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CFTR Heterozygotes Are at Increased Risk of Respiratory Infections: A Population-Based Study

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Background. Patients heterozygous for mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene may be more susceptible to respiratory infections than the general population.

Methods. We conducted a retrospective case–control study using health insurance claims. We identified patients as either highly likely to be *CFTR* heterozygotes (CF carriers diagnosed during genetic counseling, parents of children with a diagnosis of CF, and children of mothers diagnosed with CF) or likely *CFTR* heterozygotes (children of CF carriers diagnosed during genetic counseling and parents of CF carriers diagnosed during genetic counseling). Next, we examined the rates of respiratory infections and antimicrobial prescriptions between both groups of *CFTR* patients and only the highly likely subcohort, compared with age/sex-matched controls. We examined the presence of any claim using McNemar's test and the number of claims using the sign test.

Results. *CFTR* heterozygotes (the pooled highly likely and likely heterozygotes) were more prone to have at least 1 claim for a respiratory infection (odds ratio [OR], 1.28; $P = .020$) and to have a greater number of claims for respiratory infections (53.5%; $P = .043$) than controls. Patients in the highly likely cohort were also more prone to have at least 1 claim for a respiratory infection (OR, 1.30; $P = .028$) and more claims (54.3%; $P = .039$) than controls. In addition, the highly likely *CFTR* heterozygotes were more prone to be prescribed an antibiotic used to treat respiratory infections (OR, 1.34; $P = .018$) and to have more of these prescriptions (54.3%; $P = .035$) than controls.

Conclusions. Patients heterozygous for *CFTR* mutations are at higher risk for respiratory infections. Future work to describe clinical outcomes for *CFTR* heterozygotes is needed.

Keywords. antimicrobial; *CFTR* heterozygote; respiratory infection.

Cystic fibrosis (CF) is an autosomal recessive disorder resulting from mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene [1–3]. The *CFTR* gene encodes a chloride and bicarbonate channel expressed mainly on the surface of epithelial cells. Patients must be homozygous for the mutated *CFTR* gene to develop CF. Clinical manifestations of CF include viscous mucous, airway inflammation, recurrent pulmonary and sinus infections, and the development of bronchiectasis [1–3].

Individuals carrying 1 *CFTR* mutation have approximately 50% normal *CFTR* function, a level originally believed to be sufficient for maintaining health [4]. Some reports even suggest that *CFTR* heterozygotes have a survival advantage, citing the high prevalence of *CFTR* heterozygotes among Caucasians [5–10]. However, a few studies suggest that CF carriers may be at higher risk for some of the same diseases that people with CF develop. For example, the *CFTR* carrier state may be associated with more frequent cases of sinusitis [11, 12]. Pulmonary infections with nontuberculous mycobacteria are also relatively common in people with CF [13], and carriers are also reported to be at higher risk for these infections [14, 15].

Most studies regarding the health implications of the CF carrier state have been small and focused on a single population (eg, patients with chronic sinusitis). Because CF is an autosomal recessive and monogenic disorder, the biologic parents of each child with CF will have a *CFTR* mutation. Thus, we used a large longitudinal cohort of insured patients to investigate the rates of respiratory and sinus infections in parents of children with CF, persons who tested positive for a single *CFTR* mutation, and children of mothers with CF.

METHODS

Design Overview

We conducted a retrospective case–control study, using a de-identified data set of fully insured commercial health insurance claims from Iowa and South Dakota hosted by the University of Iowa. These Midwestern states, according to the US Census Bureau, are 91.4% and 85.2% Caucasian, respectively [16]. This repository provides longitudinal inpatient, outpatient, home health, extended care/skilled nursing, and outpatient pharmacy health care claims data for insured members and their covered family members. These data also include insurance coverage, limited demographic

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information, diagnosis codes, procedure codes, dates of service, and outpatient pharmacy data, including fill dates and drug-days supplied. This study was approved by the University of Iowa Institutional Review Board (HawkIRB #201606825).

