poorer pulmonary function, lower body mass index, B. cepacia infection, absence of S. aureus infection, allergic bronchopulmonary aspergillosis, liver disease, prior organ transplantation, and corticosteroid use.

Interpretation: Individuals with CF die earlier with diabetes, which, if delayed or better treated, might reasonably extend survival, and merits testing.
Cystic fibrosis (CF) is the most common autosomal recessive disease leading to premature death in white populations. Due to improvements in care, both survival - with a life-expectancy to the mid-thirties - and, as a consequence, the prevalence of complications have increased dramatically (1)(2) (3). The influence of birth year and sex on mortality has been described in the British CF population, (2) (4) but little is documented about the association between complications and specifically, diabetes mellitus, and mortality.

The majority of patients with CF die from respiratory complications. In CF, there is a high incidence of diabetes (5) which has been shown to increase the risk of death in the US. (6) Yet, little exists worldwide that documents the absolute mortality rates associated with diabetes in CF. Using national registry data, this study estimates the impact of diabetes on survival in adults and children with CF in Britain taking into account recognized and potential risk factors for death. This study documents mortality rates, estimates the risk increase associated with diabetes, and calculates the population attributable fraction for diabetes associated with death.

METHODS
Subjects - This retrospective cohort study identified 8,029 individuals aged 0-65 years registered on the United Kingdom Cystic Fibrosis Registry from 1996-2005. The registry, administered by the UK CF Trust, records information about the health and treatment of patients from birth.(7) Data are collected from 50 British CF care centers in a standardized anonymous fashion after patient consent. Data gathering is an on-going effort and the registry is updated annually.

Of 8,029 CF patients, 6,678 had baseline data comprised of registration followed by at least one clinic visit and an annual review within the same calendar year. We considered the first visit as the start of follow-up. We excluded 786 individuals without further follow-up, leaving 5,892 patients for analyses of mortality rates. Of these, we included 4,234 individuals with complete data in analyses of risk factors for mortality. Individuals with complete data were older because of the difficulties testing pulmonary function in young children, and were more likely to be white.

Endpoint and potential risk factors - Whether a patient had died, and the date of death, was taken from the CF registry. The registry did not contain information about individuals' identities, and we could not obtain death certificates.

Potential risk factors for death measured at baseline included age, sex, ethnicity, body mass index (BMI), pulmonary function, diabetes, respiratory infections, class of CF transmembrane conductance regulator (CFTR) class, diagnosis of CF by neonatal screening, prior organ transplantation, and other medical interventions as described below. We categorized ethnicity as white or non-white. BMI was calculated as weight in kilogram divided by height in meters squared, and we computed BMI z-scores using a UK reference population.(8) We coded CFTR alleles into five classes reflecting, for CFTR protein, defective production, processing, regulation, conductance and quantity (9), and further categorized as high- (Class I-III) and low- (Class IV-V) risk for mortality. (5)(10) Pulmonary function was measured as forced expiratory volume at one second.
(FEV\textsubscript{1}) and forced vital capacity (FVC), both expressed as percentage predicted.\cite{11} We considered diabetes present if a patient had, at least one of: 1) diagnosed diabetes 2) used insulin or oral hypoglycemic drugs 3) values consistent with diabetes on oral glucose tolerance testing per World Health Organization criteria. We considered an individual infected if bacteria or fungi were cultured at baseline from sputum or a throat swab, or if a physician had diagnosed chronic infection. Organisms included \textit{Pseudomonas aeruginosa}, \textit{Staphylococcus aureus}, \textit{Burkholderia cepacia complex}, \textit{Haemophilus influenzae}, \textit{Methicillin-resistant staphylococcus aureus} (MRSA) and \textit{Aspergillus fumigatus}. Allergic broncho-pulmonary aspergillosis (ABPA) was diagnosed clinically. We defined liver disease as one of: 1) abnormal liver function tests, 2) cirrhosis with portal hypertension, or 3) use of supplementary bile acids, and pancreatic insufficiency as supplementation with oral pancreatic enzymes. We defined corticosteroid use as any oral or inhaled use in the year prior to baseline, and nutritional supplementation as feeds of any kind ranging from oral supplements to parenteral feedings.

