



## Original Article

Higher risk of hospitalization among females with cystic fibrosis<sup>☆</sup>

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**Abstract**

**Background:** Persons with cystic fibrosis (CF) who tend to be hospitalized have poorer overall survival and quality of life. Whether differences exist in hospitalization rates between males and females with CF is unknown. The objective was to assess sex-specific differences in hospitalization rates after adjusting for clinically important factors within a universal health care system.

**Methods:** A provincial-based longitudinal study using national CF registry data linked to health administrative databases examined differences in annual hospitalization rates estimated by Poisson regression using generalized estimating equations with adjustment for markers of CF disease severity.

**Results:** Among those aged 7 to 19 years, the RR of respiratory-related annual hospitalizations among females vs. males was 1.38 (95% CI 1.11–1.73). Among those over 19 years, the corresponding RR was 1.30 (95% CI 1.06–1.59).

**Conclusions:** Females affected by CF are at a higher risk of respiratory-related hospitalization, which may extend beyond classic clinical measures of disease severity.

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**Keywords:** Cystic fibrosis; Sex differences; Hospitalizations

**1. Introduction**

Among persons with cystic fibrosis (CF), hospitalizations for pulmonary exacerbations are associated with poorer overall survival, health-related quality of life, neurocognitive function and sleep, while contributing to higher health care costs [1–6]. Hospitalizations also expose CF patients to antibiotic-resistant bacteria [7]. About 35% of US patients with CF are hospitalized

each year, associated with advancing age, poorer pulmonary function and, possibly, female sex [8,9]. However, prior studies were restricted to adults with CF who harboured multi-drug resistant bacteria [1], or were done in areas with private health coverage [8,9], potentially limiting the generalizability of their results. Furthermore, registries that depend on self-reported data may not account for all aspects of health care utilization [10], or may underestimate the total number of hospitalizations. No study has systematically captured predictors of hospitalization in CF patients using a combination of health administrative data and clinical registry data, particularly while adjusting for clinically important factors.

We evaluated whether sex-specific differences in hospitalization rates exist within a large cohort of pediatric and adult CF patients, cared for under a universal health care system.

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## 2. Patients and methods

### 2.1. General design

We completed a retrospective longitudinal cohort study of CF patients across the Province of Ontario, Canada.

### 2.2. Data sources

The Canadian CF Patient Data Registry (CPDR) contains detailed clinical information on all CF patients receiving clinical care, including 10 CF centres in Ontario. The CPDR contains annual records for each participant on demographic and clinical variables, including height, weight, lung function, sputum bacteriology (reported as *any* positive culture in a given year), pancreatic status and CF-related co-morbidities. Nutritional markers and lung function are recorded from the first clinic visit of the year while other variables captured within the registry are determined throughout the year.

Linked administrative health care databases, housed at the Institute for Clinical Evaluative Sciences (ICES), were used for this study. The databases include the Canadian Institute for Health Information Discharge Abstracts Database (CIHI-DAD), which describes all hospital admissions; the Registered Persons Database (RPDB), which describes demographics and vital statistics; the Ontario Home Care Administrative System (OHCAS) Database, which describes home care services delivered; and the Ontario Health Insurance Plan (OHIP) Database, which describes physician billing for inpatient and outpatient services. Until 2002, up to 16 discharge diagnoses according to the International Classification of Disease, Ninth Revision (ICD-9) were used to characterize hospital admissions within CIHI-DAD.

The Ontario-specific CPDR was probabilistically linked to the RPDB by patient name, date of birth and sex, using AutoMatch software [11]. Resulting linkages were then completed deterministically, using an encrypted version of the patient's OHIP number, common to all administrative databases.

### 2.3. Study cohort

All CF patients aged 7 years and older were retrospectively identified between the years 1993 and 2002. In order to account for partial years, an offset variable was created representing the number of days that year an individual was eligible for the study outcome. Details on the creation of the study cohort are described in Fig. 1.

