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ORIGINAL RESEARCH ARTICLE

Exposure to Oral Fluoroquinolones and the Risk of Retinal Detachment: Retrospective Analyses of Two Large Healthcare Databases

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Abstract

Background A recent Canadian case–control study reported a 4.5-fold increased risk of retinal detachment (RD) during oral fluoroquinolone use. Of the fluoroquinolone-exposed cases, 83 % were exposed to ciprofloxacin. We sought to replicate this finding, and assess whether it applied to all fluoroquinolones.

Methods In two large US healthcare databases, we performed three case–control analyses: one replicating the recent study; one addressing additional potential confounders; and one that increased sample size by dropping the Canadian study's requirement for a prior ophthalmologist visit. We also performed a self-controlled case-series (SCCS) analysis in which each subject served as his or her own comparator.

Results In the replication case–control analyses, the adjusted odds ratios (ORs) for any exposure to fluoroquinolones or ciprofloxacin were approximately 1.2 in both databases, and were statistically significant, and the ORs for current exposure were modestly above 1 in one database, modestly below 1 in the other, and not statistically significant. In the other case–control analyses, the ORs were close to 1. In a post hoc age-stratified case–control analysis, we observed an association of RD with fluoroquinolone exposure among older subjects in one of the two databases. All estimates from the SCCS analyses were below 1.2 and none was statistically significant.

Conclusion The present study does not confirm the recent Canadian study's finding of a strong relationship between RD and current exposure to fluoroquinolones. Instead, it found a modest association between RD and current or any exposure to fluoroquinolones in the case–control analyses, and no association in the SCCS analyses.

Key Points

This study sought to replicate a recent Canadian case–control study that found a 4.5-fold increased risk of retinal detachment during oral fluoroquinolone use.

In several case–control analyses, including one that mimicked the recent study, the present study found odds ratios of approximately 1.2.

In a self-controlled case-series analysis, which, like a case-crossover analysis, uses each case as its own comparator, the present study did not detect an association between fluoroquinolone exposure and the risk of retinal detachment.

1 Introduction

A recent nested case–control study [1] from administrative claims data for British Columbia, Canada, observed that "patients taking oral fluoroquinolones were at a higher risk of developing a retinal detachment compared with non-users, although the absolute risk for this condition was small." The study identified current use of fluoroquinolones in 145 cases (3.3 %) and 275 controls (0.6 %) for an adjusted rate ratio of 4.50 (95 % CI 3.56–5.70). It also

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reported the absence of an association of retinal detachment (RD) with recent use of fluoroquinolones, past use of fluoroquinolones, any use of β-lactam antibiotics, and current use of β-lactam antibiotics, suggesting the fluoroquinolone-associated risk was specific to fluoroquinolones and short-term. Of the cases with current, recent, or past exposure to a fluoroquinolone, 82.7 % were exposed to ciprofloxacin. The publication did not stratify its adjusted rate ratio estimate by individual fluoroquinolone. A more recent study from Denmark reported that exposure to oral fluoroquinolones was not associated with an increased risk of RD [2].

Our primary objective was to replicate the Canadian study [1] described above in additional databases. Secondary objectives were to determine whether the association observed in that study was specific to ciprofloxacin or was seen with all fluoroquinolones, confirm the absence of an association between exposure to β-lactam antibiotics and RD, assess the relationship of individual fluoroquinolones to RD, and address some potential confounders that may have affected the finding of the Canadian study. We therefore replicated that study's case–control analysis in two large US administrative claims databases, performed a second case–control analysis that adjusted for several additional potential confounders, performed a third case–control analysis that removed a restriction on cohort entry (a requirement for a prior visit to an ophthalmologist), and stratified our results by individual fluoroquinolone. We also conducted a case-only analysis to address possible confounders, such as smoking or body mass index, that vary substantially across individuals but vary relatively little over time within individual and are not usually well-captured in claims databases. Because we were uncertain whether the results of the Canadian study reflected an association with ciprofloxacin or with all fluoroquinolones, we assessed each of these two exposures separately in our case–control analyses. We repeated the analyses in two databases and used more than one analytic approach because recent work [3, 4] suggests that results of retrospective studies from healthcare databases vary by database and by analytic method. The approach we adopted allowed us to establish, within such variation, a range of plausible values for the estimates.

2 Methods

We conducted retrospective analyses in two databases: the MarketScan Commercial Claims and Encounters (CCAE) database, 1 January 2000 to 31 January 2012, representing 91 million US patients with an average of 25 months of observation; and the Optum ClinFormatics (Optum) database, 1 September 2005 to 31 March 2012, representing 34 million US patients with an average of 27 months of observation. Each database represents administrative claims for a privately insured population, and includes information on inpatient and outpatient medical services and pharmacy dispensing claims. All analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA). Except as noted below, all analyses were done in accordance with a protocol that was developed in advance, though this protocol was modified several times during conduct of the study, usually because of ambiguities identified as computer programs were developed to conduct the analyses. Such modifications were done before generating the results they would affect.

Calculation of the minimum detectable relative risk (the smallest relative risk for which the data are sufficiently powered at alpha = 0.05 and power = 0.80) [5] suggested each database had a sufficient sample to identify relative risks $\geq$1.1 for any exposure (current, recent, or past) to ciprofloxacin or levofloxacin, and relative risks $\geq$2.0 for moxifloxacin, gatifloxacin, gemifloxacin, ofloxacin, and norfloxacin. When the term "fluoroquinolones" or "all fluoroquinolones" is used in this report it means an oral formulation of any of these seven medications.

2.1 Case–Control Analyses

2.1.1 Eligibility and Index Date

For the replication case–control analysis, patients entered the study cohort on the day of their first ophthalmologic visit and became eligible to be cases or controls after spending at least 1 year in the cohort, ignoring breaks of up to 30 days. This year of observation allowed identification of exclusion criteria and confounders. Patients left the cohort at the first of the following: meeting any exclusion criterion; having a diagnosis of RD; having a procedure to treat RD; or reaching the end of the study period for their database. Cases were those who had an RD as defined below. The index date (the estimated date of incidence of RD) for cases was the date of the first diagnosis of RD, and for controls was the index date of the corresponding case. Up to ten controls, randomly selected from those eligible, were matched to each case on index date, age (±1 year) as of the index date, and month and year of cohort entry.

2.1.2 Outcome

As in the Canadian study [1], a patient was considered to have an RD if he/she received a diagnosis of RD and a procedure for RD, e.g., surgery consisting of a sclera buckle, a vitrectomy, retinopexy, retinal cryotherapy, silicone oil fill, air gas fluid exchange (AGFE), or pneumatic retinopexy within 14 days after the diagnosis.