Identification of Cystic Fibrosis Carriers and Control Patients

We identified likely CF carriers (*CFTR* heterozygotes) using 5 approaches: (1) identifying people diagnosed as CF carriers in the course of genetic counseling, (2) identifying the parents of children with a diagnosis of CF, defined by ICD-9 code 277.0X during either an outpatient or inpatient visit, (3) identifying children of mothers diagnosed with CF (we did not include fathers because of the extremely high infertility rates among men with cystic fibrosis), (4) identifying children of parents diagnosed as CF carriers in the course of genetic counseling, (5) identifying parents of children diagnosed as gene carriers in the course of genetic counseling. For all CF carriers, we confirmed that they did not have a diagnosis code for CF (277.0X) during the study period. Individuals in these categories are not uniformly likely to be CF carriers; although groups 1–3 are very likely to be *CFTR* heterozygotes, people in groups 4 and 5 have a 50% likelihood of being heterozygotes. We expect both groups to have a much higher incidence than the 3%–5% rate in the population at large. We identified 1 highly likely group, using approaches 1–3, as described above, for a sensitivity analysis.

Identified potential carriers were each matched to a single, randomly selected control. Control patients were matched on total follow-up time (discretized to 6-month intervals), gender, state of residence (Iowa or South Dakota), and birth year (to within 1 year).

Assessment of Respiratory Infection Diagnosis and Antimicrobial Agent Prescribing Among Cystic Fibrosis Carriers and Controls

We defined respiratory infections among both CF carriers and controls as the presence of a claim with a primary diagnosis consisting of 1 of the following ICD-9CM codes: 481 pneumococcal pneumonia; 482 other bacterial pneumonia; 483 pneumonia due to other specified organism; 484 pneumonia in infectious diseases classified elsewhere; 485 bronchopneumonia, organism unspecified; 465 acute upper respiratory infections of multiple or unspecified sites; 466 acute bronchitis and bronchiolitis; 461 acute sinusitis; 473 chronic sinusitis; 490 bronchitis NOS; 491 chronic bronchitis NEC. We calculated the number of different respiratory infections for both CF carriers and controls. We chose these conditions based upon respiratory infections commonly experienced by patients with CF. In addition, we categorized each of these different respiratory infections into 4 distinct groups using the codes above: pneumonia (481–5), upper respiratory infections–unspecified (465), sinusitis (461, 473), and bronchitis (466, 490, 491).

We also examined outpatient prescription use of antimicrobials among cases and controls. Prescription medications were identified through National Drug Codes from the proprietary Multum Lexicon Database on outpatient prescription claims. We examined the number of specific prescriptions commonly used to treat respiratory infections among both likely CF carriers and controls for the following antimicrobials: amoxicillin, amoxicillin-clavulanate, azithromycin, cefdinir, cefprozil, cefuroxime, clarithromycin, levofloxacin, and moxifloxacin. We did not include antimicrobials commonly used to treat both respiratory infections and other infections (eg, doxycycline).

Because people with CF are highly susceptible to respiratory infections, parents of children with CF might exhibit health-seeking behavior; they might be more likely to visit health care care providers. This would artificially increase the number of respiratory visits for these parents even if they do not suffer from more respiratory visits than non-CF carriers. Thus, as a test of health care–seeking behavior, we also examined visits for urinary tract infections (UTIs; code: 599.0) for both cases and controls. We also examined hospitalizations with respiratory diagnoses because these are less subject to patient preferences.

We used the Charlson Comorbidity Index to measure underlying comorbidity among cases and controls. Comorbid conditions were considered "present" if the corresponding ICD-9 code was listed as a primary diagnosis on at least 1 claim during the follow-up period of the patient. The Charlson Comorbidity Index was computed using the "icd" package, version 2.2, for R, version 3.3.2 [17, 18].

