ORIGINAL ARTICLE

Clinical implications of the association between fluoroquinolones and tendon rupture: The magnitude of the effect with and without corticosteroids

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Aims: To estimate the relative, absolute and attributable risk of non-traumatic tendon rupture, at various sites, associated with use of fluoroquinolones, with and without concomitant corticosteroids.

Methods: We conducted cohort and nested case-control studies among fluoroquinolone users in the United Kingdom Clinical Practice Research Datalink Gold. We estimated the excess risk (cohort analysis) and odds ratios (ORs) (case control) of tendon rupture by fluoroquinolone (current, recent and past use versus unexposed) and corticosteroid (current versus unexposed) use.

Results: Among 740 926 patients with a fluoroquinolone prescription, 3957 cases of tendon rupture were identified. The excess risk due to current fluoroquinolone use was low: any tendon rupture 3.73 (95% confidence interval, CI, 2.08–5.39) per 10 000 person-years (PY) and Achilles tendon rupture 2.91 (1.71–4.11) per 10 000 PY. The excess risk of any tendon rupture was much higher for current concomitant fluoroquinolone and corticosteroid use versus corticosteroids alone: 21.2 (11.3–31.2) per 10 000 PY. In the case-control, OR (95% CI) among current fluoroquinolone users versus unexposed patients was elevated: any tendon rupture 1.60 (1.22–2.09), Achilles tendon 2.71 (1.76–4.17) and bicep tendon 1.53 (0.85–2.73). The risk of any tendon rupture was higher among women (OR 2.27 [1.54–3.34]), patients aged 60+ (OR 2.42 [1.74–3.37]), and concomitant corticosteroid use (OR 6.64 [3.99–11.1]).

Conclusions: Fluoroquinolones increase the risk of Achilles tendon rupture and, to a lesser extent, bicep tendon rupture, but the attributable risk is low. The risk is materially increased with concomitant use of corticosteroids.

KEYWORDS

adverse drug events, antibiotics, corticosteroids, fluoroquinolones, pharmacoepidemiology, tendon rupture

1 | INTRODUCTION

Fluoroquinolones are a class of broad-spectrum commonly used antibiotics. Cases of tendinopathy and tendon injury were reported among fluoroquinolone users soon after their introduction to the

market, and in 2008 the US Food and Drug Administration (FDA) added a “black box” warning label to fluoroquinolone medications.^{1,2}

Recently, the European Medicines Agency (EMA) has recommended restricting the use of fluoroquinolones due to rare side-effects including those involving tendons.³ Published studies have reported risks of tendon rupture among fluoroquinolone users ranging from near null to around eight-fold.^{4–12} However, many of these studies

PI statement: This study did not involve interventions or human subjects/patients.

were limited by small numbers of exposed cases or were based on case reports and did not quantify risk, and nearly all were based on data collected prior to 2007. Additionally, most studies were limited to Achilles tendon rupture and did not report risk of rupture at other sites.

Robust estimates of the absolute rate and excess risk of tendon rupture associated with use of fluoroquinolones are important for informed prescribing and clinical decision-making. To date, only two studies have reported incidence rates (IRs), both of which were based on very small numbers of exposed cases.^{6,10} Further, there is evidence that concomitant use of corticosteroids and fluoroquinolones may lead to an even greater increase in the risk of tendon rupture,^{5-9,11} though the magnitude of the effect is not well understood. Corticosteroid use increases the risk of infections, the indication for fluoroquinolone use, and is independently associated with tendon disorders; thus, the risk of tendon rupture in users of the two drugs combined could be high. Published studies of the risk of concomitant fluoroquinolone and corticosteroid use have reported varied results due to different case and exposure definitions, and most were also limited by small numbers of exposed patients.⁵⁻⁹

We conducted a cohort study to estimate the absolute rate and excess risk of non-traumatic tendon rupture at multiple sites associated with use of fluoroquinolones to provide clinicians with an estimate of the clinical magnitude of the effect of fluoroquinolones on tendon rupture. We also conducted a nested case-control analysis, carefully controlling for multiple confounders, to evaluate concomitant fluoroquinolone and corticosteroid in relation to the risk of non-traumatic tendon rupture.

2 | METHODS

2.1 | Cohort study

The study population comprised all patients who were registered in the United Kingdom Clinical Practice Research Datalink (CPRD) Gold between 1990 and October 2015, who received a prescription for fluoroquinolone (ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, moxifloxacin, nalidixic acid or temafloxacin) after the age of 10 years, and who had ≥ 2 years of follow-up between the registration date and the end of their record or age 80. The cohort entry date was defined as 2 years after registration date or age 10 (whichever came later). Patients were excluded if they had a diagnosis for a congenital tendon anomaly at any time in their record, or if they had one or more of the following prior to cohort entry: tendon rupture, alcohol abuse, drug abuse, cancer, HIV, tendon operation, organ transplant or end-stage renal disease.

Patients were followed from cohort entry date through the first tendon rupture (traumatic or non-traumatic), age 80, diagnosis of alcohol abuse, drug abuse, cancer, HIV, organ transplant, end-stage renal disease, a tendon operation (not within 30 days prior to a tendon rupture), or the end of their record (transfer out date, death or end of data collection). We accumulated person-days of exposure to

What is already known about this subject

- Fluoroquinolones are associated with increased Achilles tendon rupture, but risk at other sites is unclear.
- Number of excess cases of tendon rupture due to fluoroquinolones is unknown.
- The effect of concomitant fluoroquinolone and corticosteroid use on the rate of tendon rupture is unknown.