2.1.3 Exposure

For each oral antibiotic of interest, exposure was classified such that the case/control index date had to be included in the intervals defined as follows:Current use: from the day after the date of dispensing through the date of dispensing plus the number of days' supply.Recent use: from the day after the last day of current use through 7 days after the last day of current use.Past use: from the day after the last day of recent use through 365 days after dispensing.Non-use: all person time not classified as current, recent, or past use.For example, the exposure status of a subject whose index date was 10 days after a dispensing of 7 days of a fluoroquinolone would be recent use.

2.1.4 Exclusion

Patients who met any of the following criteria between cohort entry and the index date were excluded: a diagnostic or procedure code for RD between cohort entry and the day before the index date (to assure cases were incident); an index date that fell during a hospitalization or within 10 days after hospital discharge (to avoid current or recent exposures that were initiated during hospitalizations); or a diagnosis of endopthalmitis or a procedure code related to endopthalmitis—including vitreous biopsy or intravitreal injection of a therapeutic agent (to avoid including subjects with this strong risk factor for RD).

2.1.5 Confounders

Potential confounders addressed in this analysis were sex, and, in the year prior to the index date, a diagnosis of myopia, diabetes mellitus (defined by use of an anti-diabetic medication), number of ophthalmologist visits, cataract surgery, and, as a measure of general health, the number of distinct drug ingredients (active pharmaceutical substances) dispensed. Unless stated otherwise, confounders were assessed over the 365 days prior to the index date.

2.1.6 Revised Case–Control Analysis

The revised case–control analysis was the same as the replication case–control analysis, with the following exceptions: additional exclusions for a diagnosis or procedure code related to inflammatory, infectious, or traumatic retinitis between cohort entry and the index date (to avoid including patients who had these strong risk factors for RD); an index date that fell during current or recent exposure to more than one fluoroquinolone or both a fluoroquinolone and a β-lactam antibiotic (to avoid ambiguities in exposure classification); and a hospital admission between cohort entry and the index date (to avoid missing information from the hospitalization that could have affected exposure status, confounders, or exclusion criteria). Cases and controls were matched on the same characteristics as in the replication case–control analysis, and were also matched on sex (to avoid the need to adjust for sex as was done in the replication case–control study). The list of RD diagnoses for purposes of identifying the outcome (RD) was shortened to exclude International Classification of Diseases (ICD) 361.2 (serous RD), which is typically associated with inflammatory conditions or with ophthalmologic inflammation, tumor, or vascular diseases, ICD 361.22 (Harada's disease), which is an inflammatory condition, and ICD 361.81 (traction detachment of retina), which is typically due to contraction of a scar on the surface of the retina. These were excluded because they occur by mechanisms that differ from rhegmatogenous RD, the most common type, which is due to a break or tear in the retina [6]. In all analyses, exclusion of subjects for prior RD was based on the broader list used in the replication case–control analysis. The confounders addressed in the replication case–control analysis were addressed in the revised case–control analysis, but additional potential confounders were also addressed: history of any diabetic retinopathy; history of proliferative diabetic retinopathy; recent history (in the 30 days prior to the index date) of iridotomy or iridectomy; and recent history of eye injury.

2.1.7 Sensitivity Analysis

The sensitivity analysis was identical to the revised case–control analysis except that subjects were not required to have an ophthalmologist visit before they became eligible to be cases or controls. Thus, they entered the cohort when they entered the database, and, if they didn't meet any of the exclusion criteria, became eligible to be cases or controls a year later. We believed the ophthalmologist visit requirement excluded many subjects and could be dropped, and study power increased, without materially changing the point estimates for the association of fluoroquinolones with RD.

All case–control analysis applied multivariate conditional logistic regression, conditioned on the case–control matching, to estimate adjusted odds ratios (ORs) and associated 95 % confidence intervals.

2.2 Self-Controlled Case-Series (SCCS) Analyses (Case-Only Analyses)

The self-controlled case-series (SCCS) analyses are similar to case-crossover analyses, in which each case serves as his or her own control. Such analyses implicitly adjust for many potential confounders, e.g., body mass index and health behaviors that are not captured, or are poorly

Table 1 Characteristics of subjects in the case–control analyses

Characteristic	Replication case–control analysis		Revised case–control analysis		Sensitivity case–control analysis	
	Cases	Controls	Cases	Controls	Cases	Controls
MarketScan Commercial Claims and Encounters (CCAE)						
Number	7,844	77,654	5,050	40,012	19,101	156,989
Age at index date [mean (SD)]	55.25 (9.22)	55.23 (9.24)	55.26 (9.06)	54.86 (9.35)	52.84 (10.82)	52.28 (11.12)
Male sex [*N* (%)]	4,681 (59.68)	32,124 (41.37)	3,141 (62.19)	25,079 (62.67)	11,843 (62.00)	98,855 (62.96)
Years of follow-up (IQR)	2.4 (1.5–3.8)	2.4 (1.6–3.9)	2.2 (1.5–3.5)	2.1 (1.4–3.3)	2.6 (1.6–4.3)	2.4 (1.5–4.0)
Cataract surgery [*N* (%)]	1,319 (16.82)	1,373 (1.76)	857 (16.97)	654 (1.63)	2,020 (10.58)	731 (0.46)
Diagnosis of myopia [*N* (%)]	151 (1.92)	462 (0.59)	107 (2.11)	252 (0.62)	345 (1.81)	669 (0.42)
Diabetes mellitus [*N* (%)]	1,701 (21.69)	10,417 (13.41)	617 (12.22)	5,054 (12.63)	1,452 (7.60)	9,492 (6.04)
Medications [median (IQR)]	8 (4–13)	4 (0–10)	6 (3–11)	4 (0–8)	5.0 (2–9)	2 (0–7)
Ophthalmologist visits [median (IQR)]	1 (0–3)	0 (0–1)	1 (0–3)	0 (0–1)	0 (0–1)	0 (0–0)
Iridectomy [*N* (%)]	N/A	N/A	1 (0.01)	4 (0.00)	5 (0.00)	8 (0.00)
Eye injury [*N* (%)]	N/A	N/A	8 (0.15)	1 (0.00)	121 (0.63)	4 (0.00)
Diabetic retinopathy [*N* (%)]	N/A	N/A	181 (3.58)	546 (1.36)	350 (1.83)	533 (0.33)
Proliferative diabetic retinopathy [*N* (%)]	N/A	N/A	98 (1.94)	149 (0.37)	203 (1.06)	98 (0.06)
Optum ClinFormatics (Optum) database						
Number	3,059	30,230	2,098	17,740	6,896	59,560
Age at index date [mean (SD)]	58.18 (11.70)	58.10 (11.68)	58.19 (11.04)	57.51 (10.96)	54.38 (12.01)	53.80 (11.95)
Male sex [*N* (%)]	1,825 (59.66)	12,917 (42.73)	1,260 (60. 06)	10,647 (60.01)	4,274 (61.90)	37,225 (62.50)
Years of follow-up (IQR)	2.1 (1.5–3.2)	2.2 (1.5–3.2)	2.1 (1.4–3.0)	2.1 (1.4–3.0)	2.3 (1.3–3.5)	2.2 (1.5–3.4)
Cataract surgery [*N* (%)]	592 (19.35)	637 (2.10)	392 (18.68)	339 (1.91)	793 (11.50)	400 (0.67)
Diagnosis of myopia [*N* (%)]	152 (4.97)	596 (1.97)	111 (5.29)	352 (1.98)	396 (5.74)	901 (1.51)
Diabetes [*N* (%)]	585 (19.12)	3,273 (10.83)	247 (11.77)	1,847 (10.41)	553 (8.01)	3,644 (6.11)
Medications [median (IQR)]	8 (4–14)	3 (0–9)	7 (3–11)	3 (0–8)	5 (2–9)	2 (0–6)
Ophthalmologist visits [median (IQR)]	2 (0–4)	0 (0–1)	1 (0–3)	0 (0–1)	0 (0–2)	0 (0–0)
Iridectomy [*N* (%)]	N/A	N/A	0 (0.00)	0 (0.00)	5 (0.07)	3 (0.00)
Eye injury [*N* (%)]	N/A	N/A	8 (0.38)	0 (0.00)	57 (0.82)	1 (0.00)
Diabetic retinopathy [*N* (%)]	N/A	N/A	84 (4.00)	229 (1.29)	1.48 (2.14)	269 (0.45)
Proliferative diabetic retinopathy [*N* (%)]	N/A	N/A	37 (1.76)	61 (0.34)	66 (0.95)	54 (0.09)