Statistical Analyses

For all outcomes of interest (respiratory diagnoses, hospitalizations, antibiotic prescriptions) and ancillary/sensitivity outcomes (UTIs, comorbidities), we computed incidence rates in units per 100 000 person-years for case and control groups, as well as average outcomes in each group. We formally compared the carrier-enriched group with controls in 2 ways. First, we considered binary outcomes (presence vs absence of each outcome) and estimated a paired odds ratio, confidence interval, and associated hypothesis test using McNemar's test for paired data. Second, we considered numeric outcomes (the number of claims for each outcome). To test the null hypothesis that the median difference between case and control claim numbers was equal to 0 given our paired data, we used the sign test. This procedure is not sensitive to outliers, which can have a large impact on means and incidence rates, and is based on the proportion of non-tied pairs in which the case pair had a greater count.

To examine whether these results remained consistent for those cases in which we had the highest diagnostic confidence, we reran our analysis on the cases at most risk of being *CFTR* carriers: subjects diagnosed as CF carriers in the course of genetic counseling, subjects identified as parents of children with a diagnosis of CF, and subjects who were children of mothers diagnosed with CF.

All analyses were performed using the R statistical computing environment, version 3.3.2, whereas SAS, version 9.4, was used for data processing and interaction with the claims database. Hypothesis tests were conducted at the .05 level, and both confidence intervals and *P* values are provided. We note that, under the global null hypothesis, we would expect an average of 0.9 type 1 errors per table (each contains 18 hypothesis tests).

RESULTS

We identified 1024 potential cases from among more than 230 million claim records and 2 million unique patients insured between 2003 and 2014. Appropriately matched controls were obtained for 1011, approximately 98.7% of patients. Most of the matched pairs (89.7%) were followed for more than 12 months. The population was evenly divided between males and females (52.4% of matched pairs identified as female). Patients' age ranged from 4 to 78 years, with 80% between 10 and 56 years of age.

The largest numbers of cases were identified as parents of children diagnosed with CF (n = 409), followed by children of mothers with CF (n = 198). Fewer patients were identified directly by genetic testing (n = 162), as the child of a diagnosed gene carrier (n = 132), or as the parent of a diagnosed gene carrier (n = 125). These groups are not mutually exclusive. However, overlap was not common across groups, with only 15 patients matching to more than 1 group.

Considering the binary outcomes, case patients were significantly more likely to have at least 1 respiratory infection claim (odds ratio [OR], 1.28; *P* = .020). On a more granular level, case patients were more likely to have at least 1 claim with any upper respiratory infection (OR, 1.28; *P* = .021), sinusitis (OR, 1.29; *P* = .0183), bronchitis (OR, 1.24; *P* = .048), or a respiratory hospitalization (OR, 1.83; *P* = .049), but not pneumonia (OR, 2.14; *P* = .136) or UTI (OR, 1.14; *P* = .35). We did not detect significant evidence overall that cases were prescribed at least 1 antibiotic more frequently than controls (OR, 1.24; *P* = .057); however, cases were significantly more likely to have a claim for amoxicillin clavulanate (OR, 1.27; *P* = .030) or cefdinir (OR, 1.41; *P* = .014). The full results are presented in Table 1.

Considering the continuous outcomes, case patients had a higher median number of respiratory infection–related claims (53.6%; *P* = .043) and respiratory hospitalizations (64.7%; *P* = .049). Within respiratory infection subgroups, case patients had significantly more bronchitis claims than control patients (55.2%; *P* = .034). We did not detect a difference in the odds of pneumonia, upper respiratory infection, sinusitis, or UTIs between cases and controls. Cases had almost 1 more prescription on average than controls (4.46 vs 3.64), but this result was not significant (53.5%; *P* = .053). Significantly more prescriptions were detected among cases for those antibiotic agents with the most prescriptions: amoxicillin-clavulanate (57.1%; *P* = .004) and cefdinir (58.2%; *P* = .014). Table 2 presents a complete summary of these results.