### 2.4. Study exposure, covariates and outcome

Data for each participant included sex, date of CF diagnosis, date of death, date of transplant, pancreatic status (determined by the use of pancreatic enzymes), pulmonary function, height, weight, CF-related complications and sputum bacteriology. The Wang and Hankinson pulmonary function equations for children and adults were used to calculate the predicted norms for forced expiratory volume in 1 s ( $FEV_1$ ), in litres [12,13]. The percent

predicted  $FEV_1$  was calculated as follows: (measured  $FEV_1$  / predicted  $FEV_1$ )  $\times$  100. For those over the age of 19 years, body mass index (BMI) was expressed in  $kg/m^2$ . Because BMI in children and adolescents varies with age and sex, Centres for Disease Control (CDC) growth charts were used to calculate age- and sex-adjusted Z-score BMI for those aged 7 to 19 years [14]. Once a subject received a transplant, subsequent data was excluded from the analysis. Multiple imputation was used to estimate missing clinical values [15].

The primary exposure of interest was a participant's sex. The primary study outcome was the annual number of respiratory-related hospital admissions. Respiratory-related hospital admissions were identified for each subject using any ICD-9 diagnosis code related to the respiratory system that was identified in CIHI-DAD as being the most responsible diagnosis. Of the 110 potential codes related to respiratory disease, 65 were deemed as potentially indicative of a respiratory-related CF admission; the most common was "cystic fibrosis", accounting for 78% of the hospital admissions documented herein. In addition, courses of home intravenous (IV) antibiotic therapy following a hospital admission or started directly from the outpatient clinic setting were included as hospitalizations. The initiation of home IV antibiotic therapy was defined as a hospital admission of less than 3 days duration with an associated home care claim within 1 week of discharge with no homecare claims within the 4 weeks preceding the hospitalization date. In order to capture home IV antibiotic therapy initiated *directly* from the outpatient clinic, a clinic visit was identified using physician claims within the OHIP database, which captures all physician billing claims. If a homecare claim was registered within 7 days of the clinic visit date, with no homecare claims in the preceding 4 weeks, this was assumed to represent an individual who was started on home IV antibiotic therapy directly from clinic without a hospital admission.

### 2.5. Sensitivity analyses

We performed separate sensitivity analyses to evaluate the robustness of our findings. Firstly, the main analysis was carried out excluding missing data, without using multiple imputation. The algorithm used to identify home intravenous antibiotic therapy has not been validated; therefore we analyzed the data using only those respiratory-related hospitalizations identified by an inpatient hospital stay as part of a second sensitivity analysis.

### 2.6. Statistical analysis

Means (SD) were reported for continuous variables, and proportions (%) reported for categorical variables. Unpaired t-tests were used to compare continuous variables and the Chi-squared test to compare categorical variables between males and females. The risk of hospitalization between females vs. males was estimated using Poisson regression and generalized estimating equations (GEE), which accounts for repeated measures [16], with adjustment for other covariates, as listed

