Decreased Lung Function in Female but not Male Subjects With Established Cystic Fibrosis–Related Diabetes

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OBJECTIVE — Although cystic fibrosis–related diabetes (CFRD) is associated with decreased lung function, sex is not known to influence CFRD. However, compared with male subjects with cystic fibrosis, female subjects with cystic fibrosis have increased morbidity. This study examines the association between female subjects with CFRD and poor lung function relative to male subjects using the percent predicted forced expiratory volume in 1 s (FEV_1) as a surrogate measure of morbidity.

RESEARCH DESIGN AND METHODS — We compared 323 patients with established CFRD with 489 cystic fibrosis control subjects with normal glucose tolerance (NGT) listed in the U.K. Cystic Fibrosis Database. Patients stratified by sex and chronic *Pseudomonas aeruginosa* infection were compared using binary logistic regression, and patients with new CFRD diagnoses were compared prospectively for the year 2002.

RESULTS — CFRD in female subjects (but not male subjects) without chronic *P. aeruginosa* infection had a 20% lower percent predicted FEV_1 compared with control subjects with NGT (95% CI −11.7 to −27.7; $P < 0.0001$). Genotype, age, treatment center, age at diagnosis of cystic fibrosis, pregnancy, liver function, or dose of pancreatic enzyme replacement therapy did not confound this female disadvantage. Comparison of female subjects with newly diagnosed CFRD free of chronic *P. aeruginosa* infection with matched control subjects with NGT showed no FEV_1 disadvantage in the 1st year after CFRD diagnosis.

CONCLUSIONS — Only female subjects with CFRD have significantly decreased lung function compared with sex-matched NGT control subjects. The absence of poor lung function in the first 12 months after diagnosis of diabetes suggests that an opportunity may exist to intervene and possibly prevent a decline in lung function, which can be as much as 20% in female subjects with CFRD.

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Cystic fibrosis is the most common lethal autosomal recessive disease in whites, affecting ~1 in 2,500 births (1). Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (2). Cystic fibrosis–related diabetes (CFRD) occurs in 30–40% of adults and is associated with increased morbidity and mortality (3), accelerated decline in lung function, decreased BMI (4,5), and increased likelihood of infection with *Pseudomonas* species. (5).

Female cystic fibrosis patients without CFRD have decreased lung function, earlier acquisition of chronic mucoid *Pseudomonas aeruginosa* infection (6), reduced survival (7), increased risk of premature death (7), reduced energy intake (8), and higher resting energy requirements (9) than their male counterparts. The excess female mortality produces a rising male-to-female ratio of 1.6:1 in patients aged >35 years in the U.K. (10). This prompted a study of CFRD to test the association between CFRD and cystic fibrosis morbidity in female subjects, using the validated measure of future mortality, forced expiratory volume in 1 s (FEV_1) (11). To overcome the potentially confounding effect of chronic *P. aeruginosa* infection (12), we stratified our cystic fibrosis patients by chronic *P. aeruginosa* status. We show that established CFRD is associated with a significant decline in lung function in female but not male subjects. However, a window of opportunity for intervention may exist that could improve the female outcome.

RESEARCH DESIGN AND METHODS

— Patient data were obtained from the U.K. Cystic Fibrosis Database (UKCFD). Data for 2000–2002 were submitted by 41 specialist cystic fibrosis centers and 12 smaller cystic fibrosis clinics as recently described (13). Patients were eligible for inclusion if, in addition to biographical data, annual clinical data were available in both 2001 and 2002. Full details of data validation have