In the high-risk subgroup analysis, despite the smaller sample size, the results were similar to the large group; these are presented in Tables 3 and 4. Many of the same significant trends were detected, and the point estimates were more extreme. Cases in this group were more likely to experience a respiratory infection (OR, 1.30; *P* = .028) or a respiratory hospitalization (OR, 0.25; *P* = .025) and experienced higher numbers

Table 1. Main Analysis: Any Claims (n = 1011 Pairs)

Variable	Odds Ratio (95% CI)	Case Mean	Control Mean	Case Incidence Rate	Control Incidence Rate	*P* Value
Respiratory Infection	**1.28 (1.05–1.57)**	**0.66**	**0.62**	**994.8**	**926.46**	**.020**
Pneumonia	2.14 (0.87–5.26)	0.02	0.01	23.76	11.88	.136
Upper respiratory infection	**1.28 (1.04–1.58)**	**0.38**	**0.34**	**571.62**	**504.80**	**.021**
Sinusitis	**1.29 (1.05–1.59)**	**0.34**	**0.30**	**513.71**	**445.41**	**.018**
Bronchitis	**1.24 (1.01–1.52)**	**0.28**	**0.24**	**424.63**	**366.72**	**.048**
Respiratory infection hospitalization	**1.83 (1.03–3.26)**	**0.03**	**0.02**	**49.00**	**26.72**	**.050**
UTI	1.14 (0.88–1.49)	0.15	0.14	228.65	206.38	.349
Comorbidity index	1.04 (0.83–1.29)	0.23	0.22	337.03	328.12	.780
Antibiotics	1.24 (0.99–1.54)	0.70	0.67	1055.63	1002.18	.057
Amoxicillin	1.09 (0.90–1.31)	0.45	0.44	680.00	654.76	.434
Amoxicillin-clavulanate	**1.27 (1.03–1.56)**	**0.29**	**0.25**	**439.48**	**377.12**	**.030**
Azithromycin	1.07 (0.88–1.30)	0.45	0.43	671.09	650.31	.519
Cefdinir	**1.41 (1.07–1.85)**	**0.16**	**0.13**	**242.01**	**188.56**	**.016**
Cefprozil	1.02 (0.68–1.53)	0.05	0.05	80.17	78.69	1.000
Cefuroxime	1.13 (0.76–1.68)	0.06	0.05	84.63	75.72	.614
Clarithromycin	1.00 (0.70–1.43)	0.07	0.07	97.99	97.99	1.000
Levofloxacin	1.08 (0.79–1.46)	0.11	0.10	163.32	154.41	.698
Moxifloxacin	1.25 (0.69–2.25)	0.03	0.02	37.12	29.69	.5510

Abbreviations: CI, confidence interval; UTI, urinary tract infection. Statistically significant results are printed in bold type.

Table 2. Main Analysis: No. of Claims (n = 1011 Pairs)

Variable	Proportion Case Greater (95% CI)	Case Mean	Control Mean	Case Incidence Rate	Control Incidence Rate	*P* Value
Respiratory Infection	**0.54 (0.50–0.57)**	**5.66**	**4.55**	**8497.02**	**6823.75**	**.043**
Pneumonia	0.65 (0.43–0.84)	0.16	0.05	234.58	75.72	.210
Upper respiratory infection	0.54 (0.50–0.59)	1.13	0.99	1691.09	1478.78	.065
Sinusitis	0.54 (0.49–0.59)	1.56	1.07	2347.33	1600.52	.088
Bronchitis	**0.55 (0.50–0.60)**	**0.99**	**0.74**	**1478.78**	**1113.54**	**.034**
Respiratory infection hospitalization	**0.65 (0.50–0.78)**	**0.24**	**0.11**	**360.79**	**160.35**	**.049**
UTI	0.54 (0.48–0.61)	1.01	0.83	1512.92	1245.68	.188
Comorbidity index	0.51 (0.45–0.56)	0.23	0.31	442.45	464.72	.830
Antibiotics	0.54 (0.50–0.57)	4.46	3.64	6697.55	5462.27	.053
Amoxicillin	0.53 (0.49–0.57)	1.299	1.13	1949.43	1701.48	.177
Amoxicillin-clavulanate	**0.57 (0.52–0.62)**	**0.653**	**0.48**	**979.91**	**712.66**	**.004**
Azithromycin	0.53 (0.49–0.57)	1.615	1.27	2424.54	1903.40	.220
Cefdinir	**0.58 (0.52–0.65)**	**0.337**	**0.26**	**506.29**	**384.54**	**.014**
Cefprozil	0.52 (0.41–0.62)	0.091	0.08	136.59	121.75	.841
Cefuroxime	0.54 (0.43–0.64)	0.092	0.09	138.08	136.59	.547
Clarithromycin	0.51 (0.42–0.60)	0.101	0.09	151.44	130.65	.929
Levofloxacin	0.50 (0.43–0.58)	0.23	0.23	347.42	338.51	1.000
Moxifloxacin	0.56 (0.40–0.70)	0.04	0.02	63.84	32.66	.552