**Statistical analyses** - We calculated mortality rates expressed per 100 persons per year in 5,892 individuals as the number of deaths divided by total survival time, i.e., from registration to death or the last clinic visit. Using Poisson regression we age-adjusted mortality rates separately for males and females and for those with and without diabetes. We stratified mortality rates by 10-year age groups. We calculated directly standardized mortality rates and standardized mortality ratios (SMRs) using as a standard the 2005 population of England and Wales.\cite{12}

We tested for differences in baseline characteristics between those who died and those who survived using chi square test for categorical variables, and t-tests or Kruskal-Wallis tests for normally distributed or non-normally distributed continuous variables. We identified risk factors for mortality among the 4,234 patients with complete data using Cox proportional regression; the hazard ratio estimated the relative risk. We evaluated proportional hazards assumptions examining Kaplan-Meier survival curves for categorical variables; none violated the assumptions. We chose variables for multivariate modeling if associated with mortality in univariate Cox regression analyses (p<0.05), or if a factor had been previously reported to be associated with the risk of death in CF, e.g. sex and \textit{S. aureus}. We chose the final model using a stepwise approach and likelihood ratios. We tested for two-way interactions between diabetes and each risk factor in the final multivariate model.

We calculated the population attributable fraction (PAR) as \cite{13}:

\[
\text{PAR} = \frac{pd}{RR} \left( \frac{RR - 1}{RR} \right)
\]

where \(pd\) was the proportion of deaths exposed to a risk factor (e.g. diabetes) and \(RR\) the adjusted hazard ratio from multivariate proportional hazards modeling.

We coded percent predicted FEV\textsubscript{1}, BMI-z score and age as continuous variables in proportional hazards models, and as binary variables around the approximate medians (<70\% for FEV\textsubscript{1}, < -0.23 for BMI-z score and > 16 years for age) to calculate PARs.

Analyses were performed using Access (Microsoft Corporation), R (R
Development Core Team, 2007), and STATA (Stata Corp LP).

RESULTS
Study Population - Of the 5,892 individuals, 3,155 (54%) were male. The median age at baseline was 13.4 years (interquartile range, IQR, 6.9 to 21.8). Of 4,234 individuals with data on risk factors, an equivalent proportion were male. The median age was 16.0 and 97% were white.

Mortality Rates and Standardized Mortality Ratios - The median follow-up time was 2.9 years (IQR 1.9 to 4.0). In 17,672 person-years, 393 subjects died. The mortality rates increased with increasing age (Fig 1). The crude annual mortality rate was 2.2 (95% confidence interval, CI, 2.0 to 2.5) per 100 person-years. The age-adjusted mortality rate for the cohort was 1.8 per 100 person-years (95% CI 1.6 to 2.0). Females had a higher age-adjusted mortality rate at 2.0 (CI 1.8 to 2.4) per 100 person-years than did males at 1.6 (95% CI 1.4 to 1.9) per 100 person-years.

Individuals with diabetes had considerably higher age-adjusted mortality rates at 4.2 (95% CI 3.4 to 5.1) per 100 person-years than those without diabetes (1.5, 95% CI 1.3 to 1.7 per 100 person-years). Patients with diabetes had higher absolute mortality rates at all ages with the greatest relative difference in children less than 10 years old at baseline (p=0.09) (Fig 2).

Crude and directly standardized mortality rates expressed per 1,000 person years as well as standardized mortality ratios (SMRs) are presented in Table 1. The SMRs, which measure the risk of death relative to the general population of the same age, were 55.5, 39.8 and 84.1 for the total cohort, men, and women respectively. Females with diabetes were over 200 times more likely to die relative to their counterparts in the general population.