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Abbreviations: BLR, binary logistic regression; CFRD, cystic fibrosis–related diabetes; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GTT, glucose tolerance test; NGT, normal glucose tolerance; UKCFD, U.K. Cystic Fibrosis Database.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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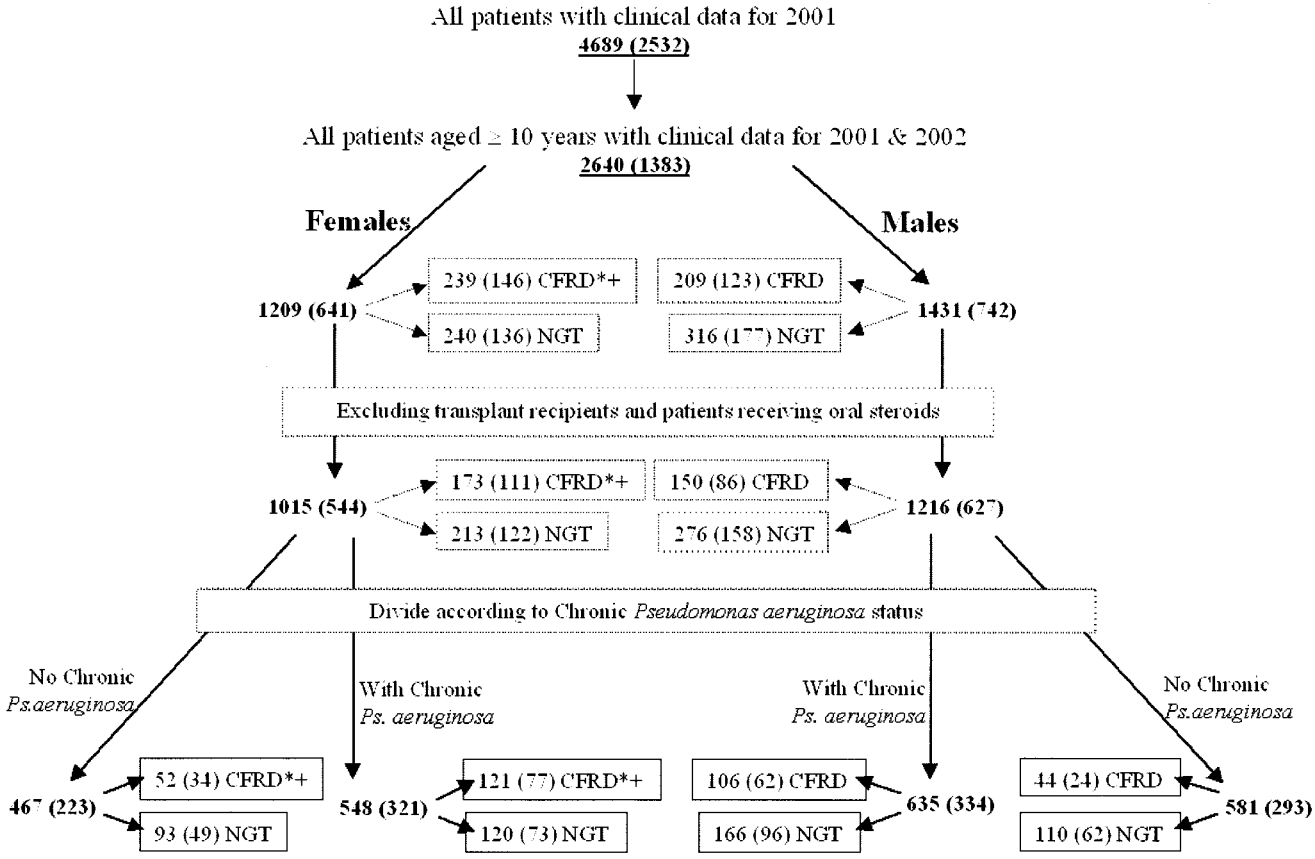

Figure 1—*Schematic diagram showing selection of CFRD and NGT study patients (patient numbers are shown within boxes). Final study cohorts are shown in solid-lined boxes at the bottom. Numbers in brackets indicate those with the ΔF508/ΔF508 genotype. +, significant difference in the proportion of ΔF508/ΔF508 patients compared with the parent population (2,640 patients); *a significant difference in the number of women with CFRD as a proportion of all women when compared (horizontally) with the equivalent male population (e.g., in the midsection, the proportion of CFRD women (173; 17%) out of 1,015 women who were not receiving oral steroids and who were not transplant recipients was significantly greater than the equivalent men with CFRD (150; 12%) out of a population of 1,216.*

been described elsewhere (10,13). All procedures were compliant with multicenter research ethics protocols and U.K. legislation on patient confidentiality (13). Because multiple data were available for height, weight, and FEV_1 per 12-month period, the means were used. *P. aeruginosa* and/or *Staphylococcus aureus* data were defined as intermittent if cultured on 1–2 occasions, or chronic if cultured on ≥3 occasions per 12-month period. Data for other organisms were analyzed as "ever cultured" per 12 months.