Abbreviations: CI, confidence interval; UTI, urinary tract infection. Statistically significant results are printed in bold type.

of respiratory infections (54.3%; $P = .039$) and hospitalizations (0.69; $P = .024$). In addition, unlike the larger group, we detected a significant increase in the odds of having an antibiotic prescription (OR, 1.36; $P = .018$), a higher number of antibiotic prescriptions (54.3%; $P = .035$), and a diagnosis of pneumonia (OR, 5.00; $P = .043$). Cases were more likely to have a diagnosis of bronchitis than controls (OR, 1.35; $P = .016$). They were not more likely to have a UTI claim (OR, 1.16; $P = .36$) or higher numbers of UTI claims (54.8%; $P = .20$).

DISCUSSION

Our results demonstrate that CF carriers were at substantially greater risk of having more respiratory infections compared with both age- and sex-matched controls. In addition, CF

Table 3. Higher-Risk Subgroup: Any Claims (n = 762 Pairs)

Variable	Odds Ratio (95% CI)	Case Mean	Control Mean	Case Incidence Rate	Control Incidence Rate	*P* Value
Respiratory Infection	**1.30 (1.035–1.638)**	**0.66**	**0.61**	**748.30**	**690.39**	**.028**
Pneumonia	**5.00 (1.096–22.82)**	**0.01**	**0.04**	**16.33**	**4.45**	**.043**
Upper respiratory infection	1.22 (0.966–1.547)	0.36	0.32	408.30	366.72	.107
Sinusitis	1.18 (0.938–1.493)	0.35	0.32	400.87	365.24	.174
Bronchitis	**1.35 (1.065–1.721)**	**0.29**	**0.24**	**329.61**	**268.73**	**.016**
Respiratory infection hospitalization	**2.25 (1.140–4.441)**	**0.04**	**0.02**	**40.09**	**17.82**	**.025**
UTI	1.16 (0.862–1.567)	0.16	0.14	181.14	161.83	.362
Comorbidity index	1.12 (0.872–1.445)	0.24	0.22	271.70	250.92	.403
Antibiotics	**1.36 (1.059–1.733)**	**0.71**	**0.66**	**806.20**	**748.3**	**.018**
Amoxicillin	1.24 (0.997–1.542)	0.45	0.41	513.71	461.75	.060
Amoxicillin-clavulanate	1.26 (0.989–1.595)	0.30	0.26	338.51	292.49	.069
Azithromycin	1.05 (0.836–1.312)	0.44	0.43	500.35	489.96	.730
Cefdinir	**1.54 (1.116–2.127)**	**0.16**	**0.12**	**182.62**	**133.62**	**.010**
Cefprozil	0.87 (0.546–1.436)	0.05	0.06	56.42	62.36	.712
Cefuroxime	1.00 (0.642–1.559)	0.06	0.06	65.33	65.33	1.000
Clarithromycin	1.12 (0.764–1.65)	0.08	0.07	87.60	78.69	.624
Levofloxacin	1.07 (0.772–1.494)	0.12	0.12	138.08	130.65	.736
Moxifloxacin	1.47 (0.761–2.827)	0.03	0.02	32.66	22.27	.324

Abbreviations: CI, confidence interval; UTI, urinary tract infection. Statistically significant results are printed in bold type.