IQR interquartile range, *N* number of subjects, *N/A* not applicable, *SD* standard deviation

captured, in most health services databases, and thus may be the optimal perspective for assessing the relationship of fluoroquinolone exposure to RD. The SCCS analyses were performed using the cases from the sensitivity analysis, with 30 days after the start of exposure to any fluoroquinolone, ciprofloxacin, or levofloxacin as the time-at-risk and prior time as the reference period. Inclusion and exclusion criteria were similar to those in the sensitivity case–control analysis.

3 Results

3.1 Replication Case–Control Analysis

The study cohorts consisted of 6,518,408 subjects in the CCAE database and 3,233,453 in the Optum database. The numbers of cases and matched controls and their characteristics are described in Table 1. In both databases, cases were more likely than controls to be male, have had cataract surgery (almost tenfold more likely), myopia, diabetes, more ophthalmologic visits, and more medications dispensed (Table 1), and more likely to be exposed to a fluoroquinolone (Table 2). In both databases, the adjusted ORs associated with any exposure to fluoroquinolones or ciprofloxacin were approximately 1.2 and were statistically significant. In the CCAE database, the adjusted ORs for current exposure to any fluoroquinolone or ciprofloxacin were also modestly above 1, approximately 1.3, and were not statistically significant. In the Optum database the ORs for current exposure to any fluoroquinolone or ciprofloxacin were 0.9 and were not statistically significant. In both databases, the adjusted ORs associated with any exposure or current exposure to β-lactam antibiotics were above 1, not statistically significant, and consistent with those observed for fluoroquinolones (Table 2).

Table 2 Association of retinal detachment with fluoroquinolone exposure: replication case–control analysis

	Exposure	Cases [*N* (%)]	Controls [*N* (%)]	Crude OR (95 % CI)	Adjusted OR (95 % CI)
MarketScan Commercial Claims and Encounters (CCAE) database					
Any FQ	No	6,500 (82.87)	68,879 (88.70)	Reference	Reference
	Yes	1,344 (17.13)	8,775 (11.30)	1.62 (1.52–1.73)	1.17 (1.09–1.26)
	Current	66 (0.84)	319 (0.41)	2.20 (1.69–2.88)	1.33 (0.99–1.80)
	Recent	39 (0.50)	215 (0.28)	1.92 (1.36–2.71)	1.19 (0.81–1.76)
	Past	1,239 (15.80)	8,241 (10.61)	1.59 (1.49–1.70)	1.17 (1.08–1.26)
Ciprofloxacin	No	7,149 (91.14)	73,266 (94.35)	Reference	Reference
	Yes	695 (8.86)	4,388 (5.65)	1.62 (1.49–1.76)	1.24 (1.11–1.36)
	Current	29 (0.37)	154 (0.20)	1.95 (1.31–2.90)	1.33 (0.85–2.07)
	Recent	20 (0.25)	87 (0.11)	2.38 (1.40–3.87)	1.54 (0.89–2.68)
	Past	646 (8.23)	4,147 (5.34)	1.59 (1.46–1.74)	1.20 (1.11–1.35)
Any β-lactam	No	5,750 (73.30)	63,146 (81.32)	Reference	Reference
	Yes	2,094 (26.60)	14,508 (18.68)	1.59 (1.51–1.68)	1.05 (0.99–1.12)
	Current	89 (1.13)	511 (0.66)	1.91 (1.52–2.40)	1.15 (0.89–1.48)
	Recent	58 (0.73)	362 (0.47)	1.78 (1.34–2.35)	1.13 (0.83–1.55)
	Past	1,947 (24.80)	13,635 (17.56)	1.57 (1.49–1.66)	1.05 (0.98–1.12)
Optum ClinFormatics (Optum) database					
Any FQ	No	2,500 (81.72)	27,326 (90.39)	Reference	Reference
	Yes	559 (18.27)	2,904 (9.61)	2.13 (1.92–2.35)	1.22 (1.09–1.38)
	Current	13 (0.42)	72 (0.24)	1.94 (1.07–3.52)	0.93 (0.48–1.81)
	Recent	9 (0.29)	58 (0.19)	1.72 (0.85–3.47)	0.74 (0.33–1.63)
	Past	537 (17.55)	2,774 (9.18)	2.14 (1.93–2.37)	1.25 (1.11–1.49)
Ciprofloxacin	No	2,767 (90.45)	28,685 (94.89)	Reference	Reference
	Yes	292 (9.55)	1,545 (5.11)	1.96 (1.72–2.24)	1.21 (1.04–1.40)
	Current	8 (0.26)	37 (0.12)	2.21 (1.02–4.76)	0.88 (0.38–2.07)
	Recent	4 (0.13)	28 (0.09)	1.49 (0.52–4.25)	0.52 (0.16–1.64)
	Past	280 (9.15)	1,480 (4.89)	1.96 (1.71–2.24)	1.24 (1.06–1.45)
Any β-lactam	No	2,242 (73.29)	25,658 (84.88)	Reference	Reference
	Yes	817 (26.71)	4,572 (15.12)	2.06 (1.89–2.25)	1.08 (0.97–1.20)
	Current	29 (0.95)	144 (0.47)	2.35 (1.57–3.51)	1.35 (0.86–2.14)
	Recent	18 (0.58)	111 (0.36)	1.88 (1.14–3.10)	1.02 (0.58–1.78)
	Past	770 (25.17)	4,317 (14.28)	2.06 (1.88–2.25)	1.07 (0.90–1.19)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