What this study adds

- Excess risk of tendon rupture due to fluoroquinolones is low: four excess cases per 10 000 person-years (PY) for any tendon; three excess cases per 10 000 PY for Achilles tendon.
- Risk is higher with concomitant corticosteroids: 21 excess cases per 10 000 PY.
- Risk is higher among females, people age 60+ and chronic fluoroquinolone users.

a fluoroquinolone as: current use (period of filled use +30 days), recent use (days 31–60 after the end of filled use), past use (days 61–180 after end of filled use), and unexposed time (all days before current use or after past use). If the patient received a subsequent fluoroquinolone prescription, they again became currently exposed and we restarted accumulation of exposed person-days as described above. Person-time was stratified by age, sex and current exposure to a systemic corticosteroid (the 30 days following a systemic corticosteroid prescription).

Cases were patients with a diagnosis of tendon rupture identified using Read codes, and categorized by site as Achilles, bicep, supraspinatus and other/unspecified. Patients with traumatic tendon ruptures were excluded from the case population and were identified by either a Read code for tendon rupture with an open wound or a code designating a major trauma (e.g. car accident) within 90 days before the tendon rupture diagnosis. We identified a set of Read codes present in the 2 weeks before or after the tendon rupture that provided supporting evidence that the tendon rupture diagnosis was valid: tendon operations, fitting of plaster cast, visit to fracture clinic, orthopaedic clinic or physiotherapist.

2.2 | Nested case control analysis

We conducted a nested case-control analysis to evaluate the effect of concomitant fluoroquinolone and corticosteroid use in non-traumatic

tendon rupture cases compared to matched controls without tendon rupture. We selected up to four controls for each case using risk set sampling and matched on index date (same index date as their matched case), sex, general practice, birth year (± 2 years), year of CPRD registration (± 2 years, unless both case and control had ≥ 10 years' data prior to index date). Controls were subject to the same exclusion criteria as cases. Cases without matched controls were excluded from the case-control analysis.

We assessed fluoroquinolone use at the index date categorized by time between the last fluoroquinolone prescription and the index date as current, recent, past or unexposed as described above. Corticosteroid use was categorized in two ways: any systemic corticosteroid within 6 months before the index date, as well as the number of corticosteroid prescriptions within the year before index date. We evaluated the following covariates as potential confounders: body mass index or obesity, smoking, diabetes mellitus, osteoarthritis, gout, chronic kidney disease and autoimmune diseases.

2.3 | Statistical analyses

2.3.1 | Cohort analysis

We estimated IRs and incidence rate differences (IRDs, i.e. excess risk) with 95% confidence intervals (CIs) for all non-traumatic tendon ruptures, overall and by rupture site, for current, recent and past fluoroquinolone users compared with unexposed. We also estimated stratified IRs and IRDs by age, sex and corticosteroid use. Using Poisson regression, we estimated incidence rate ratios (IRRs) and 95% CIs for all non-traumatic tendon ruptures and separately by site for current, recent and past fluoroquinolone use compared with unexposed for all patients, overall and stratified by age, sex and corticosteroid use.

2.3.2 | Nested case-control analysis

We estimated crude and adjusted (adj) ORs and 95% CI for non-traumatic tendon rupture (overall and by site) by timing of fluoroquinolone use compared to unexposed using conditional logistic regression. We also estimated ORs and 95% CIs, stratified by age, sex, calendar time and corticosteroid use. Finally, we conducted sensitivity analyses to assess the impact of potential case and exposure misclassification.

2.4 | Ethics review

This study is based in part on data from the CPRD obtained under license from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The data is provided by patients and collected by the NHS as part of their care and support. This study was approved by the Independent Scientific Advisory Committee (ISAC) for the MHRA database research (protocol no: 17_102R), and the protocol was made available to the journal reviewers upon request. The

interpretation and conclusions contained in this study are those of the authors alone.

3 | RESULTS

3.1 | Cohort analysis

The 740 926 fluoroquinolone users who met our study criteria contributed 114 656 person-years (PY) of current exposed time, 77 689 PY of recent exposed time, 273 959 PY of past exposed time, and 8 370 259 PY of unexposed person-time. We identified 3957 cases of non-traumatic tendon rupture. The most common rupture sites were Achilles (31.9%) and bicep tendons (22.0%) (Table A1).

The IR of any non-traumatic tendon rupture among current fluoroquinolone users was 8.11 (95% CI 6.59–9.89) per 10 000 PY, with an excess risk of 3.73 (95% CI 2.08–5.39) per 10 000 PY compared to unexposed patients. This equates to around four excess cases per 100 000 fluoroquinolone prescriptions. However, among patients with current use of both fluoroquinolones and corticosteroids, the IR of any non-traumatic tendon rupture was 30.0 (95% CI 21.6–41.5) per 10 000 PY, with an excess risk of 21.2 (95% CI 11.3–31.2) per 10 000 PY compared with corticosteroids alone (Table 1).

When we calculated the IRs by rupture site (Table 2), the IR of Achilles tendon rupture among current fluoroquinolone users was 4.27 (95% CI 3.20–5.60) with an excess risk of 2.91 (95% CI 1.71–4.11), or around three excess cases per 100 000 prescriptions. The excess risk due to fluoroquinolones on bicep tendon rupture was not significantly different from zero.