Table 4. Higher-Risk Subgroup: No. of Claims (n = 762 Pairs)

Variable	Proportion Case Greater (95% CI)	Case Mean	Control Mean	Case Incidence Rate	Control Incidence Rate	*P* Value
Respiratory Infection	**0.54 (0.50–0.58)**	**5.93**	**4.52**	**6710.91**	**5116.33**	**.039**
Pneumonia	0.77 (0.46–0.95)	0.12	0.01	136.59	10.39	.092
Upper respiratory infection	0.55 (0.49–0.60)	1.07	0.92	1205.59	1037.82	.084
Sinusitis	0.52 (0.47–0.58)	1.72	1.17	1946.46	1319.91	.354
Bronchitis	**0.57 (0.52–0.63)**	**1.02**	**0.75**	**1156.59**	**843.32**	**.001**
Respiratory infection hospitalization	**0.69 (0.52–0.83)**	**0.26**	**0.07**	**292.49**	**74.24**	**.024**
UTI	0.55 (0.48–0.62)	1.06	0.85	1204.10	957.64	.202
Comorbidity index	0.53 (0.46–0.59)	0.32	0.30	365.24	341.48	.427
Antibiotics	**0.54 (0.50–0.58)**	**4.58**	**3.64**	**5175.72**	**4115.63**	**.035**
Amoxicillin	0.55 (0.50–0.59)	1.27	1.04	1441.66	1177.38	.052
Amoxicillin-clavulanate	**0.58 (0.52–0.63)**	**0.68**	**0.48**	**766.11**	**544.89**	**.006**
Azithromycin	0.53 (0.48–0.58)	1.66	1.31	1873.71	1484.71	.257
Cefdinir	**0.60 (0.52–0.67)**	**0.34**	**0.24**	**380.09**	**270.22**	**.010**
Cefprozil	0.49 (0.37–0.61)	0.08	0.09	84.63	99.48	.906
Cefuroxime	0.51 (0.39–0.62)	0.10	0.11	114.32	121.75	1.000
Clarithromycin	0.54 (0.44–0.64)	0.12	0.09	136.59	100.96	.497
Levofloxacin	0.51 (0.43–0.59)	0.28	0.26	319.21	291.00	.936
Moxifloxacin	0.60 (0.42–0.75)	0.05	0.02	59.39	25.24	.324

Abbreviations: CI, confidence interval; UTI, urinary tract infection. Statistically significant results are printed in bold type.

carriers were substantially more likely to be prescribed a greater number of antimicrobials commonly used to treat respiratory infections. Finally, when we analyzed the subgroup most likely to be CF carriers, despite a substantially smaller sample, we still found a higher risk of more respiratory infections and more antimicrobial prescriptions compared with controls.

Given the high prevalence of CF carriers (approximately 1 in 25 people of Northern European descent), the potential number of respiratory infections and corresponding antibiotic use attributable to the *CFTR* heterozygote state may be substantial. Also, the heterozygote state may contribute to recurrent respiratory infections caused by resistant organisms. Finally, because CF carriers are at higher risk for respiratory infections, presumably due to their *CFTR* mutations, newly developed *CFTR* modulators could play a role in treating or preventing respiratory infections in CF carriers. These drugs (eg, ivacaftor) are designed to correct malfunctioning proteins

Table 5. Nonparent Subgroup: Any Claims (n = 359 Pairs)