3.2 Revised Case–Control Analysis

The cases and controls for the revised case–control analysis came from the same cohorts as in the above analysis and are described in Table 1. Though cases and controls were matched on sex, the proportion of males among cases and controls were similar but not identical because not all cases could be matched to ten controls. In both databases, cases were more likely than controls to have had cataract surgery, myopia, eye injury, diabetic retinopathy, proliferative diabetic retinopathy, had more medications dispensed (Table 1), and were more likely to be exposed to a fluoroquinolone (Table 3). Unlike the replication case–control analysis, in this analysis and the sensitivity analysis described below, the proportion of cases with diabetes was not substantially different from the proportion of controls with diabetes. Diabetes is associated with hospital admission and examination of the steps at which potential subjects were screened out indicated a substantial number of potential subjects were excluded from the revised case–control analysis and the sensitivity analysis due to hospital admission between cohort entry and index date. In the CCAE database, the adjusted ORs for any exposure or current exposure to any fluoroquinolone or ciprofloxacin ranged from 1.1 to 1.4 and were not statistically significant. In the Optum database, the OR for any exposure to any fluoroquinolone was 1.3 and was statistically significant. The adjusted ORs for current exposure to any fluoroquinolone and for current or any exposure to ciprofloxacin were not statistically significant, were not substantially above 1, and were not substantially

Table 3 Association of retinal detachment with fluoroquinolone exposure: revised case–control analysis

	Exposure	Cases [*N* (%)]	Controls [*N* (%)]	Crude OR (95 % CI)	Adjusted OR (95 % CI)
MarketScan Commercial Claims and Encounters (CCAE) database					
Any FQ	No	4,457 (88.26)	36,801 (91.97)	Reference	Reference
	Yes	593 (11.74)	3,211 (8.03)	1.53 (1.39–1.68)	1.04 (0.93–1.15)
	Current	27 (0.53)	96 (0.24)	2.29 (1.49–3.52)	1.40 (0.86–2.26)
	Recent	14 (0.28)	75 (0.19)	1.49 (0.84–2.65)	1.17 (0.62–2.18)
	Past	552 (10.93)	3,040 (7.60)	1.51 (1.37–1.66)	1.02 (0.91–1.14)
Ciprofloxacin	No	4,763 (94.32)	38,553 (96.35)	Reference	Reference
	Yes	287 (5.68)	1,459 (3.65)	1.61 (1.41–1.83)	1.12 (0.96–1.29)
	Current	13 (0.26)	50 (0.12)	2.04 (1.11–3.77)	1.15 (0.58–2.29)
	Recent	5 (0.10)	31 (0.08)	1.33 (0.51–3.44)	1.04 (0.38–2.86)
	Past	269 (5.32)	1,378 (3.44)	1.60 (1.39–1.83)	1.12 (0.96–1.30)
Any β-lactam	No	3,897 (77.17)	33,528 (83.79)	Reference	Reference
	Yes	1,153 (22.83)	6,484 (16.21)	1.55 (1.44–1.67)	1.03 (0.94–1.12)
	Current	50 (0.99)	222 (0.55)	1.98 (1.45–2.71)	1.20 (0.85–1.69)
	Recent	32 (0.63)	148 (0.36)	1.86 (1.26–2.74)	1.28 (0.84–1.97)
	Past	1,071 (21.21)	6,114 (15.28)	1.53 (1.42–1.64)	1.01 (0.93–1.11)
Optum ClinFormatics (Optum) database					
Any FQ	No	1,807 (86.13)	16,521 (93.13)	Reference	Reference
	Yes	291 (13.87)	1,219 (6.87)	2.23 (1.94–2.57)	1.30 (1.11–1.52)
	Current	2 (0.09)	32 (0.18)	0.58 (0.14–2.45)	0.37 (0.08–1.64)
	Recent	5 (0.24)	16 (0.09)	2.93 (1.07–8.04)	1.44 (0.46–4.49)
	Past	284 (13.53)	1,171 (6.60)	2.27 (1.97–2.61)	1.30 (1.12–1.55)
Ciprofloxacin	No	1,962 (93.52)	17,133 (96.58)	Reference	Reference
	Yes	136 (6.48)	607 (3.42)	1.90 (1.63–2.41)	1.16 (0.93–1.44)
	Current	0 (0.00)	20 (0.11)	No estimate	No estimate
	Recent	2 (0.09)	9 (0.05)	2.00 (0.43–9.31)	0.73 (0.13–4.01)
	Past	134 (6.39)	578 (3.26)	2.05 (1.68–2.50)	1.21 (0.97–1.51)
Any β-lactam	No	1,612 (76.84)	15,404 (86.83)	Reference	Reference
	Yes	486 (23.16)	2,336 (13.17)	2.03 (1.81–2.27)	1.11 (0.98–1.27)
	Current	19 (0.91)	68 (0.38)	2.73 (1.62–4.58)	1.48 (0.82–2.66)
	Recent	9 (0.43)	53 (0.29)	1.67 (0.81–3.40)	0.86 (0.40–1.86)
	Past	458 (21.83)	2,215 (12.49)	2.02 (1.80–2.26)	1.11 (0.97–1.27)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

higher than the adjusted ORs for β-lactam antibiotics (Table 3). Except for any exposure to levofloxacin in the Optum database, the adjusted ORs for any exposure or current exposure to levofloxacin and moxifloxacin were consistent with random variation (Table 4). There were no cases with current exposure to gatifloxacin, gemifloxacin, ofloxacin, or norfloxacin, and none of the adjusted ORs for any exposure to any of these fluoroquinolones was statistically significantly different from 1 (data not shown).