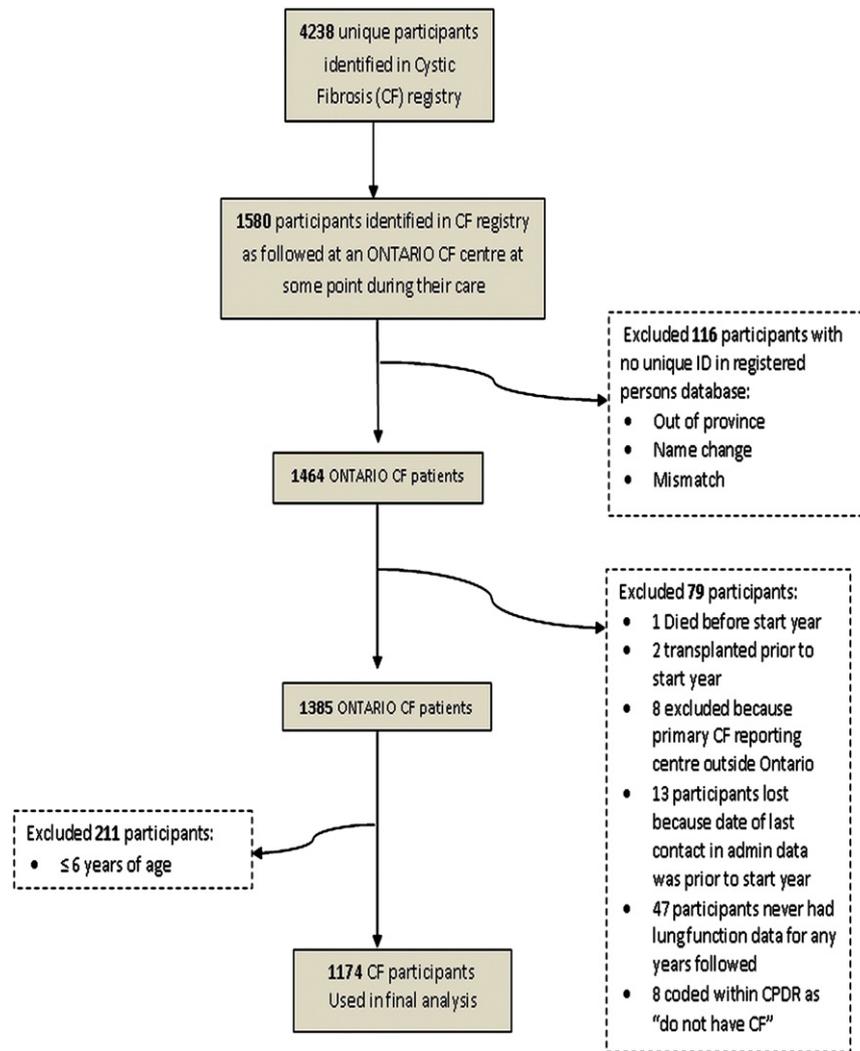


Fig. 1. Creation of study cohort.

in the footnote of Table 2. Adjusted rate ratios (RR) and 95% confidence intervals (CI) for respiratory-related hospitalizations between females vs. males were further stratified according to markers of CF-related disease severity, chosen *a priori*.

Because of inherent age-related differences in CF severity and measures of lung function, all analyses were separately performed in children aged 7 to 19 years and adults aged 20 years and older. Over- and under-dispersion of the data was evaluated by comparing the Poisson and negative binomial distributions, and the goodness of fit of the models. The zero-inflated Poisson regression model was also used to examine whether the data consisted of an excessive number of participants having zero hospitalizations. Linearity of continuous variables was assessed using a quadratic term and/or categorization to assess for a threshold effect.

A two-sided P-value <0.05 was set for statistical significance. All analyses were done using SAS 9.1 statistical software.

The research study received ethics approval from the Research Ethics Board of Sunnybrook Health Sciences Centre. Prior to 2002, individual patient consent was not required for

registries. At the time the Registry data was requested for this study, only data to the end of 2002 were available for release.

### 3. Results

Of 1580 CPDR participants identified as being followed in Ontario, 1464 (93%) were successfully linked to the administrative databases, of which 1174 participants were aged 7 years and older, and 45% were female (Fig. 1). Forty-three percent of the cohort was followed for the entire 10-year period, and 74% were followed for 5 years or more. No significant differences were noted in follow-up time between males and females. The most recent clinical measurements performed on each participant are listed in Table 1.

#### 3.1. Hospitalizations

##### 3.1.1. All participants

Among the 1174 participants, there were 6194 hospitalizations (all cause), of which 4931 (80%) were inpatient hospitalizations

Table 1  
Characteristics of study participants according to their last recorded clinical measurements.

	Age group (years)			
	7–19		Over 19	
	Females (n=366)	Males (n=420)	Females (n=274)	Males (n=355)
Mean (SD) age, years	14.7 (4.1)	14.9 (4.1)	30.6 (9.0)	31.0 (7.9)
Mean (SD) age at diagnosis, years	2.1 (3.6)	2.1 (3.5)	7.8 (11.7)	6.3 (9.6)
Mean (SD) % predicted FEV <sub>1</sub>	71.9 (26.3)	72.8 (25.9)	51.7 (23.4)	50.3 (24.3)
Mean (SD) BMI <sup>a</sup>	−0.27 (1.0)*	−0.46 (1.2)*	21.8 (4.1)*	22.7 (3.6)*
Percent pancreatic insufficient	90.2	91.4	77.4	82.3
Percent diabetes mellitus	12.8†	4.3†	29.2†	16.3†
Percent <i>Pseudomonas aeruginosa</i> bacteriology	73.5	73.6	77.7	71.0
Percent <i>Burkholderia cepacia</i> bacteriology	10.9	13.6	28.5*	36.1*

\*p<0.05; †p<0.001 noted for differences between males and females for each age category; Chi-squared test was used for dichotomous covariates and Student's t-test for continuous covariates.