Risk Factors Associated with Mortality in CF - The characteristics and results of univariate analyses of the individuals who died or survived are shown (Online Appendix Table 1 at http://care.diabetesjournals.org). In univariate Cox regression analyses evaluating 325 deaths in 12,930 person years, increasing age, diabetes, decreasing pulmonary function, and a high risk CFTR class were all associated with an increased risk of death. Diabetes was associated with a 4-fold increase in risk of death relative to those without diabetes (hazard ratio (HR) 4.04, 95% confidence interval, CI, 3.23 to 5.07, p<0.001). In univariate analyses, infection with P. aeruginosa, B. cepacia complex, H. influenzae, A. fumigatus, use of corticosteroids, presence of ABPA, use of nutritional supplements, and decreased BMI z-score were all associated with an increased risk of death. Other characteristics that differed between subjects who died and those who survived were a history of liver disease, pancreatic insufficiency, and a history of organ transplantation. Patients with CF whose disease had been detected by neonatal screening had a lower risk of death compared to those not detected through screening, as did individuals infected with S. aureus relative to uninfected individuals. Not significantly associated with death in univariate analyses were sex (p=0.057) and infection with MRSA.

Given the relationship between complications, we evaluated the independent role of each risk factor in multivariate modelling. The final age-adjusted model showed an increased risk of death associated with each of
diabetes, decreasing pulmonary function, female sex, decreasing BMI z-score, infection with \textit{B. cepacia complex}, diagnosis of ABPA, history of liver disease, prior organ transplantation, and the use of corticosteroids (Figure 3). Infection with \textit{S. aureus} was independently associated with a decreased risk of death. Diabetes was associated with a 29\% (CI 1 to 64) increase in risk of death, independent of other complications of CF. Females were 71\% more likely to die than males, all other factors being equal.

Including high- and low-risk genotypes classes and pancreatic insufficiency in the multivariate model described above did not render insignificant any factor nor change the hazard ratio for death associated with diabetes. We found no interactions.

**Population attributable risk of death in CF** - The estimated PAFs for mortality are shown (Online Appendix Table 2). With continuous variables coded as binary variables, nutritional supplementation was associated with an increased risk of death. Of modifiable factors contributing to mortality, poor pulmonary function defined as a predicted FEV$_1$ <70\% accounted for the greatest proportion of risk at 78\%. Low body mass index (BMI z-score <-0.23) accounted for the next largest component of risk. The PAF for diabetes was 14\% (8 to 19).

**DISCUSSION**

This report highlights the specific contribution of diabetes mellitus to mortality in Britain’s population with CF. Using nationally-representative and systematically-collected data, this report estimates the absolute, relative, and attributable risk of death associated with diabetes. As some of the factors are potentially modifiable, then, if also causal, this provides hope and identifies research targets to further extend the lives of individuals with CF.

In Britain, where the incidence of diabetes in CF approximates 2 – 7\% per year (5), we estimate that diabetes accounts for some 14\% of deaths. That the components from PAF modelling add up to greater than 100\%, while not intuitive, assumes that risk factors interrelate and that each risk factor is the first to be eliminated. (14). This increased risk associated with diabetes is not explained by previously identified risk factors for death including poor pulmonary function, (15) other complications, (6), sex (16) (17) or genotype (18), all of which are also associated with an increased risk of diabetes. (5) It is likely that the metabolic derangements associated with diabetes nonetheless predispose to infection, worsen pulmonary function, and make maintaining body weight difficult.

The present study found a disproportionately increased albeit insignificant relative risk of death associated with diabetes in children under age 10 relative to individuals over age 10. French research has shown that individuals with CF who develop abnormal glucose metabolism as children have higher mortality rates than those who developed dysglycemia as adults.(19) In our study, of the under-ten year olds, only a very small proportion would be expected to have autoimmune-mediated diabetes (type 1), given the low prevalence in the UK general population. (20) As screening for diabetes in CF in the UK is encouraged for adults during period of clinical stability, but not for children under 12 years, diabetic children at presentation may have more severe hyperglycemia. We could not address degree of hyperglycemia, duration of
diabetes, or age of its onset in these analyses.