3.3 Sensitivity Analysis on the Revised Case–Control Analysis

In the sensitivity analysis on the revised case–control analysis there was no requirement for an ophthalmologist visit prior to the diagnosis of RD. The study cohorts consisted of 91,343,346 subjects in the CCAE database and 34,646,669 in the Optum database. The numbers of cases and controls and their characteristics are described in Table 1, and their exposure status is described in Tables 5, 6. Based on the controls, the most frequently used fluoroquinolones were ciprofloxacin, levofloxacin, and moxifloxacin. In both databases, cases were more likely than controls to have had cataract surgery, myopia, eye injury, diabetic retinopathy, proliferative diabetic retinopathy, and more medications dispensed (Table 1), and to be exposed to a fluoroquinolone (Tables 5 and 6). In the CCAE database, the adjusted OR for any exposure to any fluoroquinolone was 1.05 (1.04 in the revised case–control analysis), current exposure to any fluoroquinolone was 1.39

Table 4 Association of retinal detachment with fluoroquinolone exposure: revised case–control analysis

	Exposure	Cases [*N* (%)]	Controls [*N* (%)]	Crude OR (95 % CI)	Adjusted OR (95 % CI)
MarketScan Commercial Claims and Encounters (CCAE) database					
Levofloxacin	No	4,836 (95.76)	38,741 (96.82)	Reference	Reference
	Yes	214 (4.24)	1,271 (3.18)	1.30 (1.16–1.56)	0.95 (0.80–1.12)
	Current	10 (0.20)	37 (0.09)	2.16 (1.07–4.36)	1.56 (0.71–3.43)
	Recent	6 (0.12)	32 (0.08)	1.36 (0.56–3.27)	1.09 (0.41–2.89)
	Past	198 (3.92)	122 (3.00)	1.32 (1.13–1.54)	0.92 (0.78–1.10)
Moxifloxacin	No	4,971 (98.44)	39,610 (99.00)	Reference	Reference
	Yes	79 (1.56)	402 (1.00)	1.55 (1.22–1.99)	1.05 (0.80–1.38)
	Current	4 (0.08)	6 (0.01)	5.88 (1.65–20.93)	3.19 (0.74–13.83)
	Recent	3 (0.06)	9 (0.02)	2.88 (0.77–10.70)	2.27 (0.53–9.64)
	Past	72 (1.42)	387 (0.97)	1.47 (1.14–1.90)	0.99 (0.75–1.32)
Optum ClinFormatics (Optum) database					
Levofloxacin	No	1,977 (94.24)	17,283 (97.42)	Reference	Reference
	Yes	121 (5.76)	457 (2.58)	2.36 (1.92–2.91)	1.46 (1.16–1.85)
	Current	1 (0.04)	11 (0.06)	0.78 (0.10–6.09)	0.60 (0.07–4.93)
	Recent	2 (0.09)	4 (0.02)	4.50 (0.81–24.71)	2.48 (0.37–16.3)
	Past	118 (5.62)	442 (2.49)	2.39 (1.93–2.95)	1.48 (1.16–1.87)
Moxifloxacin	No	2,066 (98.47)	17,604 (99.23)	Reference	Reference
	Yes	32 (1.52)	136 (0.77)	2.06 (1.40–3.04)	1.16 (0.70–1.81)
	Current	1 (0.04)	1 (0.01)	9.48 (0.59–151.80)	10.46 (0.58–185.91)
	Recent	1 (0.05)	3 (0.02)	2.57 (0.26–24.79)	3.23 (0.22–45.83)
	Past	30 (1.43)	132 (0.74)	1.99 (1.33–2.98)	1.08 (0.68–1.72)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

(1.40 in the revised case–control analysis), any exposure to ciprofloxacin was 1.09 (1.12 in the revised case–control analysis), and current exposure to ciprofloxacin was 1.33 (1.15 in the revised case–control analysis) (see Tables 3 and 5). In the Optum database, the OR for any exposure to any fluoroquinolone was 1.12 (1.30 in the revised case–control analysis), current exposure to any fluoroquinolone was 1.19 (0.37 in the revised case–control analysis based on only two exposed cases), any exposure to ciprofloxacin was 1.15 (1.16 in the revised case–control analysis), and current exposure to ciprofloxacin was 1.68 (zero in the revised case–control analysis) (see Tables 3 and 6). As in the revised case–control analysis, the ORs for β-lactam antibiotics were close to 1.

The ORs for any exposure or current exposure to levofloxacin and for moxifloxacin were not statistically significant (Tables 5, 6), and nor were the ORs for gatifloxacin, gemifloxacin, norfloxacin, or ofloxacin, with substantially fewer exposed cases (data not shown).

3.4 SCCS Analyses

Consistent with the case–control studies, the SCCS analyses did not detect associations between RD and exposure to fluoroquinolones, ciprofloxacin, or levofloxacin in either the CCAE or Optum database. All rate ratios were between 0.65 and 1.17, and none was statistically significant, although the rate ratio associated with exposure to any fluoroquinolone in the CCAE database narrowly missed this criterion (rate ratio 1.13, 95 % CI 0.99–1.29) (Table 7).

3.5 Additional Analyses

To understand features of our replication case–control analysis that might explain the difference between our findings and those of the recent Canadian publication [1], we performed three additional analyses not included in the study protocol. First, in the replication analysis we had treated the number of distinct drug ingredients dispensed in the past year as a categorical variable, in quintiles. As a sensitivity analysis we treated it as a linear variable. Second, in the replication analysis we had excluded any RD that was a hospital discharge diagnosis or was diagnosed within the 10 days after hospitalization. As a sensitivity analysis we made no such exclusion and defined the exposure status during hospitalization as the exposure status at hospital admission. Neither of these sensitivity analyses yielded results appreciably different from those of the replication case–control analysis.