<sup>a</sup> Z-scores were used for those aged 7–19 years, and kg/m<sup>2</sup> for those aged 20 years and over.

and 1263 (20%) same-day admissions. Out of the 4931 inpatient hospitalizations, 3676 (75%) were coded as respiratory-related. Fifty-eight percent of all participants had 1 or more respiratory-related hospitalizations over the study period, ranging from 0 to 15 hospitalizations per year. There was no evidence of under- or over-dispersion (dispersion factor=0.94), and the dataset did not have an excessive number of zero-count hospitalizations. No significant sex interactions were identified.

### 3.1.2. Participants aged 7–19 years

A total of 786 young participants contributed 4408 person-years of observation. The absolute difference in the annual rate of hospitalizations was higher in females than males, equivalent to an adjusted RR of 1.37 (95% CI 1.10–1.71) (Table 2).

### 3.1.3. Participants aged 20 years and older

A total of 629 adult participants contributed 4036 person-years of observation. The adjusted RR of respiratory-related hospitalization comparing females vs. males was 1.30 (95% CI 1.06–1.59) (Table 2).

### 3.1.4. Stratified analysis

In both young and adult CF patients, the increased RR of respiratory-related hospitalizations among females was consis-

tently seen across the majority of markers of CF disease severity (Fig. 2).

## 4. Discussion

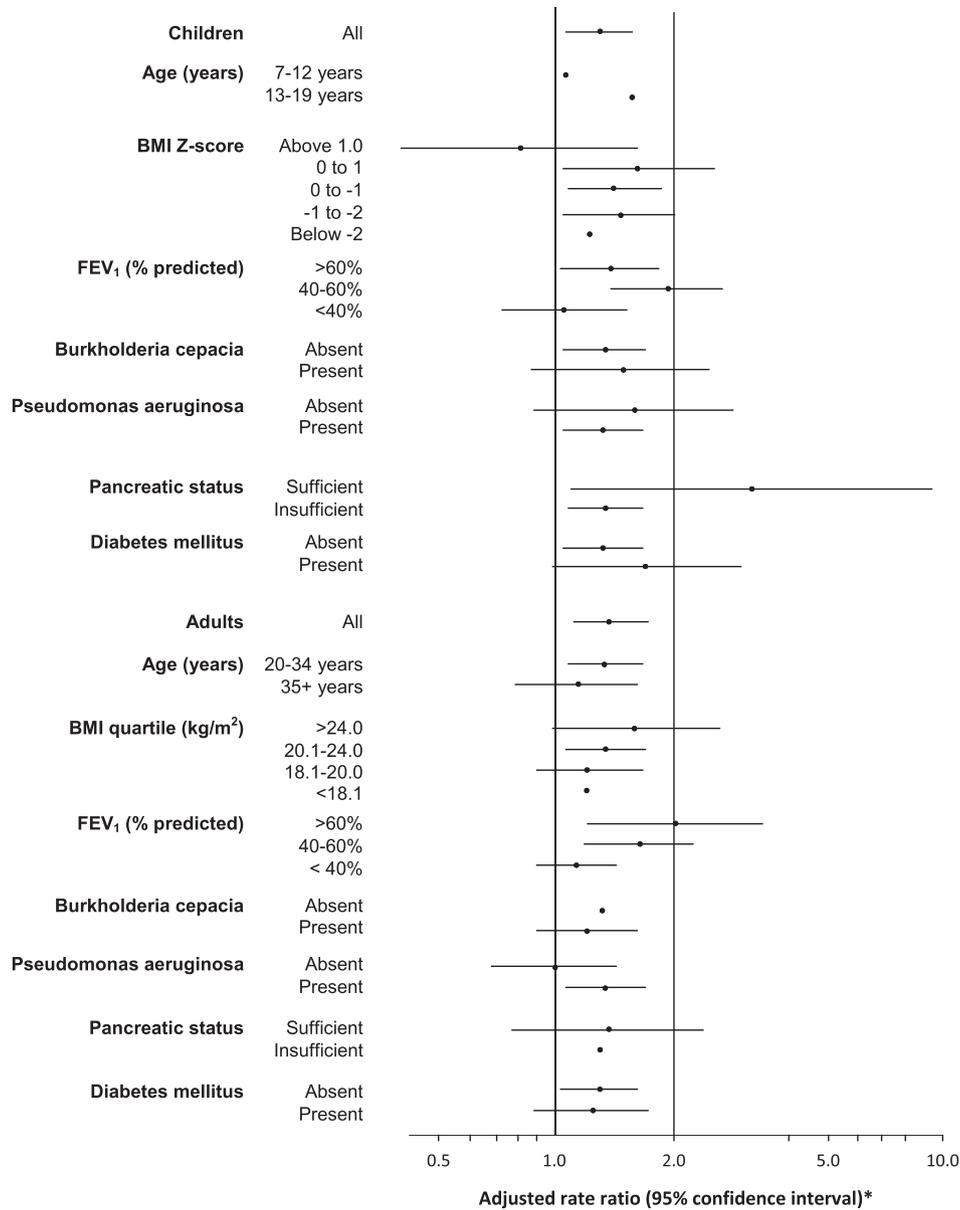
We observed a higher risk of respiratory-related hospitalizations among adolescent and adult females with CF. This was so even after adjusting for clinically important covariates, suggesting that this phenomenon cannot be fully explained by traditional markers of CF disease severity. Furthermore, the higher risk in females was noted across several clinical subgroups and the results of sensitivity analyses were consistent with this finding (data not shown).