3.2 | Nested case control analysis

We matched 3802 cases of non-traumatic tendon rupture to 14 002 controls. Characteristics of cases and controls at the index date are provided in Table 3; characteristics of exposed and unexposed controls are provided in Appendix Table A2. Cases were more likely than controls to have arthritis, particularly rheumatoid arthritis, less likely to be current smokers, and more likely to be currently exposed to corticosteroids before the index date. Exposed controls were more likely to be older and to have arthritis, diabetes, chronic kidney disease, asthma, chronic obstructive pulmonary disease (COPD) or other autoimmune disorders, and more likely to be currently exposed to corticosteroids before the index date compared to unexposed controls.

Patients with current exposure to fluoroquinolones had a higher risk of non-traumatic tendon rupture at any site compared to unexposed patients (crude OR 1.84; 95% CI 1.42–2.40) (Table 4). The risk was similar for bicep tendon rupture (crude OR 1.77; 95% CI 1.01–3.13) and higher for Achilles tendon rupture (crude OR 3.26; 95% CI 2.13–4.97). The risk of rupture of other tendons was not materially different from the null (data not shown). These risks were attenuated after adjusting for current corticosteroid exposure (use in the previous

TABLE 1 Cohort study: Incidence rates (IR), incidence rate differences (IRD) and incidence rate ratios (IRR) for tendon rupture among users of fluoroquinolones

Fluoroquinolone use	Tendon ruptures	Person-time	IR per 10 000 PY (95%CI)	IRD per 10 000 PY (95% CI)	IRR (95% CI)
All patients					
Unexposed	3664	8370 259	4.38 (4.24, 4.52)	0.0 (Reference)	1.0 (Reference)
Current	93	114 656	8.11 (6.59, 9.89)	3.73 (2.08, 5.39)	1.85 (1.50, 2.26)
Recent	51	77 689	6.56 (4.94, 8.56)	2.19 (0.38, 3.99)	1.50 (1.12, 1.95)
Past	149	273 959	5.44 (4.62, 6.37)	1.06 (0.18, 1.95)	1.24 (1.05, 1.46)
Male					
Unexposed	2383	3731 454	6.39 (6.13, 6.65)	0.0 (Reference)	1.0 (Reference)
Current	46	49 762	9.24 (6.85, 12.2)	2.86 (0.17, 5.54)	1.45 (1.07, 1.91)
Recent	26	32 233	8.07 (5.39, 11.6)	1.68 (−1.43, 4.79)	1.26 (0.84, 1.82)
Past	87	114 431	7.60 (6.13, 9.33)	1.22 (−0.40, 2.83)	1.19 (0.95, 1.46)
Female					
Unexposed	1281	4638 805	2.76 (2.61, 2.92)	0.0 (Reference)	1.0 (Reference)
Current	47	64 894	7.24 (5.39, 9.54)	4.48 (2.40, 6.56)	2.62 (1.93, 3.47)
Recent	25	45 456	5.50 (3.65, 7.99)	2.74 (0.58, 4.90)	1.99 (1.31, 2.89)
Past	62	159 528	3.89 (3.01, 4.95)	1.12 (0.15, 2.10)	1.41 (1.08, 1.80)
Age <40					
Unexposed	444	2458 815	1.81 (1.64, 1.98)	0.0 (Reference)	1.0 (Reference)
Current	NR	27 663	0.72 (0.14, 2.32)	^c	^c
Recent	6	19 817	3.03 (1.26, 6.24)	1.22 (−1.21, 3.65)	1.68 (0.66, 3.42)
Past	11	73 125	1.50 (0.80, 2.60)	−0.30 (−1.21, 0.60)	0.83 (0.43, 1.44)
Age 40–60					
Unexposed	1371	3101 089	4.42 (4.19, 4.66)	0.0 (Reference)	1.0 (Reference)
Current	26	39 184	6.64 (4.44, 9.57)	2.21 (−0.35, 4.78)	1.50 (0.99, 2.16)
Recent	12	26 672	4.50 (2.46, 7.62)	0.08 (−2.48, 2.63)	1.02 (0.54, 1.71)
Past	47	95 442	4.92 (3.66, 6.49)	0.50 (−0.92, 1.93)	1.11 (0.82, 1.47)
Age 60+					
Unexposed	1849	2810 355	6.58 (6.28, 6.88)	0.0 (Reference)	1.0 (Reference)
Current	65	47 809	13.60 (10.6, 17.2)	7.02 (3.70, 10.3)	2.07 (1.60, 2.62)
Recent	33	31 200	10.58 (7.41, 14.7)	4.00 (0.38, 7.62)	1.61 (1.12, 2.23)
Past	91	105 392	8.63 (6.99, 10.6)	2.06 (0.26, 3.85)	1.31 (1.06, 1.61)
Corticosteroid^a					
Unexposed	294	323 848	9.08 (8.08, 10.2)	0.0 (Reference)	1.0 (Reference)
Current	36	11 876	30.3 (21.6, 41.5)	21.2 (11.3, 31.2)	3.34 (2.32, 4.65)
Recent	9	4 928	18.3 (9.02, 33.3)	9.18 (−2.79, 21.2)	2.01 (0.96, 3.67)
Past	21	15 630	13.4 (8.57, 20.2)	4.36 (−1.48, 10.2)	1.48 (0.92, 2.24)
No corticosteroid^b					
Unexposed	3370	8046 411	4.19 (4.05, 4.33)	0.0 (Reference)	1.0 (Reference)
Current	57	102 780	5.55 (4.24, 7.13)	1.36 (−0.09, 2.80)	1.32 (1.01, 1.70)
Recent	42	72 761	5.77 (4.22, 7.72)	1.58 (−0.17, 3.34)	1.38 (1.00, 1.84)
Past	128	258 329	4.95 (4.15, 5.87)	0.77 (−0.10, 1.64)	1.18 (0.99, 1.40)