Table 5 Association of retinal detachment with fluoroquinolone exposure: sensitivity case–control analysis, MarketScan Commercial Claims and Encounters (CCAE) database

	Exposure	Cases [*N* (%)]	Controls [*N* (%)]	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Any FQ	No	17,212 (90.11)	146,740 (93.48)	Reference	Reference
	Yes	1,889 (9.89)	10,249 (6.52)	1.56 (1.48–1.65)	1.05 (0.99–1.12)
	Current	74 (0.39)	308 (0.19)	2.04 (1.00–2.64)	1.39 (1.00–1.88)
	Recent	46 (0.24)	255 (0.16)	1.55 (1.13–2.12)	0.91 (0.62–1.32)
	Past	1,769 (9.26)	9,686 (6.16)	1.55 (1.47–1.64)	1.05 (0.98–1.11)
Ciprofloxacin	No	18,179 (95.17)	152,046 (96.86)	Reference	Reference
	Yes	922 (4.83)	4,943 (3.14)	1.54 (1.43–1.66)	1.09 (1.01–1.10)
	Current	35 (0.18)	160 (0.10)	1.83 (1.27–2.65)	1.33 (0.87–2.04)
	Recent	26 (0.14)	116 (0.07)	1.89 (1.23–2.89)	1.23 (0.74–2.04)
	Past	861 (4.51)	4,667 (2.97)	1.52 (1.41–1.64)	1.08 (0.99–1.18)
Any β-lactam	No	15,113 (79.12)	132,872 (84.64)	Reference	Reference
	Yes	3,988 (20.88)	24,117 (15.36)	1.47 (1.42–1.53)	0.99 (0.94–1.03)
	Current	157 (0.82)	761 (0.48)	1.84 (1.55–2.19)	1.26 (1.03–1.53)
	Recent	106 (0.55)	656 (0.42)	1.43 (1.16–1.76)	0.93 (0.74–1.18)
	Past	3,725 (19.50)	22,700 (14.46)	1.46 (1.40–1.52)	0.98 (0.93–1.03)
Levofloxacin	No	18,420 (96.43)	153,187 (97.58)	Reference	Reference
	Yes	681 (3.56)	3,802 (2.42)	1.48 (1.36–1.61)	0.98 (0.89–1.08)
	Current	28 (0.14)	103 (0.06)	2.24 (1.47–3.41)	1.48 (0.90–2.41)
	Recent	15 (0.08)	101 (0.06)	1.25 (0.72–2.15)	0.66 (0.35–1.27)
	Past	638 (3.34)	3,598 (2.29)	1.47 (1.34–1.6)	0.97 (0.88–1.08)
Moxifloxacin	No	18,862 (98.75)	155,833 (99.27)	Reference	Reference
	Yes	239 (1.25)	1,156 (0.73)	1.71 (1.49–1.97)	1.18 (1.00–1.39)
	Current	9 (0.04)	33 (0.02)	2.22 (1.06–4.65)	1.31 (0.53–3.20)
	Recent	5 (0.03)	32 (0.02)	1.26 (0.48–3.25)	0.73 (0.20–2.14)
	Past	225 (1.18)	1,091 (0.69)	1.71 (1.40–1.98)	1.19 (1.01–1.41)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

Finally, because our populations were appreciably younger than the population in the previous study (mean age 55 and 52 years for the replication and sensitivity case–control analyses from the CCAE database, respectively; 58 and 54 years for the corresponding analyses from the Optum database, vs. 61 years in the Canadian study), we stratified the estimates from the replication and sensitivity case–control analyses by age to assess whether age may have contributed to the difference in findings. The age quintiles were based on the cases and age-matched controls in the main case–control analyses. In the CCAE database, the estimates for current exposure to any fluoroquinolone and for current exposure to ciprofloxacin from the sensitivity analysis showed a clear and substantial increase in the adjusted OR with age (Table 8). None of the other age-stratified estimates from either database did so, but the numbers of fluoroquinolone-exposed cases in the estimates from the Optum database were relatively small (Tables 8, 9).

4 Discussion

We attempted to replicate, in two large US databases, the findings of a Canadian study of British Columbia administrative claims that found a substantial increased risk of RD during current use of fluoroquinolones. In both US databases and across all analyses performed, we were unable to identify a risk of similar magnitude. All our point estimates for the adjusted ORs associated with any exposure or current exposure to fluoroquinolones and to ciprofloxacin were below 1.5, and many had confidence intervals whose lower end fell below 1 and whose upper end was below 2. In contrast to the Canadian study [1], the ORs associated with fluoroquinolones were not strikingly different from those associated with β-lactam antibiotics. The SCCS analyses, which adjust for confounders that are not well captured in most health services databases, did not show a statistically significant association, suggesting the modest association found in some of the case–control analyses

Table 6 Association of retinal detachment with fluoroquinolone exposure: sensitivity case–control analysis, Optum ClinFormatics (Optum) database

	Exposure	Cases [*N* (%)]	Controls [*N* (%)]	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Any FQ	No	6,105 (88.50)	55,433 (93.07)	Reference	Reference
	Yes	791 (11.40)	4,127 (6.93)	1.75 (1.62–1.90)	1.12 (1.02–1.23)
	Current	18 (0.26)	109 (0.18)	1.49 (0.90–2.46)	1.19 (0.68–2.06)
	Recent	16 (0.23)	86 (0.14)	1.71 (1.00–2.92)	0.99 (0.53–1.84)
	Past	757 (10.98)	3,932 (6.60)	1.76 (1.62–1.90)	1.12 (1.01–1.23)
Ciprofloxacin	No	6,510 (94.40)	57,586 (96.6)	Reference	Reference
	Yes	386 (5.59)	1,974 (3.31)	1.73 (1.55–1.94)	1.15 (1.01–1.31)
	Current	12 (0.17)	50 (0.08)	2.06 (1.09–3.88)	1.68 (0.80–3.43)
	Recent	6 (0.08)	44 (0.07)	1.20 (0.51–2.82)	0.73 (0.28–1.85)
	Past	368 (5.33)	1,880 (3.16)	1.73 (1.54–1.95)	1.15 (1.01–1.31)
Any β-lactam	No	5,440 (78.80)	50,983 (85.60)	Reference	Reference
	Yes	1,456 (21.10)	8,577 (14.40)	1.63 (1.53–1.73)	1.02 (0.95–1.10)
	Current	59 (0.85)	281 (0.47)	2.04 (1.53–2.71)	1.19 (0.85–1.65)
	Recent	40 (0.58)	219 (0.37)	1.75 (1.24–2.45)	1.09 (0.75–1.60)
	Past	1,357 (19.60)	8,077 (13.56)	1.61 (1.51–1.72)	1.01 (0.90–1.09)
Levofloxacin	No	6,594 (95.60)	57,899 (97.21)	Reference	Reference
	Yes	302 (4.30)	1,661 (2.79)	1.60 (1.41–1.82)	1.02 (0.89–1.18)
	Current	3 (0.04)	43 (0.07)	0.61 (0.19–1.98)	0.46 (0.13–1.58)
	Recent	4 (0.05)	32 (0.05)	1.12 (0.39–3.19)	0.86 (0.29–2.60)
	Past	295 (4.27)	1,586 (2.66)	1.64 (1.44–1.86)	1.04 (0.90–1.21)
Moxifloxacin	No	6,804 (98.60)	59,118 (99.26)	Reference	Reference
	Yes	92 (1.33)	442 (0.74)	1.81 (1.44–2.27)	1.17 (0.89–1.52)
	Current	3 (0.04)	14 (0.02)	1.82 (0.52–6.37)	1.92 (0.53–6.86)
	Recent	6 (0.08)	419 (0.70)	1.72 (1.36–2.19)	1.10 (0.84–1.46)
	Past	83 (1.20)	9 (0.01)	5.70 (2.05–16.3)	3.08 (0.78–12.08)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