Variable	Odds Ratio (95% CI)	Case Mean	Control Mean	Case Incidence Rate	Control Incidence Rate	*P* Value
Respiratory Infection	1.32 (0.94–1.85)	0.71	0.65	375.63	347.42	.124
Pneumonia	3.00 (0.61–14.86)	0.02	0.01	10.39	4.45	.288
Upper respiratory infection	1.12 (0.81–1.56)	0.41	0.39	218.25	206.38	.557
Sinusitis	1.30 (0.92–1.85)	0.32	0.27	170.74	145.50	.159
Bronchitis	1.46 (1.01–2.11)	0.28	0.22	149.96	117.29	.053
Respiratory infection hospitalization	**3.40 (1.25–9.22)**	**0.05**	**0.01**	**25.24**	**7.42**	**.019**
UTI	1.30 (0.83–2.05)	0.15	0.12	77.21	62.36	.302
Comorbidity index	1.16 (0.79–1.70)	0.21	0.19	114.32	102.45	.497
Antibiotics	1.17 (0.81–1.70)	0.72	0.70	384.54	371.18	.452
Amoxicillin	1.32 (0.95–1.83)	0.52	0.46	274.67	244.98	.12
Amoxicillin-clavulanate	1.07 (0.77–1.50)	0.32	0.31	170.74	163.32	.736
Azithromycin	0.84 (0.60–1.19)	0.43	0.46	228.65	244.98	.379
Cefdinir	**1.97 (1.28–3.03)**	**0.23**	**0.15**	**123.23**	**78.69**	**.003**
Cefprozil	1.10 (0.61–1.980)	0.08	0.08	44.54	41.57	.880
Cefuroxime	1.67 (0.82–3.41)	0.06	0.04	32.66	20.79	.216
Clarithromycin	0.83 (0.45–1.52)	0.06	0.07	31.18	37.12	.643
Levofloxacin	1.06 (0.54–2.10)	0.06	0.06	32.66	31.18	1.000
Moxifloxacin	2.00 (0.60–6.64)	0.02	0.01	11.88	5.94	.387

Abbreviations: CI, confidence interval; UTI, urinary tract infection. Statistically significant results are printed in bold type.

Table 6. Nonparent Subgroup: No. of Claims (n = 359 Pairs)

Variable	Proportion Case Greater (95% CI)	Case Mean	Control Mean	Case Incidence Rate	Control Incidence Rate	*P* Value
Respiratory Infection	**0.57 (0.52–0.63)**	**8.11**	**4.68**	**4320.52**	**2494.32**	**.014**
Pneumonia	0.67 (0.30–0.93)	0.20	0.02	103.93	10.39	.508
Upper respiratory infection	0.54 (0.47–0.61)	1.47	1.25	785.41	663.67	.321
Sinusitis	0.56 (0.48–0.64)	2.13	0.66	1132.84	348.91	.156
Bronchitis	0.59 (0.50–0.67)	1.25	0.65	666.64	347.42	.052
Respiratory infection hospitalization	**0.77 (0.55–0.92)**	**0.43**	**0.05**	**228.65**	**28.21**	**.017**
UTI	0.60 (0.48–0.70)	1.01	0.580	537.47	308.82	.101
Comorbidity index	0.55 (0.46–0.65)	0.28	0.22	148.47	115.81	.303
Antibiotics	0.54 (0.48–0.60)	5.52	4.05	2941.22	2160.26	.243
Amoxicillin	0.56 (0.49–0.63)	1.68	1.35	896.77	721.57	.093
Amoxicillin-clavulanate	0.55 (0.47–0.63)	0.81	0.53	430.57	282.10	.241
Azithromycin	0.50 (0.43–0.57)	1.94	1.44	1034.85	764.63	.945
Cefdinir	**0.65 (0.56–0.74)**	**0.53**	**0.35**	**282.1**	**184.1**	**.002**
Cefprozil	0.54 (0.39–0.68)	0.13	0.14	71.27	74.24	.672
Cefuroxime	0.63 (0.44–0.79)	0.11	0.05	56.42	26.72	.215
Clarithromycin	0.45 (0.30–0.61)	0.10	0.09	50.48	46.03	.644
Levofloxacin	0.57 (0.40–0.73)	0.19	0.10	100.96	51.97	.511
Moxifloxacin	0.67 (0.35–0.90)	0.03	0.02	17.82	8.91	.388

Abbreviations: CI, confidence interval; UTI, urinary tract infection. Statistically significant results are printed in bold type.

made by specific mutations of the *CFTR* gene. Such strategies aim to reduce antibiotic use, which in turn could reduce the number of antimicrobial-associated adverse events in this population.