^aFluoroquinolone use among corticosteroid users.^bFluoroquinolone use among non-users of corticosteroids.^cCell size too small to estimate effect measure.

CI, confidence interval; NR, not reportable due to small cell size.

TABLE 2 Cohort study: Incidence rates (IR), incidence rate differences (IRD) and incidence rate ratios (IRR) for non-traumatic tendon rupture among **current** users of fluoroquinolones, by tendon rupture site

Fluoroquinolone use ^a	Tendon ruptures	Person-time	IR per 10 000 PY (95% CI)	IRD per 10 000 PY (95% CI)	IRR (95% CI)
All sites					
Unexposed	3664	8370 259	4.38 (4.24, 4.52)	0.0 (Reference)	1.0 (Reference)
Current	93	114 656	8.11 (6.59, 9.89)	3.73 (2.08, 5.39)	1.85 (1.50, 2.26)
Achilles					
Unexposed	1143	8370 259	1.37 (1.29, 1.45)	0.0 (Reference)	1.0 (Reference)
Current	49	114 656	4.27 (3.20, 5.60)	2.91 (1.71, 4.11)	3.13 (2.32, 4.12)
Bicep					
Unexposed	821	8370 259	0.98 (0.92, 1.05)	0.0 (Reference)	1.0 (Reference)
Current	18	114 656	1.57 (0.96, 2.43)	0.59 (−0.14, 1.32)	1.60 (0.97, 2.47)
Supraspinatus					
Unexposed	403	8370 259	0.48 (0.44, 0.53)	0.0 (Reference)	1.0 (Reference)
Current	8	114 656	0.70 (0.33, 1.32)	0.22 (−0.27, 0.70)	1.45 (0.66, 2.72)
Other^b/Unspecified					
Unexposed	1297	8370 259	1.55 (1.47, 1.64)	0.0 (Reference)	1.0 (Reference)
Current	18	114 656	1.57 (0.96, 2.43)	0.02 (−0.71, 0.75)	1.01 (0.61, 1.56)

^aRates of tendon rupture during recent or past fluoroquinolone exposure not shown.

^bRotator cuff, other shoulder, other upper arm, other ankle, foot, knee, upper leg, hand, wrist and forearm.

CI, confidence interval.

6 months) (adj ORs 1.60 [95% CI 1.22–2.09] for any tendon rupture, 2.71 [95% CI 1.76–4.17] for Achilles tendon rupture, and 1.53 [95% CI 0.85–2.73] for bicep tendon rupture). No other potential confounders materially changed the effect estimates.

Among current fluoroquinolone users, the risk of any tendon rupture was higher among patients who had received two or more fluoroquinolone prescriptions in the year prior to the index date (adj OR 2.15; 95% CI 1.43–3.22) and among patients with a cumulative dose >10 000 mg in the year before the index date, (adj OR 2.07; 95% CI 1.35–3.17), compared with unexposed patients (Table 4). There was no material increase of risk among patients with recent or past exposure to fluoroquinolones for tendon rupture at any site. The majority (86%) of fluoroquinolone prescriptions were ciprofloxacin; thus, we were unable to assess differences in effect according to specific fluoroquinolone received.

The risk of non-traumatic tendon rupture with current use of fluoroquinolones was higher among women than men, among patients over age 60 compared to younger patients, and in calendar years 1990–1999 compared to later years (Table 5).

To further evaluate the additional effect of concomitant corticosteroid use on this association, we conducted analyses categorizing fluoroquinolone exposure by concurrent corticosteroid use (Table 6). Among patients currently exposed to both fluoroquinolone and corticosteroids, the OR of any tendon rupture was 6.64 (95% CI 3.99–11.1) compared to patients who were not exposed to either drug. This effect was higher than the increased risk among patients with current fluoroquinolone use alone or current corticosteroid use alone (OR 1.30; 95% CI 0.93–1.81 and OR 2.54; 95% CI 2.24–2.88, respectively).

The risk of tendon rupture was also higher among those with current fluoroquinolone use and repeated use of corticosteroids (OR 9.03; 95% CI 4.71–17.28) (data not shown). The risk of Achilles tendon rupture was 10.98 (95% CI 4.80–25.0) among patients exposed to both fluoroquinolones and corticosteroids compared to patients unexposed to both drugs (Table 6).

The results did not materially change when we conducted several sensitivity analyses to assess potential case and exposure misclassification: We (i) restricted the analysis to cases with supporting codes that provided evidence that the rupture was confirmed, (ii) removed cases and controls with hospitalization in the 30 days before the index date which could have resulted in misclassified exposure, (iii) restricted the analysis to cases with ≥4 years of registration before the index date to minimize the inclusion of prevalent cases, and (iv) moved the index date to an earlier tendonitis diagnosis date when tendonitis closely preceded the tendon rupture.