Patients receiving oral corticosteroids and transplant recipients were excluded (Fig. 1). The remaining patients were grouped by glucose tolerance test (GTT) result: *1*) diabetic (including patients previously known to be diabetic), *2*) equivocal (not shown), and *3*) normal glucose tolerance (NGT). Patients who had not had a GTT performed in 2001 were designated as "not tested." The categories of "not tested" and "equivocal" were excluded from the analyses. Potential bias may have been introduced by these exclusions. However, no differences were found in the percent predicted FEV_1 between NGT and "not tested" male subjects with chronic *P. aeruginosa* infection (−1.0% [95% CI −5.7 to 3.7]) or NGT and "not tested" female subjects irrespective of chronic *P. aeruginosa* infection (without chronic *P. aeruginosa* infection −4.1% [−9.2 to 0.9]; with chronic *P. aeruginosa* infection −2.1% [−7.0 to 2.7]). NGT male subjects without chronic *P. aeruginosa* infection had lower percent predicted FEV_1 compared with "not tested" males without chronic *P. aeruginosa* infection (−8.6% [−3.9 to −13.3]; $P < 0.001$) (see CONCLUSIONS).

Cross-sectionally, we compared patients aged ≥10 years who had CFRD in 2001 with NGT control subjects because the incidence of CFRD rises in the second decade of life. Patients were stratified into four populations according to sex and chronic *P. aeruginosa* status (Fig. 1). Using binary logistic regression (BLR), we compared CFRD and NGT patients within each stratified population. The model included the following covariates: percent predicted FEV_1 (or percent predicted forced vital capacity [FVC] where indicated), age in 2001, age at cystic fibrosis diagnosis, pancreatic enzyme replacement dose (lipase · kg^{-1} · day^{-1}), and height and weight *Z* scores. The following cofactors were also included in the model: diagnosis by neonatal screening, presence of intermittent *P. aeruginosa* infection, presence of liver dysfunction, pregnancy, and prescription of nutritional supplements. Because genotype influences survival (10), a subgroup analysis of the ΔF508/ΔF508 patients within each stratified population was performed. To determine the influence of the center's policy,

we compared age (±3 years)-, sex-, and center-matched NGT control subjects to CFRD patients. As there is a cohort effect in cystic fibrosis survival (14) and the prevalence of CFRD increases with age (15), we divided the stratified populations into 10-year age-groups. To validate our results, we repeated the BLR using data from all final study cohorts (a total of 812 study patients as defined in Fig. 1), modeling sex, chronic *P. aeruginosa*, and covariables that significantly differentiated CFRD and NGT patients in the four stratified populations. We tested for significant interactions between sex with chronic *P. aeruginosa*, sex with covariables, and chronic *P. aeruginosa* with covariables. Because of the small number of patients per center, it was not possible to include treatment center in this model.

Prospectively, we determined whether differences identified between the established CFRD and NGT populations were present in patients with newly diagnosed CFRD in 2002. After excluding transplant recipients and those receiving oral steroids, we identified 21 female and 25 male patients with newly diagnosed CFRD in 2002 without chronic *P. aeruginosa* infection. We compared the percent predicted FEV_1 in newly diagnosed male and female diabetic patients with their equivalent chronic *P. aeruginosa*–free NGT control subjects to determine the acute effect of CFRD.

Statistical analysis

For analyses we used Microsoft Access and Excel (Microsoft, Redmond, WA) and SigmaPlot (SigmaPlot for Windows 4.01; SPSS, Chicago, IL). Statistical analyses and binary logistic modeling were performed using Minitab 13.1 (Minitab, State College, PA). As the covariate data were not normally distributed, comparison of populations and 10-year age-groups was performed using the Mann-Whitney two-sample rank test. The difference between proportions was performed using the normal approximation to the binomial; data were large enough for the central limit theorem to apply (16).

RESULTS — From 4,689 UKCFD patients with clinical data recorded in 2001 (Fig. 1), 2,640 patients aged ≥10 years also had data recorded for 2002. This population of 2,640 contained 1,209 female and 1,431 male subjects, from which we identified 239 female (20%) and 209 male (15%) subjects with CFRD. Female subjects formed a significantly higher proportion of the CFRD subpopulation (53%; $P = 0.007$) despite a lower percentage (46% female) in the parent (2,640) population. The same sex difference was found in all mixed genotype subpopulations and also in the ΔF508/ΔF508 parent and associated subpopulations. Additionally, in the parent and all subpopulations, ΔF508/ΔF508 CFRD females formed a significantly higher proportion of the total ΔF508/ΔF508 female population compared with equivalent ΔF508/ΔF508 male populations (i.e., in the parent population: 146/641 female [23%] vs. 123/742 male [17%]) subjects.