Although our results differ from previous studies in that we used a population-based approach, our results are consistent with the few existing studies exploring the risks of infection associated with being a *CFTR* heterozygote. Raman et al. found that among 58 pediatric patients with chronic rhinosinusitis, a higher proportion of this cohort had single *CFTR* mutations [19]. Among adults, Wang et al. reported similar findings from a case–control study involving 147 patients diagnosed with chronic rhinosinusitis [12]. The same group reported that when surveying parents of people with CF, respondents reported substantially higher levels of chronic rhinosinusitis than the general population [11]. In addition to sinus infection, nontuberculous mycobacterial pulmonary infections, bronchiectasis [15], and allergic bronchopulmonary aspergillosis [20] are more common among CF carriers [14, 15].

Rather than starting with a population defined by a disease (eg, chronic rhinosinusitis), we used a population-based approach to examine the effects of being a *CFTR* heterozygote on the frequency of respiratory infections. Specifically, we classified subjects at a substantially higher risk of being *CFTR* carriers and explored respiratory infection–related outcomes compared with control subjects. Our approach allowed us to determine the risk of *CFTR* status on common respiratory infections compared with controls.

One possible limitation of this study is related to our inability to identify CF carriers with absolute certainty. Only a minority of our cases underwent genetic testing, and our data do not include the type of mutation. For the remainder of presumed CF carrier cases, we identified parents of children with CF or children of mothers with CF. We assume that the parents of record are the actual biological parents. There are situations (eg, remarriages, adoptions, etc.) where the recorded parents are not the biological parents. However, such identification problems should bias our findings toward the null, diluting their significance.

Another limitation to our work is that parents of children with CF might exhibit different health-seeking behaviors. To help control for health care–seeking behavior, we performed additional analyses. The results are not consistent with health-seeking behaviors as a driver of the observed associations. First, we did not find evidence that diagnoses of UTI, an infection not likely associated with *CFTR* mutations, were more common among *CFTR* heterozygotes. We also examined hospitalizations for respiratory infections, as hospitalizations are less related to health-seeking behaviors than outpatient visits. Hospitalizations were significantly higher among *CFTR* heterozygotes than controls. Also, in a model including highly likely carriers who are not parents of individuals with CF, the sample size was not large (359 pairs), but the number of pooled respiratory infections remained significantly higher in cases than controls (57.2%; $P = .0135$), and the odds of a respiratory hospitalization were significantly higher (OR, 3.4; $P = .019$). The full results for this subgroup are given in Tables 5 and 6. Finally, there were no significant differences between cases and controls in terms of comorbidities.

Our work is subject to some additional limitations. First, we rely on administrative data to identify infections. However, this should affect the cases and controls similarly. Second, we studied a privately insured population, and most subjects were under the age of 65 years. Accordingly, our results may not be generalizable to other populations (eg, uninsured patients). Third, it may be possible that some of the cases may have mild and thus undetected cases of CF rather than being merely *CFTR* carriers. CF is usually diagnosed in the first decade of life, but mild cases may be diagnosed later in life [21–23]. The misclassification of mild CF cases as *CFTR* heterozygotes could falsely increase the association between *CFTR* heterozygotes and respiratory infections. Finally, we were unable to control for race/ethnicity, which is associated with *CFTR* status. Even so, the states of Iowa and South Dakota have a high proportion of people of European ancestry. Thus, the vast majority of our cases and controls are likely of European ancestry.

CONCLUSIONS

Among our relatively young and insured population, we found that presumptive CF carriers had more respiratory infections and used more antimicrobials. Future work using multivariate or hierarchical approaches and other, larger data sets may confirm our findings, help develop criteria for determining who should be tested for *CFTR* mutations, and help estimate the risk that CF carriers face for specific respiratory infections. Ultimately, such work could lead to new diagnostic and treatment approaches for recurrent respiratory infections among carriers of *CFTR* mutations.

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