4 | DISCUSSION

In this cohort study of 740 926 users of a fluoroquinolone antibiotic in the UK who filled nearly 1.2 million prescriptions for fluoroquinolones, there were 3957 cases of non-traumatic tendon rupture among whom 93 were currently exposed to a fluoroquinolone. The risk of rupture attributable to fluoroquinolones was low: less than four excess cases of any tendon rupture and three excess cases of Achilles tendon rupture for every 10 000 PY of fluoroquinolone use. However, the absolute risk of tendon rupture was much

TABLE 3 Nested case-control: Patient characteristics among cases and controls at index date

Characteristic	Cases <i>n</i> = 3802 (%)	Controls <i>n</i> = 14 002 (%)	Univariable OR (95% CI)
Sex: Male	2438 (64.1)	8916 (63.7)	a
Female	1364 (35.9)	5086 (36.3)	
Age: <40	444 (11.7)	1599 (11.4)	a
40–59	1403 (37.3)	5191 (37.1)	
60+	1955 (51.4)	7212 (51.5)	
Index year: 1990–1994	206 (5.4)	784 (5.6)	a
1995–1999	499 (13.1)	1913 (13.7)	
2000–2004	855 (22.5)	3201 (22.9)	
2005–2009	1103 (29.0)	4028 (28.9)	
2010–2015	1139 (30.0)	4076 (29.1)	
Length of record before index date:			a
2 years	191 (5.0)	586 (4.2)	
3–5 years	587 (15.4)	2035 (14.5)	
6–10 years	1046 (27.5)	3765 (26.9)	
11–15 years	913 (24.0)	3470 (24.8)	
16+ years	1065 (28.0)	4146 (29.6)	
Smoking: Current	598 (15.7)	2599 (18.6)	0.79 (0.71, 0.88)
Past	1206 (31.7)	4145 (29.6)	1.01 (0.93, 1.10)
Never	1763 (46.4)	6163 (44.0)	1.0 (Reference)
Unknown	224 (5.9)	1095 (7.8)	0.68 (0.57, 0.80)
BMI: <18.5 kg/m ²	35 (1.0)	210 (1.5)	0.70 (0.48, 1.00)
18.5–25 kg/m ²	980 (25.8)	4107 (29.3)	1.0 (Reference)
25–29 kg/m ²	1465 (38.5)	5145 (36.7)	1.19 (1.08, 1.31)
30+ kg/m ²	1098 (28.9)	3632 (25.9)	1.27 (1.15, 1.41)
Unknown	224 (5.9)	908 (6.5)	1.01 (0.85, 1.20)
History of			
Arthritis	1212 (31.9)	3370 (24.1)	1.65 (1.51, 1.81)
Gout	238 (6.2)	729 (5.2)	1.21 (1.03, 1.41)
Diabetes	368 (9.7)	1371 (9.8)	0.97 (0.86, 1.10)
Obesity	334 (8.8)	1041 (7.4)	1.21 (1.06, 1.39)
Chronic kidney disease	208 (5.5)	719 (5.1)	1.06 (0.89, 1.27)
Acute kidney injury	9 (0.2)	37 (0.3)	0.94 (0.45, 1.96)
Asthma	823 (21.6)	2701 (19.3)	1.18 (1.08, 1.29)
COPD	269 (7.1)	862 (6.2)	1.18 (1.02, 1.37)
Rheumatoid arthritis	191 (5.0)	349 (2.5)	2.22 (1.84, 2.67)
Psoriatic arthritis	21 (0.6)	62 (0.4)	1.23 (0.74, 2.03)
Other autoimmune disorders	330 (8.7)	1070 (7.6)	1.16 (1.01, 1.32)
Prescriptions (Rx) before index date			
Thyroxine in prior 6 months	200 (5.3)	773 (5.5)	0.97 (0.82, 1.14)
Corticosteroids in prior 6 months	556 (14.6)	933 (6.7)	2.52 (2.24, 2.83)
# Corticosteroid Rx in prior year			
0	3079 (81.0)	12 637 (90.3)	1.0 (Reference)
1	268 (7.0)	615 (4.4)	1.90 (1.63, 2.21)

(Continues)

TABLE 3 (Continued)

Characteristic	Cases <i>n</i> = 3802 (%)	Controls <i>n</i> = 14 002 (%)	Univariable OR (95% CI)
2	116 (3.0)	224 (1.6)	2.27 (1.80, 2.86)
3+	339 (8.9)	526 (3.8)	2.82 (2.43, 3.27)

^aMatching criteria.

CI, confidence interval; Rx, prescriptions.