In the absence of chronic *P. aeruginosa*, male and female subjects manifested different discriminatory elements between the CFRD and NGT subpopulations. For the 467 female and 581 male subjects (Fig. 1), 52 CFRD female subjects were discriminated from 93 NGT females only by a significantly lower percent predicted FEV_1 (−20.0%, [95% CI −11.75 to −27.68]; $P < 0.0001$) (Fig. 2*A*). In contrast, although the percent predicted FEV_1 was nondiscriminatory (2.38%, [−6.38 to 11.26]; NS) (Fig. 2*A*), 44 CFRD male subjects were discriminated from 110 NGT males by an older age in 2001 (7.0 years [10.0–4.0]; $P < 0.0001$) and an earlier age at cystic fibrosis diagnosis (−6 months [0 to −10.0]; $P < 0.001$), no difference was found when the subpopulations were compared directly (Table 1). Comparable results were obtained when FVC was substituted for FEV_1 (BLR data not shown; for direct comparisons see Table 1). Comparable discriminatory variables and significant differences on direct comparison (Table 1 and Fig. 2*A*) were also found when ΔF508/ΔF508 CFRD female and male subjects were compared with genetically matched NGT control subjects. Additionally, when matched against NGT control subjects for age, sex, and clinic (Fig. 2*A*), female subjects also had significantly worse percent predicted FEV_1 (−16.1% [−28.35 to −0.79]; $P < 0.05$) than male subjects (9.1% [−4.69 to 25.82]; NS).

Chronic *P. aeruginosa*–infected CFRD females were discriminated by a lower percent predicted FEV_1 (−14.0% [95% CI 8.11–19.91]; $P < 0.0001$) (Fig. 2*B*) and an older age in 2001 (7.0 years [5.0–8.0]; $P < 0.0001$) than chronic *P. aeruginosa*–infected NGT control subjects. Chronic *P. aeruginosa*–infected CFRD males were also older in 2001 (5.0 years [4.0–7.0]; $P < 0.0001$) but were additionally shorter (−0.54 SD, [−0.15 to −0.66]; $P = 0.0015$) than chronic *P. aeruginosa*–infected NGT control subjects. For males, although the percent predicted FEV_1 was not discriminatory, direct comparison showed that chronic *P. aeruginosa*–infected CFRD males had a significantly lower percent predicted FEV_1 (−10.0% [−4.30 to −16.07]; $P = 0.0006$) (Fig. 2*B* and Table 1) compared with their chronic *P. aeruginosa*–infected NGT control subjects. Similar findings were observed in ΔF508/ΔF508 chronic *P. aeruginosa*–infected populations (females −17.0% [−20.44 to −4.79]; $P = 0.002$ and males −10.8% [−19.95 to −5.00]; $P = 0.001$) (Fig. 2*B*). On comparison of chronic *P. aeruginosa*–infected CFRD patients to age-, sex-, and center-matched control subjects, CFRD female but not male subjects still had significantly lower percent predicted FEV_1 compared with matched NGT control subjects (females−9.35% [−16.41 to −0.96]; $P < 0.05$ and males−3.39% [−8.74 to 2.70[; NS) (Fig. 2*B*).

When the BLR analysis was repeated using the final study cohort of 812 patients (Fig. 1), female subjects had a greater likelihood of having CFRD than male subjects (odds ratio [OR] 12.38 [95% CI 2.6–59.0]; $P = 0.002$). CFRD patients, irrespective of sex or *P. aeruginosa* status, were discriminated by a lower percent predicted FEV_1 (0.94 [0.91–0.97]; $P < 0.001$), height *Z* score (0.74 [0.57–0.95]; $P = 0.017$) and older age in 2001 (1.07 [1.01–1.14[; $P = 0.022$) from NGT control subjects. Of the interactions studied, a significant interaction was observed only between percent predicted FEV_1 and sex (1.02 [1.01–1.04]; $P = 0.003$), whereby CFRD female subjects were more likely than CFRD male subjects to be associated with a lower percent predicted FEV_1 compared with NGT control subjects.