Important strengths of this study include its large population-based sample of 1174 children and adults with CF, its longitudinal design, and the combined use of administrative and patient-level data. Moreover, we adjusted for traditional markers of CF disease severity. As a limitation, respiratory-related hospitalizations were defined by an ICD-9 code that described the most responsible diagnosis after admission, based on an algorithm that has not been formally validated. This may have introduced some error, in that some admissions were incorrectly attributed to respiratory complications. At the same time, we do not see why this would be biased for females over

Table 2  
Risk of annual hospitalizations for respiratory-related causes comparing females and males.

Age group	Total number of respiratory hospitalizations over the 10-year study period		Annual respiratory hospitalization rate for respiratory-related causes per 100 patient-years		Rate ratio of annual respiratory hospitalizations comparing females vs. males	
	Females	Males	Females	Males	Crude	Adjusted <sup>a</sup>
7 to 19 years	807	678	45.1	32.0	1.46 (1.11–1.91)	1.37 (1.10–1.71)
≥20 years	1136	1055	77.3	51.3	1.45 (1.16–1.82)	1.30 (1.06–1.59)

<sup>a</sup> The models were adjusted for age (continuous in years), FEV<sub>1</sub> (continuous in percent predicted [aged 7–19 years]) and categorical (FEV<sub>1</sub> percent predicted: mild>60; moderate 40–60; severe<40 [aged ≥20 years]), body mass index (continuous z-score [aged 7–19 years] or continuous kg/m<sup>2</sup> [aged ≥20 years]), pancreatic status (insufficient vs. sufficient), diabetes mellitus (present vs. absent), *Pseudomonas aeruginosa* or *Burkholderia cepacia* sputum bacteriology positivity [once a subject became positive they were coded as such for subsequent years] (present vs. absent), age at diagnosis (continuous), and birth year (continuous). Among those aged ≥20 years, the model was also adjusted for the number of outpatient clinic visits per year.



\* For children and adults, the stratified models were adjusted for each of the variables presented, but not for the stratification variable, with the exception of the age stratum, in which age (continuous in years) was also included in the model. For children, year of birth was also adjusted for in all models, while for adults, number of outpatient clinic visits was also adjusted for.