Registry data from the US shows that diabetes, controlling for other factors, is associated with a 55% increase in mortality risk in CF (6); we estimate a more modest 30% increase in risk. Acknowledging imprecision in estimates and the potential misclassification of diabetes, real difference may exist. This may represent in the UK, relative to the US, earlier detection of diabetes, less detection bias (diagnosing diabetes in sicker patients with more frequent medical attention), or better glycemic control (for which evidence linking better control to mortality in CF is sparse). A differences could represent different statistical models; the US model does not include organ transplantation or use of corticosteroids, both risk factors for diabetes (5) and, in this study, for death.

These findings imply that delaying diabetes – possibly through avoidance of corticosteroids - or assuring earlier and better treatment for diabetes in CF may lengthen survival. Yet, no evidence for prevention of diabetes in CF exists, and trials of treatment are few. (21) A randomized trial of lowering blood glucose has shown improvements in BMI, but not in pulmonary function. (22) In the general population, weight loss and exercise can prevent or delay type 2 diabetes, (23) but this has minimal relevance to cystic fibrosis-related diabetes where beta-cell dysfunction and decreased insulin production predominate. In type 1 diabetes, trials of early treatment to prevent diabetes have failed. (24, 25)

For other risk factors for death, the present study shows, consistent with others, (16) that females die earlier than males. The increased risk of death in females does not appear to be because of a higher prevalence of complications in females;. this is to say, females with a given set of co-morbidities fared worse than same-aged males with the same problems. We confirm that lower BMI, pulmonary complications, and infection with *B. cepacia complex* are associated with an increased risk of death in CF, and that infection with *S. aureus* is associated with a decreased risk of death. (6) Increasing age was not itself associated with death in CF, reflecting, perhaps, that death rates stabilized after above age 20 years (Figure 1 and 2). Our models incorporated age-dependent variables (percent predicted FEV$_1$ and BMI z-score); when modelling instead using absolute values for FEV$_1$ and BMI, increasing age was associated with an increased death rate. Separate analyses for children and adults (age <16 vs ≥16 years) showed that in multivariate modelling, pulmonary function was associated with mortality in both groups, while BMI was associated with mortality only in adults. We do not know of another study showing that corticosteroids are associated with an increase in the risk of death independent of other complications; for oral corticosteroids there is evidence of short-term benefit in pulmonary function, but the balance of risk in the long term is not clear. Or, physicians may simply offer corticosteroids to patients at greatest risk of dying.

The high SMRs we report reconfirm that mortality in the CF population in Britain far exceeds that of the general population. (4) For individuals with diabetes, these values are higher at nearly 120 times the general population. Our findings from directly standardized mortality rates show that the CF population in the UK, with a median age of 13 years, has a mortality rate
similar to that of 70–74 year olds in the general population of England and Wales. (12)

The strengths of this study are its size and its systematically-collected longitudinal data. Potential limitations include ascertainment of death from the registry rather than from death records and possible misclassification of individuals with diabetes. Under-detection of diabetes is likely lessened by universal and free access to health care in Britain. If unwell individuals with stress hyperglycaemia were labeled diabetic, this would suggest that the value for risk associated with diabetes we report underestimates the truth. Likewise, if factors associated with the risk of death were more apt to be detected in the sickest patients, the relative risks we report would overestimate the true associations, but would not bias the overall mortality rates.

In summary, this report documents recent mortality statistics for adults and children with CF in Britain. This study identifies complications including diabetes which, if delayed or better treated, might reasonably extend the lives of individuals with CF in the UK. Advances in life-expectancy to date support this opportunity while the population attributable fraction quantifies potential gains.