Table 7 Self-controlled case series analysis

	CCAE database 19,191 cases [rate ratio (95 % CI)]	Optum database 6,896 cases [rate ratio (95 % CI)]
All FQs	1.13 (0.99–1.29)	0.85 (0.66–1.09)
Ciprofloxacin	1.17 (0.96–1.44)	1.00 (0.99–1.01)
Levofloxacin	1.13 (0.90–1.43)	0.65 (0.41–1.01)

CCAE MarketScan Commercial Claims and Encounters, *FQ* fluoroquinolone, *Optum* Optum ClinFormatics

may have been due to confounding. Thus, in contrast to the Canadian study [1], the present study suggests no substantial increase in the incidence of RD is associated with exposure to oral fluoroquinolones. The present study also identified no significant differences in the incidence of RD among the three most widely used fluoroquinolones: ciprofloxacin, levofloxacin, and moxifloxacin. The results of the Canadian study [1] raised concerns about the safety of fluoroquinolones [7] that are not supported by the results of the current study.

Patients in the present study were younger than those in the previous study [1] and a smaller proportion had prior cataract surgery. Both studies addressed age through matching and cataract surgery by adjustment, so these differences do not appear to explain the difference in their findings. Nonetheless, the possibility remained that the difference in findings might be due to an association of RD with fluoroquinolone exposure that was entirely or mainly confined to the older subjects and therefore was observed in the previous study but missed in the present study with its younger population. We therefore stratified our estimates by quintile of age and found a clear increase in the adjusted OR for current exposure to any fluoroquinolone or to ciprofloxacin with age in the sensitivity analysis on the CCAE database, but in none of the other age-stratified analyses. This suggests the possibility of an association of RD risk with current exposure to ciprofloxacin, or to any fluoroquinolone, in the elderly. However, the evidence for this from the present study is not conclusive. This finding was in the context of examining many hypotheses and reflected a subgroup analysis from a broader analysis that

Table 8 Adjusted odds ratio by quintile of age: MarketScan Commercial Claims and Encounters (CCAE) database

	Any exposure			Current exposure		
	Age group[a]	Exposed cases	Adjusted OR (95 % CI)	Age group[a]	Exposed cases	Adjusted OR (95 % CI)
Replication case–control study						
Any FQ						
	3–50	234	1.09 (0.9–1.32)	3–50	10	1.2 (0.51–2.85)
	51–55	244	1.3 (1.08–1.55)	51–55	12	1.79 (0.86–3.76)
	56–59	326	1.14 (0.98–1.32)	56–59	11	0.76 (0.39–1.49)
	60–62	307	1.23 (1.05–1.43)	60–62	19	1.77 (1.01–3.1)
	63–71	233	1.14 (0.96–1.35)	63–71	14	1.61 (0.83–3.1)
Ciprofloxacin						
	3–50	109	1.24 (0.96–1.6)	3–50	3	1.2 (0.34–4.17)
	51–55	125	1.4 (1.11–1.76)	51–55	6	1.81 (0.63–5.19)
	56–59	165	1.14 (0.94–1.38)	56–59	5	0.92 (0.34–2.53)
	60–62	169	1.36 (1.13–1.65)	60–62	8	1.71 (0.74–3.93)
	63–71	127	1.16 (0.94–1.44)	63–71	7	1.47 (0.58–3.74)
Any β-lactam						
	3–50	446	1.07 (0.92–1.24)	3–50	24	1.77 (1.00–3.13)
	51–56	354	0.98 (0.84–1.14)	51–56	12	0.88 (0.45–1.71)
	57–61	465	1.04 (0.91–1.19)	57–61	23	1.42 (0.86–2.35)
	62–65	448	1.10 (0.96–1.26)	62–65	15	0.83 (0.46–1.51)
	66–96	381	1.08 (0.93–1.25)	66–96	15	1.04 (0.57–1.91)
Sensitivity case–control study						
Any FQ						
	3–46	281	1.07 (0.91–1.26)	3–46	8	0.6 (0.19–1.84)
	47–53	369	1.08 (0.94–1.24)	47–53	9	0.68 (0.27–1.69)
	54–57	387	1.04 (0.91–1.19)	54–57	21	1.61 (0.92–2.81)
	58–60	359	1.06 (0.92–1.22)	58–60	15	1.85 (1–3.43)
	61–77	493	1.05 (0.93–1.19)	61–77	21	1.79 (1.02–3.12)
Ciprofloxacin						
	3–46	139	1.1 (0.89–1.36)	3–46	3	0.07 (0.01–0.97)
	47–53	178	1.18 (0.97–1.42)	47–53	3	0.4 (0.09–1.81)
	54–57	181	0.98 (0.81–1.18)	54–57	8	1.74 (0.77–3.91)
	58–60	172	1.12 (0.92–1.35)	58–60	7	1.87 (0.76–4.58)
	61–77	252	1.15 (0.98–1.35)	61–77	14	2.64 (1.27–5.49)
Any β-lactam						
	5–46	777	0.94 (0.84–1.04)	5–46	30	1.14 (0.73–1.78)
	47–53	757	0.93 (0.84–1.04)	47–53	37	2.05 (1.37–3.06)
	54–58	770	0.97 (0.87–1.07)	54–58	27	1.09 (0.68–1.72)
	59–62	716	1.10 (0.99–1.22)	59–62	36	1.61 (1.06–2.45)
	63–96	968	1.03 (0.94–1.13)	63–96	27	0.85 (0.54–1.32)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

[a] Range of each quartile of age is in years

did not show an association, and thus may have produced an association that cannot be replicated.