CFRD male and female subjects were significantly older than sex-matched NGT control subjects (Table 1). However, when stratified into three 10-year age-groups, CFRD females without chronic *P. aeruginosa* infection (but not males) retained significantly lower percent predicted FEV_1 compared with NGT control subjects (Table 2) in all age-groups. For chronic *P. aeruginosa*–infected popula-

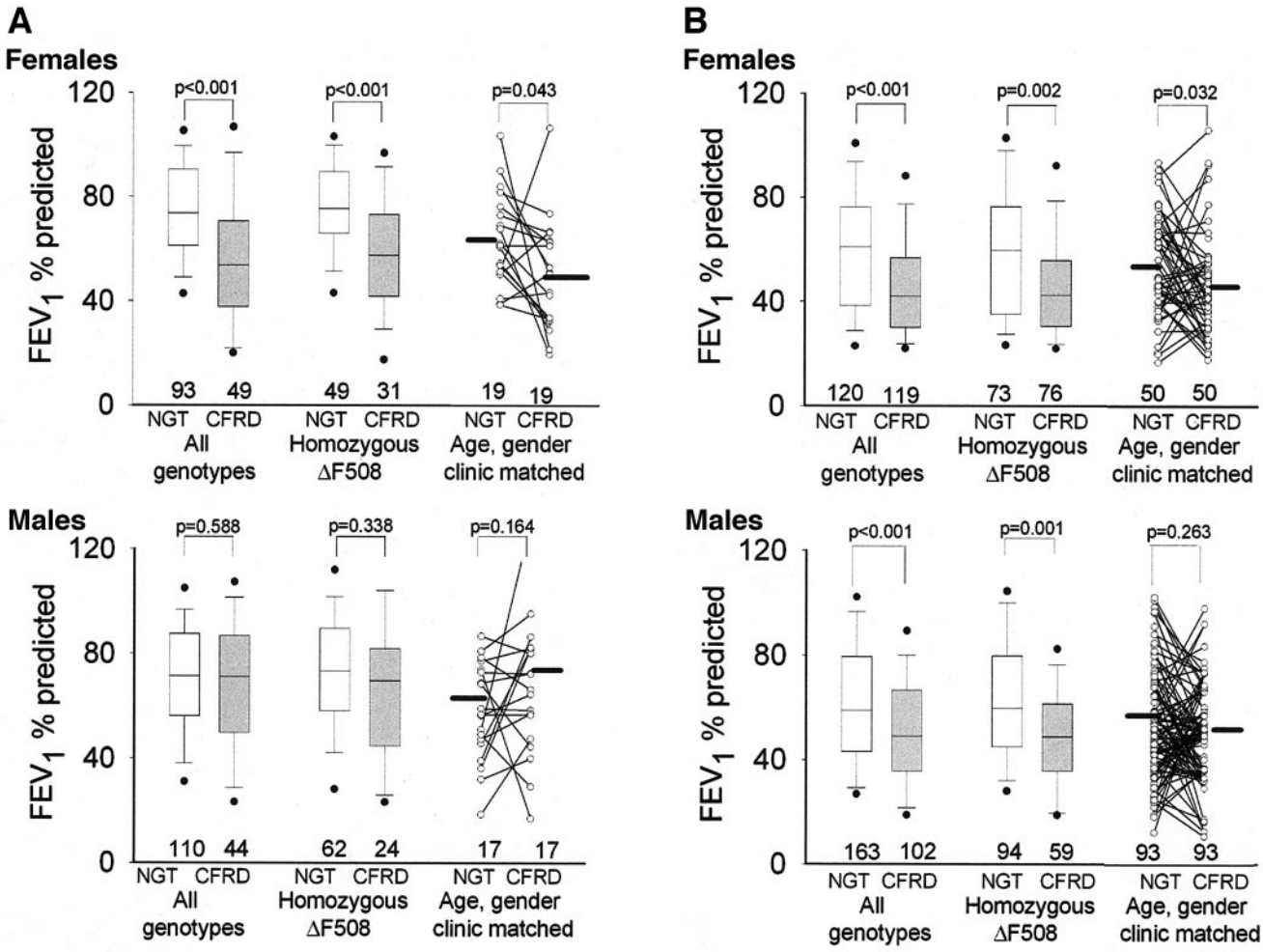

Figure 2—*Adverse impact of CFRD on female predicted FEV_1 percentage when stratified by chronic* P. aeruginosa *(PA) infection.* A*: Chronic* P. aeruginosa*–free females and males.* B*: Chronic* P. aeruginosa*–present females and males. Box plots in the* left *and* middle panels *show median FEV_1 in female and male subjects with CFRD (▨) compared with control subjects with NGT (□). 95% CIs are also indicated (●).* Left panels *show all patients,* middle panels *show ΔF508/ΔF508 patients, and* right panels *show FEV_1 for age-, sex-, and center-matched CFRD and NGT patients. Median FEV_1 is indicated by black bar. The number of patients in each group is shown on the abscissa.*

tions, only CFRD male and female subjects aged 10–19 years had significantly lower percent predicted FEV_1 compared with matched NGT control subjects (Table 2). No other significant confounders due to infection were present (Table 2).

To determine whether females with CFRD had a diminished percent predicted FEV_1 before diagnosis, we identified cohorts of females and males free from chronic *P. aeruginosa* and without CFRD at the time of annual review in 2001 in whom CFRD was subsequently diagnosed by the time of annual review in 2002 and matched these to NGT control subjects. Males with newly diagnosed CFRD but nonequivalent females had significantly lower percent predicted FEV_1 compared with NGT control subjects (male subjects −15.7% [95% CI −24.9 to −5.8; $P = 0.003$; females 1.7% [−8.95 to 11.64]; NS). This suggests that the decline in percent predicted FEV_1 in female but not in male subjects occurs after 1 year of CFRD (see Fig. 3 in the online appendix at http://care.diabetesjournals.org).