TABLE 4 Nested case-control: Odds of non-traumatic tendon rupture by timing of fluoroquinolone exposure

Fluoroquinolone exposure	Cases <i>n</i> (%)	Controls <i>n</i> (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Any tendon rupture	<i>n</i> = 3802	<i>n</i> = 14002		
Unexposed	3533 (92.9)	13 235 (94.5)	1.0 (Reference)	1.0 (Reference)
Current	85 (2.2)	178 (1.3)	1.84 (1.42, 2.40)	1.60 (1.22, 2.09)
<i>Number of Rx^b</i>				
1 Rx	45 (1.2)	114 (0.8)	1.53 (1.08, 2.17)	1.29 (0.90, 1.84)
2+ Rx	40 (1.1)	64 (0.5)	2.38 (1.60, 3.55)	2.15 (1.43, 3.22)
<i>Cumulative dose^b</i>				
< 10 000 mg	50 (1.3)	119 (0.8)	1.62 (1.16, 2.27)	1.37 (0.97, 1.93)
≥ 10 000 mg	35 (0.9)	59 (0.4)	2.28 (1.50, 3.47)	2.07 (1.35, 3.17)
Recent	47 (1.2)	134 (1.0)	1.31 (0.94, 1.85)	1.11 (0.79, 1.57)
Past	137 (3.6)	455 (3.2)	1.11 (0.91, 1.36)	0.96 (0.79, 1.18)
Achilles tendon rupture only	<i>n</i> = 1207	<i>n</i> = 4453		
Unexposed	1103 (91.4)	4202 (94.4)	1.0 (Reference)	1.0 (Reference)
Current	41 (3.4)	49 (1.1)	3.26 (2.13, 4.97)	2.71 (1.76, 4.17)
Recent	18 (1.5)	41 (0.9)	1.60 (0.90, 2.83)	1.42 (0.79, 2.53)
Past	45 (3.7)	161 (3.6)	1.09 (0.78, 1.54)	1.00 (0.71, 1.41)
Bicep tendon rupture only	<i>n</i> = 833	<i>n</i> = 3060		
Unexposed	789 (94.7)	2871 (93.9)	1.0 (Reference)	1.0 (Reference)
Current	18 (2.2)	38 (1.2)	1.77 (1.01, 3.13)	1.53 (0.85, 2.73)
Recent	6 (0.7)	31 (1.0)	0.75 (0.31, 1.81)	0.56 (0.22, 1.39)
Past	20 (2.4)	120 (3.9)	0.61 (0.37, 0.98)	0.49 (0.30, 0.80)

^aAdjusted for corticosteroid use in 6 months before index date.^bNumber of prescriptions or cumulative dose in year before index date, among current users.

CI, confidence interval; Rx, prescriptions.

higher among patients with concomitant fluoroquinolone and corticosteroid use: 21 excess cases of tendon rupture per 10 000 PY were due to fluoroquinolone use beyond the risk associated with corticosteroids alone.

The relative risks of non-traumatic tendon rupture among patients with current fluoroquinolone exposure were consistently elevated in both the cohort (IRR 1.85) and case control analyses (OR 1.84), although in the case-control analysis we were able to further adjust for concomitant corticosteroid use (adj OR 1.60).

The OR for tendon rupture in current users of fluoroquinolones was highest for Achilles tendon rupture, but was also elevated for bicep tendon rupture, and only minimally elevated for ruptures at

other sites. We found effect modification by age and sex: the risk of tendon rupture was highest in females and people over age 60. Most notably, the risk of tendon rupture was highest in users of both fluoroquinolones and corticosteroids: Compared to patients not exposed to either drug, the risk of Achilles tendon rupture for concomitant users was increased nearly 11-fold, whereas the risk was around two-fold for current users of fluoroquinolones without corticosteroids.

It is also notable that the increased risk of non-traumatic tendon rupture was concentrated in current fluoroquinolone users who were prescribed more than one prescription or more than 10 000 mg cumulative dose in the year prior to the index date. Many of these were

TABLE 5 Nested case-control: Odds of non-traumatic tendon rupture by timing of fluoroquinolone exposure, stratified by sex, age, and index year

	Cases, n (%)	Controls, n (%)	OR (95% CI)
Sex			
Female	n = 1364	n = 5086	
Unexposed	1240 (90.9)	4798 (94.3)	1.0 (Reference)
Current	42 (3.1)	74 (1.5)	2.27 (1.54, 3.34)
Recent + Past	82 (6.0)	214 (4.2)	1.49 (1.14, 1.95)
Male	n = 2438	n = 8916	
Unexposed	2293 (94.1)	8437 (94.6)	1.0 (Reference)
Current	43 (1.8)	104 (1.2)	1.57 (1.09, 2.24)
Recent + Past	102 (4.2)	375 (4.2)	0.98 (0.78, 1.23)
Age			
Age <60	n = 1847	n = 6790	
Unexposed	1750 (94.7)	6464 (95.2)	1.0 (Reference)
Current	26 (1.4)	84 (1.2)	1.19 (0.76, 1.86)
Recent + Past	71 (3.8)	242 (3.6)	1.06 (0.80, 1.40)
Age 60+	n = 1955	n = 7212	
Unexposed	1783 (91.2)	6771 (93.9)	1.0 (Reference)
Current	59 (3.0)	94 (1.3)	2.42 (1.74, 3.37)
Recent + Past	113 (5.8)	347 (4.8)	1.22 (0.98, 1.53)
Calendar year			
1990–1999	n = 705	n = 2697	
Unexposed	657 (93.2)	2597 (96.3)	1.0 (Reference)
Current	16 (2.3)	29 (1.1)	2.33 (1.24, 4.37)
Recent + Past	32 (4.5)	71 (2.6)	1.80 (1.17, 2.79)
2000–2009	n = 1958	n = 7229	
Unexposed	1796 (91.7)	6767 (93.6)	1.0 (Reference)
Current	50 (2.6)	110 (1.5)	1.76 (1.25, 2.47)
Recent + Past	112 (5.7)	352 (4.9)	1.22 (0.97, 1.52)
2010–2015	n = 1139	n = 4076	
Unexposed	1080 (94.8)	3871 (95.0)	1.0 (Reference)
Current	19 (1.7)	39 (1.0)	1.78 (1.03, 3.10)
Recent + Past	40 (3.5)	166 (4.1)	0.80 (0.56, 1.15)

CI, confidence interval.

chronic fluoroquinolone users treated for conditions such as recurrent urinary tract infections.