Acknowledgements

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REFERENCES


Table 1. Crude, directly standardized mortality rates (per 1,000 person-years) and standardized mortality ratios (SMRs) by sex and diabetes in patients with cystic fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Person-years at risk</th>
<th>Number of deaths</th>
<th>Crude mortality rate (95% CI)</th>
<th>Directly standardized mortality rate * (95% CI)</th>
<th>SMR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5,892</td>
<td>17672</td>
<td>393</td>
<td>22.2 (20.1 – 24.6)</td>
<td>26.8 (19.0 – 40.5)</td>
<td>55.5 (40.8 – 70.1)</td>
</tr>
<tr>
<td>Males</td>
<td>3,155</td>
<td>9425</td>
<td>191</td>
<td>20.3 (17.6 – 23.4)</td>
<td>23.5 (14.9 – 43.3)</td>
<td>39.8 (24.7 – 55.0)</td>
</tr>
<tr>
<td>Females</td>
<td>2,737</td>
<td>8247</td>
<td>202</td>
<td>24.5 (21.3 – 28.1)</td>
<td>30.9 (19.0 – 56.5)</td>
<td>84.1 (53.4 – 114.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>696</td>
<td>1953</td>
<td>141</td>
<td>72.2 (61.2 – 85.1)</td>
<td>48.4 (27.7 – 106.2)</td>
<td>123.4 (74.7 – 172.1)</td>
</tr>
<tr>
<td>Males</td>
<td>349</td>
<td>970</td>
<td>61</td>
<td>62.9 (48.9 – 80.8)</td>
<td>41.9 (22.2 – 106.8)</td>
<td>82.2 (33.6 – 130.9)</td>
</tr>
<tr>
<td>Females</td>
<td>347</td>
<td>983</td>
<td>80</td>
<td>81.4 (65.4 – 101.3)</td>
<td>56.1 (24.0 – 209.8)</td>
<td>208.7 (99.4 – 318.0)</td>
</tr>
<tr>
<td>Without diabetes</td>
<td>5,196</td>
<td>15718</td>
<td>252</td>
<td>16.0 (14.2 – 18.1)</td>
<td>20.6 (13.3 – 35.7)</td>
<td>42.4 (28.1 – 56.7)</td>
</tr>
<tr>
<td>Males</td>
<td>2,806</td>
<td>8454</td>
<td>130</td>
<td>15.4 (12.9 – 18.3)</td>
<td>16.7 (9.5 – 41.4)</td>
<td>32.1 (16.9 – 47.2)</td>
</tr>
<tr>
<td>Females</td>
<td>2,390</td>
<td>7264</td>
<td>122</td>
<td>16.8 (14.1 – 20.1)</td>
<td>25.4 (13.9 – 53.9)</td>
<td>60.4 (31.3 – 89.5)</td>
</tr>
</tbody>
</table>

* using the 2005 population of England and Wales as a standard population

Figure legends:

Fig 1. Mortality rates with 95% confidence interval by age and sex in CF patients: White bars for male, and black bars for females.  * difference between sexes, p < 0.05

Fig 2. Mortality rates with 95% confidence interval by age and diabetes in CF patients: white bars for patients without diabetes, and black bars for those with diabetes.  * difference between individuals with and without diabetes, p < 0.05

Fig 3. Risk factors for death in cystic fibrosis. Cox proportional hazards modelling adjusted for age and all risk factors in the figure. (n = 4,234)
Figure 3

<table>
<thead>
<tr>
<th>Risk factor (reference)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (yes/no)</td>
<td>1.31 (1.03, 1.67)</td>
</tr>
<tr>
<td>% predicted FEV₁ (1% ↓)</td>
<td>1.06 (1.05, 1.07)</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>1.71 (1.36, 2.14)</td>
</tr>
<tr>
<td>BMI z-score (1 unit ↓)</td>
<td>1.20 (1.10, 1.31)</td>
</tr>
<tr>
<td>B. cepaciae (yes/no)</td>
<td>2.38 (1.79, 3.16)</td>
</tr>
<tr>
<td>S. Aureus (yes/no)</td>
<td>0.71 (0.56, 0.89)</td>
</tr>
<tr>
<td>ABPA (yes/no)</td>
<td>1.69 (1.17, 2.43)</td>
</tr>
<tr>
<td>Liver disease (yes/no)</td>
<td>1.32 (1.04, 1.67)</td>
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<tr>
<td>Corticosteroid use (yes/no)</td>
<td>1.57 (1.21, 2.05)</td>
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<tr>
<td>Organ transplantation (yes/no)</td>
<td>2.96 (1.91, 4.60)</td>
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