CONCLUSIONS — CFRD adds an additional burden of care for cystic fibrosis patients already taking many drugs to maintain lung function. We find that female but not male subjects with established CFRD but without chronic *P. aeruginosa* infection had 20% worse percent predicted FEV_1 than sex-matched NGT control subjects. These results could not be explained by genotype, local cystic fibrosis center policies, age, or chronic *S. aureus* infection. This suggests that the combination of CFRD and female sex might have an adverse impact on survival because a low percent predicted FEV_1 is predictive of premature mortality (17). These results are in agreement with survival data recently reported by Moran (18), who showed that females with cystic fibrosis and CFRD had a reduced survival by at least 17 years (median survival 30.7 years) compared with females with cystic fibrosis without CFRD (47.0 years) or males with cystic fibrosis irrespective of CFRD (47.4 with CFRD and 49.5 years without CFRD). We also report that although CFRD has greater morbidity in females, the onset of this adverse outcome is not present within 12 months of the initial diagnosis. Although caution must

be exercised given the small numbers in our final study cohorts, we believe that this is a potentially important observation because it could provide a therapeutic window in which to test strategies to attenuate a long-term decrease in female lung function. Further, our data suggest that CFRD males may have a transient decrease of FEV_1 percentage immediately after CFRD diagnosis.

Many studies report that CFRD induces decreased lung function compared with that in NGT control subjects (19), but they do not separate their study populations by chronic *P. aeruginosa* infection and sex. Koch et al. (19) compared patients with and without *P. aeruginosa*, where infection was defined as the presence of at least one positive culture in a 12-month period and found that infected CFRD patients had significantly lower percent predicted FEV_1 compared with infected non-CFRD patients, irrespective of sex. However, they did not distinguish between the transient or chronic nature of the infection. When we reanalyzed our data using the infection model reported by Koch et al. (19), both CFRD female and male subjects with *P. aeruginosa* had significantly lower FEV_1 than NGT control subjects, thus masking our reported sex effect (data not shown).

Why do females with established CFRD have worse lung function than males?