Systematic reviews^{13,14} and recent literature on tendon rupture associated with fluoroquinolone use include nine studies: six case-control, one case-crossover, and two cohort.^{4–12} However, four of these studies were limited by small numbers of exposed cases (between 0 and 14).^{4–6,10} Six studies estimated the relative risk of Achilles tendon rupture among current fluoroquinolone users to be between null and 4.3.^{5,6,9–12} All studies that evaluated the combined effect of fluoroquinolones and corticosteroids, including an earlier study in the CPRD, found that the risk was consistently higher among

users of both drugs with effect sizes ranging from around 4 to over 40, with the highest risk in people age 60 and over; however, most of these estimates were based on small samples.^{6–9,11} A single cohort study estimated an IR of Achilles tendon rupture of 17.7 per 100 000 first fluoroquinolone prescriptions with an excess risk of 12.0 per 100 000 first fluoroquinolone prescriptions, based on five currently exposed cases.¹⁰ Morales et al. estimated the excess risk of tendon rupture in a similar population of UK general practice patients with results consistent with those of this study: adjusted rate difference of any tendon rupture 2.9 per 10 000 patients for fluoroquinolone exposure and 10.9 per 10 000 patients for fluoroquinolone and corticosteroid exposure.¹¹ The results of our study were broadly consistent with the results of these other studies. However, we were able to estimate the attributable risk as well as the relative effects with information based on 93 cases of any type of tendon rupture, among which 49 cases of Achilles tendon rupture were currently exposed to fluoroquinolones (cohort analysis).

4.1 | Limitations

To assess the potential for case misclassification, we conducted two sensitivity analyses to minimize the inclusion of non-cases or prevalent cases of tendon rupture. The results of these analyses were not materially different from the main analysis, suggesting that case misclassification was not a major concern in this study. Exposure to fluoroquinolones was based on prescriptions written, not dispensed, thus there may be some exposure misclassification in this study. However, there is good agreement between written and filled prescriptions in CPRD Gold. CPRD Gold does not capture hospital prescription data; however, the results of the sensitivity analysis excluding patients with a recent hospitalization did not differ materially from the main analysis. Any misclassification of exposure is likely to be small and would be non-differential between cases and non-cases; thus, if present, it would have biased the effect measure towards the null. However, as the relative risks were consistently elevated in both the cohort and case control studies, exposure misclassification does not explain our findings.

4.2 | Strengths

This study was a population-based study where we identified all cases in a defined population of people who all had access to health care through the NHS. There was no recall bias as all information in the patient record is recorded prospectively and without knowledge of the study question. We were able to identify the largest number of fluoroquinolone exposed cases of non-traumatic tendon rupture described to date and to also estimate the attributable and relative risk of fluoroquinolone-attributed tendon rupture. Fluoroquinolones are effective, widely prescribed antibiotics, and thus it is important to understand the magnitude of the risk of tendon rupture on the general patient population.

TABLE 6 Nested case-control: Odds of non-traumatic tendon rupture by timing of fluoroquinolone exposure with and without corticosteroid use

Quinolone exposure	Corticosteroid exposure ^a	Cases	Controls	OR (95% CI)
Any tendon rupture		n = 3802	n = 14 002	
Unexposed	No	3066 (80.6)	12 454 (88.9)	1.0 (Reference)
	Yes	467 (12.3)	781 (5.6)	2.54 (2.24, 2.88)
Current	No	47 (1.2)	152 (1.1)	1.30 (0.93, 1.81)
	Yes	38 (1.0)	26 (0.2)	6.64 (3.99, 11.1)
Recent	No	33 (0.9)	102 (0.7)	1.33 (0.89, 1.98)
	Yes	14 (0.4)	32 (0.2)	1.88 (1.00, 3.53)
Past	No	100 (2.6)	361 (2.6)	1.09 (0.87, 1.37)
	Yes	37 (1.0)	94 (0.7)	1.74 (1.18, 2.57)
Achilles tendon rupture		n = 1207	n = 4453	
Unexposed	No	999 (82.8)	3998 (89.8)	1.0 (Reference)
	Yes	104 (0.9)	204 (4.6)	2.11 (1.63, 2.72)
Current	No	21 (1.7)	41 (0.9)	2.08 (1.22, 3.53)
	Yes	20 (1.7)	8 (0.2)	10.98 (4.80, 25.0)
Recent	No	12 (1.0)	33 (0.7)	1.38 (0.71, 2.74)
	Yes	6 (0.5)	8 (0.2)	3.19 (1.10, 9.24)
Past	No	34 (2.8)	139 (3.1)	0.99 (0.67, 1.46)
	Yes	11 (0.9)	22 (0.5)	2.35 (1.11, 4.96)
Bicep tendon rupture		n = 833	n = 3060	
Unexposed	No	649 (77.9)	2664 (87.1)	1.0 (Reference)
	Yes	140 (16.8)	207 (6.8)	2.82 (2.22, 3.57)
Current	No	8 (1.0)	32 (1.0)	1.08 (0.49, 2.36)
	Yes	10 (1.2)	6 (0.2)	7.96 (2.84, 22.3)
Recent + Past ^b	No	21 (2.5)	103 (3.4)	0.84 (0.52, 1.37)
	Yes	5 (0.6)	38 (1.6)	0.45 (0.18, 1.14)

^aCorticosteroid use in 6 months prior to index date.