Both the Canadian study and the present study defined recent exposure as the 7 days after the end of current exposure. Comparison of the prevalence of current fluoroquinolone exposure to recent fluoroquinolone exposure among controls in the Canadian study suggested the mean duration of current exposure was approximately 21 days. A similar comparison in the replication case–control analysis in the present study suggested a mean duration of current exposure of 9–10 days. However, in the Canadian study the mean time from the start of fluoroquinolone exposure to the

Table 9 Adjusted odds ratio by quintile of age: Optum Clinformatics Database

	Any exposure			Current exposure		
	Age group[a]	Exposed cases	Adjusted OR (95 % CI)	Age group[a]	Exposed cases	Adjusted OR (95 % CI)
Replication case–control study						
Any FQ						
	3–50	94	1.56 (1.15–2.12)	3–50	4	1.85 (0.38–9.14)
	51–56	96	1.22 (0.92–1.62)	51–56	2	1.15 (0.24–5.47)
	57–61	130	1.3 (1.02–1.67)	57–61	2	0.56 (0.1–2.99)
	62–65	112	1.18 (0.91–1.54)	62–65	2	0.68 (0.15–3.12)
	66–96	127	1.04 (0.8–1.33)	66–96	3	0.77 (0.18–3.2)
Ciprofloxacin						
	3–50	55	1.94 (1.32–2.87)	3–50	2	2.21 (0.15–31.94)
	51–56	44	1.07 (0.74–1.54)	51–56	1	0.83 (0.1–7.28)
	57–61	67	1.29 (0.94–1.76)	57–61	2	1.24 (0.23–6.69)
	62–65	64	1.27 (0.92–1.75)	62–65	1	0.51 (0.06–4.21)
	66–96	62	0.87 (0.63–1.21)	66–96	2	0.69 (0.12–4.01)
Any β-lactam						
	3–50	151	0.99 (0.76–1.27)	3–50	5	1.54 (0.50–4.76)
	51–56	159	1.32 (1.04–1.68)	51–56	7	1.81 (0.69–4.70)
	57–61	175	1.04 (0.84–1.30)	57–61	6	1.59 (0.60–4.21)
	62–65	157	1.19 (0.94–1.51)	62–65	6	1.60 (0.58–4.39)
	66–96	175	0.97 (0.77–1.21)	66–96	5	0.64 (0.22–1.88)
Sensitivity case–control study						
Any FQ						
	5–46	123	1.11 (0.87–1.43)	5–46	3	1.45 (0.36–5.87)
	47–53	148	1.31 (1.05–1.63)	47–53	2	1.09 (0.24–4.88)
	54–58	164	1.09 (0.89–1.34)	54–58	7	2.26 (0.92–5.6)
	59–62	151	1.11 (0.9–1.38)	59–62	1	0.55 (0.07–4.23)
	63–96	205	1.06 (0.88–1.28)	63–96	5	0.73 (0.25–2.16)
Ciprofloxacin						
	5–46	58	1.19 (0.86–1.66)	5–46	2	1.41 (0.22–8.84)
	47–53	71	1.23 (0.91–1.66)	47–53	1	1.52 (0.18–12.55)
	54–58	78	1.11 (0.84–1.47)	54–58	3	2.25 (0.57–8.92)
	59–62	72	1.20 (0.89–1.61)	59–62	1	0.82 (0.1–6.69)
	63–96	107	1.10 (0.86–1.42)	63–96	5	1.93 (0.54–6.86)
Any β-lactam						
	5–46	270	0.90 (0.75–1.07)	5–46	17	1.44 (0.75–2.73)
	47–53	262	1.02 (0.85–1.22)	47–53	8	0.78 (0.31–1.96)
	54–58	312	1.00 (0.85–1.17)	54–58	11	1.03 (0.47–2.26)
	59–62	253	1.05 (0.88–1.25)	59–62	14	1.77 (0.93–3.36)
	63–96	359	1.22 (1.04–1.42)	63–96	19	0.84 (0.36–1.92)

FQ fluoroquinolone, *N* number of subjects, *OR* odds ratio

[a] Range of each quartile of age is in years

diagnosis of RD was 4.8 days, so the substantially shorter duration of use of fluoroquinolones in the present study does not seem likely to explain the difference in the findings of the two studies.

In addition to the usual limitations of any retrospective study, e.g., the possibility of unmeasured confounders, and questions about whether associations are causal, this study had the following specific limitations. It is unknown whether, or to what extent, the CCAE and Optum databases may overlap. To the extent that they do so, the analyses in the two databases would not be independent. To the extent that the dates of RDs or the start and end dates of exposure to the medication of interest are inaccurately recorded, their associations will also be inaccurately estimated. This

may happen if RDs are diagnosed late, or the date of dispensing or using antibiotics differs from the date of the bill, or the date of end of use of antibiotics differs from the calculated date. A possible explanation for the difference in findings between the prior Canadian study and our replication is differential data capture across different health systems, as the Canadian study was based on claims processing in British Columbia, where, for example, the prevalence of recent cataract surgery was substantially higher and the median number of medications dispensed was substantially larger than in the privately insured US populations we studied. The inability to adjust for possible confounders not captured in the database (e.g., education), limited ability to adjust for diagnoses that may be underreported (e.g. myopia), and adjustment in broad categories (e.g., diabetes present or absent) may leave appreciable confounding by these factors even in the adjusted estimates, especially in the case–control analyses. Confounding by many of these factors is better controlled in the SCCS analyses, in which each subject serves as his or her own comparator. Finally, the generalizability of the results is limited by the features of the study population that differ from the population at large and may be relevant to any observed association, e.g., the subjects in the present study were privately insured and were far more likely than the general population to be aged less than 65 years.

5 Conclusions

Though it examined two large databases using multiple analytic approaches, including one that mimicked the analysis used by the recent Canadian study, the present study does not confirm the recent Canadian study's finding of a strong relationship between RD and current exposure to fluoroquinolones. The present study found a modest association between RD and current or recent exposure to fluoroquinolones in the case–control analyses, an association that was statistically significant in some, but not all, of the case–control analyses, and a possible relationship between RD and current fluoroquinolone exposure among the older subjects. In the SCCS analyses, the analyses that may be the least subject to confounding because they compared each subject to his or her own experience, the present study did not find an association between fluoroquinolones and RD.

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Conflict of interest At the time of the study Daniel Fife, Vivienne Zhu, Erica Voss, and Patrick Ryan were full-time employees of Janssen Pharmaceutical Research and Development, LLC, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA, and Grace Levy-Clarke was a full-time employee of Vistakon, 7500 Centurion Parkway #100, Jacksonville, FL 32256, USA. Both Janssen Pharmaceutical Research and Development and Vistakon are units of Johnson & Johnson, which markets levofloxacin, a fluoroquinolone. All the authors had pension rights with Johnson & Johnson, and all except Vivienne Zhu held stock. Daniel Fife, Vivienne Zhu, Erica Voss, Grace Levy-Clarke, and Patrick Ryan have no other conflicts of interest that are directly relevant to the conduct of this study. The study was performed as part of the authors' regular work and no specific funding was received to conduct it.

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