Fig. 2. Risk of hospitalization for respiratory illness in association with female vs. male sex, stratified by markers of disease severity.

males. Hospital length of stay (LOS) was not considered herein, and each admission was considered as equivalent to another, such that males may have had fewer hospitalizations per year but a longer LOS. Missing clinical data, the accuracy of non-missing data, and the strategies used to deal with missing data could potentially have biased the study findings, but sex was unambiguously recorded for all study participants. Other literature suggests that multiple imputation strategies provide unbiased estimates, even if the missingness is not completely at random [17,18]. A sensitivity analysis excluding missing data showed higher respiratory-related hospitalization rates in females suggesting that the results are robust (data not shown). Finally, the study cohort excluded individuals younger

than 7 years of age and hospitalizations occurring after transplantation therefore our results may not be generalizable to these specific groups.

In contrast to others [1,8,9], the current study's primary focus was on sex-specific differences in respiratory-related hospitalization rates among a broad population of individuals with CF. Previous cross-sectional studies were descriptive in nature, lacking rigorous statistical methods to quantify associated risks [8,9]. In addition, earlier work failed to specify the reason for hospitalization. The only Canadian study included adults with multi-drug resistant bacteria, a small subgroup of the overall CF population [1]. Despite studying this specific group of individuals with CF, they too found that

female sex was a significant predictor of future hospital admissions for pulmonary exacerbations [1].

Sex differences in CF outcomes outside of the hospital setting have been previously reported, but the reasons why this is so remain elusive. Several studies have documented worse overall survival in female CF patients despite similar disease severity to males [19,20]. CF-related diabetes mellitus is more common in women than men [21], and females with diabetes tend to die earlier than affected males [22]. Finally, studies have shown that females are diagnosed with CF at a later age than are males [23].

Sex-based differences in disease activity and disease severity may be attributed to sociological, behavioural, hormonal or genetic factors. One sociological factor relates to “ambulatory care sensitive conditions”, in which a disease or its complication is sub-optimally managed in the outpatient setting, and is thus dealt with through an avoidable hospitalization [24]. Though a progressive genetic disease for which there is no cure, medications such as inhaled tobramycin [25], mucolytic therapy [26] and chronic oral azithromycin [27] have been shown to reduce the need for hospitalization and intravenous antibiotic therapy for pulmonary exacerbations in CF. The gender gap in hospitalization rates seen in our study could be a result of differential prescribing patterns for medications in this patient population, a variable not captured herein. Female sex hormones may modulate the symptomatology and severity of CF lung disease [28], and worsening of respiratory symptoms during menstruation has been described [29]. Coakley et al. postulated that high estrogen levels reduce the regulation of airway surface liquid volume homeostasis, resulting in decreased mucociliary clearance [30]. It is possible that hormonal differences between males and females contribute to differential hospitalization rates seen in our study and future work in this area is needed to understand the role hormones play in symptomatology in CF. Finally, hyperglycemia impairs the ability to fight infection and a higher proportion of females had diabetes in our study. It is possible that females had worse diabetic control contributing to increased respiratory hospitalization rates; however, this is unlikely to be the sole reason as the overall proportion of persons with diabetes in our study population, particularly the younger age group, was relatively low. Despite this, the impact of diabetic control on respiratory hospitalizations in CF is an interesting area for future research.

The decision to hospitalize a patient may be influenced by what is communicated to the health care provider. For example, Hawker et al. showed that, despite their equal willingness to undergo joint replacement surgery, women were less likely to discuss the option of surgery with their physician, resulting in less frequent recommendations for surgery when indicated [31]. Whether the opposite is true in CF, in which females are more likely to be admitted to hospital, is not known.

## 5. Conclusions

Using a national clinical registry linked to administrative databases, our research has shown that sex differences in hospitalization rates exist in pediatric and adult CF patients,

even after adjusting for markers of disease severity. Future research is needed to elucidate why these differences may exist, such that targeted interventions could be introduced to narrow this gender gap. Research evaluating differences in outpatient management, communication strategies between patients and health care providers and hormonal influences could shed light on this matter.

## Conflict of interest

Dr. Stephenson has no conflicts of interest to disclose. Dr. Hux has no conflicts of interest to disclose. Dr. Tullis has no conflicts of interest to disclose. Dr. Austin has no conflicts of interest to disclose. Dr. Corey has no conflicts of interest to disclose. Dr. Ray has no conflicts of interest to disclose.

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