Mismatched energy consumption and expenditure? Recently, Collins et al. (8) showed that females with cystic fibrosis have a significantly lower energy intake, possibly contributing to their reduced survival. These data were not collected in the UKCFD but the U.K. male-to-female ratio increases with age (10). Allen et al. (9) reported that females with cystic fibrosis have increased resting energy expenditure compared with healthy females without cystic fibrosis and males irrespective of cystic fibrosis. However, neither study separated their populations by CFRD status, which might be relevant because CFRD disturbs lipid metabolism. Hardin et al. (20) reported that de novo lipogenesis, an energy-wasteful state, associates with both glucose intolerance and CFRD but not NGT. Fatty acid metabolism and lung function are also intimately linked (21), and the combination of these factors could account for reduced pulmonary function (and earlier death) in

Table 1—*Patient characteristics*

	No chronic *P. aeruginosa* infection				Chronic *P. aeruginosa* infection			
	Male subjects		Female subjects		Male subjects		Female subjects	
	CFRD	NGT	CFRD	NGT	CFRD	NGT	CFRD	NGT
n	44 (24)	110 (62)	52 (34)	93 (62)	106 (62)	166 (96)	121 (77)	120 (73)
Median age (years)	25.5 (27.5)	18.0* (17.0)†	24.5 (26.0)	18.0* (17.0)†	24.5 (26.0)	19.5* (20.0)†	25.0 (25.0)	18.0* (18.0)†
Median age at diagnosis (months)	4.0 (4.0)	10.0 (5.5)	12.0 (15.0)	6.0 (6.0)†	6.0 (7.5)	6.0 (6.0)	6.0 (6.0)	5.0 (5.0)
Median % predicted FEV_1	71.1 (69.7)	71.4 (73.3)	53.6 (57.5)	73.6* (75.4)†	49.0 (49.0)	59.0* (59.8)†	42.0 (42.5)	61.0* (59.7)†
Median % predicted FVC_1	79.8 (79.3)	81.0 (81.1)	67.8 (84.5)	85.2* (71.4)†	62.1 (59.9)	70.2* (69.3)†	60.8 (62.9)	73.8* (72.1)†
Median height *Z* score	−0.91 (−0.83)	−0.42* (−0.33)	−0.78 (−0.63)	−0.46 (−0.65)	−0.98 (−0.83)	−0.44* (−0.36)†	−0.77 (−0.79)	−0.44 (−0.42)
Median weight *Z* score	−0.78 (−0.62)	−0.53 (−0.30)	−0.64 (−0.66)	−0.16* (0.06)	−0.82 (−0.94)	−0.89 (−0.89)	−0.86 (−0.83)	−0.52* (−0.42)
Median BMI (kg/m^2)	21.8* (21.9)	20.0 (20.2)	20.1 (20.2)	20.5 (20.5)	21.5 (20.9)	19.4* (19.1)†	20.0 (20.2)	19.6 (19.6)
Median lipase dose (units/kg/day)	7002 (4495)	6342 (4987)	4939 (3933)	5725 (5111)	7112 (5298)	8034 (6592)	6530 (4325)	6885 (5777)
Percent receiving CFRD medication	91 (96)		86 (88)		93 (98)		92 (91)	

Data shown are for all genotypes (homozygous ΔF508). *$P < 0.05$ between CFRD male and female subjects (all genotypes) vs. their sex-matched NGT control subjects (all genotypes); †$P < 0.05$ between homozygous ΔF508 CFRD male and female subjects vs. their genotype- and sex-matched NGT control subjects.

Table 2—*Difference in median FEV_1 percentages in CFRD patients compared with age- and sex-matched control subjects*

	Age-group		
	10–19 years	20–29 years	≥30 years
No chronic *P. aeruginosa* infection			
Females	−12.6 (−0.72 to −26.12)	−15.4 (−3.53 to −29.40)*	−15.1 (−2.76 to −31.81)*
Males	−1.1 (14.10 to −17.83)†	3.0 (21.23 to −12.75)†	6.0 (24.23 to −13.45)†
Chronic *P. aeruginosa* infection			
Females	−17.4 (−5.45 to −29.86)*	−3.4 (5.11 to −11.95)†	−6.9 (6.68 to −15.96)†

Data are medians (95% CI). *$P < 0.05$; †NS.