^bToo few cases to report recent and past separately.

CI, confidence interval.

5 | CONCLUSION

Fluoroquinolones increase the risk of Achilles tendon rupture and, to a lesser extent, bicep tendon rupture, especially among chronic users; however, the attributable risk is low and the effect of fluoroquinolones in the absence of concomitant corticosteroid use is around two-fold. There was a materially increased risk of tendon rupture with concomitant use of fluoroquinolones and corticosteroids. Thus, use of steroids should be considered when prescribing fluoroquinolones, particularly to women and elderly patients (age 60+).

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Both authors contributed to study design, acquisition of data, analysis and manuscript preparation.

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APPENDIX A

TABLE A1 Site of non-traumatic tendon rupture

Tendon rupture site(s) ^a	Cohort study cases n = 3957 (%)	Case control cases n = 3802 (%)
Upper arm/shoulder	1650 (41.7)	1586 (41.7)
Bicep	869 (22.0)	833 (21.9)
Supraspinatus	437 (11.0)	417 (11.0)
Rotator cuff	261 (6.6)	254 (6.7)
Other upper arm or shoulder	83 (2.1)	82 (2.2)
Ankle and foot	1360 (34.4)	1301 (34.2)
Achilles	1263 (31.9)	1207 (31.7)
Other ankle or foot	97 (2.5)	94 (2.5)
Hand, wrist and forearm	285 (7.2)	281 (7.4)
Knee and upper leg	226 (5.7)	216 (5.7)
Unspecified	436 (11.0)	418 (11.0)

^aMutually exclusive categories.

TABLE A2 Nested case-control: Characteristics of exposed and unexposed controls at index date

Characteristic	Controls		P-value
	Exposed ^a at index date, n = 767	Unexposed at index date, n = 13 235	
Sex: Male	479 (62.5)	8437 (63.7)	0.49
Female	288 (37.5)	4798 (36.3)	
Age: <40	76 (10.0)	1523 (11.5)	<0.001
40-59	250 (32.6)	4941 (37.3)	
60+	441 (57.5)	6771 (51.2)	
Index year: 1990-1994	23 (3.0)	761 (5.7)	<0.001
1995-1999	77 (10.0)	1836 (13.9)	
2000-2004	183 (23.9)	3018 (22.8)	
2005-2009	279 (36.4)	3749 (28.3)	
2010-2015	205 (26.7)	3871 (29.2)	
Length of record before index date:			0.009
2 years	32 (4.2)	554 (4.2)	
3-5 years	96 (12.5)	1939 (14.7)	
6-10 years	174 (22.7)	3591 (27.1)	
11-15 years	216 (28.2)	3254 (24.6)	
16+ years	249 (32.5)	3897 (29.4)	

(Continues)

TABLE A2 (Continued)

	Controls		
Characteristic	Exposed ^a at index date, n = 767	Unexposed at index date, n = 13 235	P-value
Smoking: Current	138 (18.0)	2461 (18.6)	<0.001
Past	260 (33.9)	3885 (29.4)	
Never	335 (43.7)	5828 (44.0)	
Unknown	34 (4.4)	1061 (8.0)	
BMI: <18.5 kg/m ²	13 (1.7)	197 (1.5)	0.93
18.5–25 kg/m ²	231 (30.1)	3876 (29.3)	
25–29 kg/m ²	282 (36.8)	4863 (36.7)	
30+ kg/m ²	190 (24.8)	3442 (26.0)	
unknown	51 (6.6)	857 (6.5)	
History of			
Arthritis	215 (28.0)	3155 (23.8)	0.009
Gout	33 (4.3)	696 (5.3)	0.28
Diabetes	106 (13.8)	1265 (9.6)	<0.001
Obesity	72 (9.4)	969 (7.3)	0.04
Chronic kidney disease	57 (7.4)	662 (5.0)	0.004
Acute kidney injury	5 (0.7)	32 (0.2)	0.05 ^b
Asthma	212 (27.6)	2489 (18.8)	<0.001
COPD	100 (13.0)	762 (5.8)	<0.001
Rheumatoid arthritis	23 (3.0)	326 (2.5)	0.42
Psoriatic arthritis	6 (0.8)	56 (0.4)	0.15 ^b
Other autoimmune disorders	84 (11.0)	986 (7.4)	<0.001
Prescriptions (Rx) before index date			
Thyroxine in prior 6 months	50 (6.5)	723 (5.5)	0.24
Corticosteroids in prior 6 months	152 (19.8)	781 (5.9)	<0.001
# Corticosteroid Rx in prior year			<0.001
0	584 (76.1)	12 053 (91.1)	
1	59 (7.7)	556 (4.2)	
2	37 (4.8)	187 (1.4)	
3+	87 (11.4)	439 (3.3)	

^aFilled use of last fluoroquinolone prescription within 180 days before index date.

^bFisher exact test.