CFRD females. Indeed, the dose of pancreatic enzyme replacement therapy was higher in all CFRD populations (Table 1), consistent with increased energy demands, although we found no significant sex differences. Abnormal energy balance is likely to be exacerbated by chronic *P. aeruginosa* infection (22), which further increases resting energy expenditure. This could partially explain why the magnitude of the difference in lung function is greater in chronic *P. aeruginosa*–infected CFRD females than in equivalent males. This female disadvantage is only observed in the chronic *P. aeruginosa*–infected 10- to 19-year age-group, presumably because the longer-term destruction of the lung by chronic *P. aeruginosa* infection is a sex-independent effect. Our data on the absence of a short-term effect of CFRD on female (but not male) lung function suggests a detrimental impact of CFRD >12 months after the CFRD diagnosis. Prospective studies providing a detailed comparison of clinical data for CFRD and NGT males and females are required to validate both of our hypotheses.

Psychological or adherence factors? Adherence to treatment in chronic disease is important for outcome. The impact of a diagnosis of CFRD on quality of life in cystic fibrosis is unknown. However, because it is often perceived as an end-stage complication by many patients (23), CFRD may introduce a philosophy of negativity and poor concordance. This might be worse in female subjects, given the greater likelihood of nonadherence (24) and overestimation of weight (25) compared with males. Indeed, irrespective of chronic *P. aeruginosa* infection, CFRD female but not male subjects had significantly lower weight *Z* scores compared with NGT control subjects. As the prevalence of eating disorders within the cystic fibrosis population or CFRD subpopulation is poorly understood, the relative contributions of the additional impact of CFRD and an eating disorder per se are unknown. The need to comply with peer pressure and the media's perception of the ideal body weight, particularly in females, may undermine optimum treatment regimens and contribute to poor outcome.

Study limitations

The cross-sectional nature of our analysis could have introduced selection bias, although comparison of our population profile with that of previously published studies (6,19,26,27) suggests otherwise. The higher proportion of female than male subjects with CFRD was consistent with previously published data by Yung and Hodson (27), and the higher proportion of female than male subjects with CFRD and chronic *P. aeruginosa* was also consistent with those of Demko et al. (6). The shorter stature of our CFRD population compared with NGT control subjects was in agreement with data of Ripa et al. (26). Furthermore, other factors such as pregnancy, liver dysfunction, and nutritional support were too infrequent to account for our results in women. The paucity of pregnancies in our dataset is discussed elsewhere (28).

Debate surrounds the treatment of patients with CFRD who do not have fasting hyperglycemia. Unlike those in the U.S. (29), U.K. guidelines for the treatment of CFRD advocate the initiation of insulin irrespective of fasting hyperglycemia for most patients with CFRD (30). Because the UKCFD does not collect data on fasting hyperglycemia status, it was not possible to study such patients in our analysis. We did identify a small percentage of patients who were not receiving CFRD medication (Table 1). Exclusion of these patients did not affect our results (data not shown).

Because not all patients in 2001–2002 had a GTT performed, selection bias remains an issue. NGT males without chronic *P. aeruginosa* infection but not equivalent NGT females had significantly lower percent predicted FEV_1 compared with respective "equivalent" and "not tested" patients. One possibility is that males with a decrease in FEV_1 are preferentially screened for CFRD. Although significantly more male (390) than female (313) subjects underwent a GTT, the number tested was in proportion to the number of male and female subjects in each eligible population (1,073 and 836, respectively). We have recently shown that, although GTTs are advocated in the U.K. for all cystic fibrosis patients aged >12 years (31), <50% were actually performed. This was unrelated to staffing provision (32), suggesting differences in center protocols as a primary driving force. Nevertheless, we do not believe that significant bias is introduced because our adverse findings in CFRD females were also confirmed when center-matched patients and control subjects were studied, suggesting that the frequency of testing within centers was an unlikely confounder. One conclusion from our study is that measures to increase the prevalence of screening for CFRD are needed.

In summary, we describe sex as an important factor in the relationship between CFRD and lung function. This was not confounded by lung infection. In CFRD females, but not CFRD males, we report 14–20% lower percent predicted FEV_1 and FVC, irrespective of chronic *P. aeruginosa* infection, compared with NGT control subjects that are unexplained by genotype, center effects, or age. The absence of poor lung function in the first 12 months after diagnosis of diabetes in females suggests that an opportunity may exist to intervene and possibly prevent a longer-term decline in lung function, as much as 20% in females with CFRD. The

extent to which this will materially affect the final outcome remains to be established. We recommend a study to evaluate treatment intensity in females with cystic fibrosis and newly diagnosed CFRD, using lung function as a primary outcome.

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