Relative and Absolute Risk of Tendon Rupture with Fluoroquinolone and Concomitant Fluoroquinolone/Corticosteroid Therapy

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Relative and absolute risk of tendon rupture with fluoroquinolone and concomitant fluoroquinolone/corticosteroid therapy: population-based nested case-control study

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RUNNING TITLE: Fuoroquinolones and risk of tendon rupture

MAIN POINTS

- Risk of tendon rupture with fluoroquinolones depends upon timing, cumulative dose and concomitant exposure to oral corticosteroids.
- Absolute risk varied by age and concomitant corticosteroid exposure, affecting elderly patients the greatest.

Abstract

Background and Objectives

Tendon rupture can result from fluoroquinolone exposure. The objective of this study was to quantify relative and absolute risk and determine how risk is affected by timing of exposure.

Methods

The UK Health Improvement Network primary care database was used to perform a nested case-control study measuring the association between fluoroquinolone exposure and tendon rupture. Adults with tendon rupture were matched on age, sex, general practice and calendar time to four controls selected from a cohort prescribed systemic fluoroquinolone or co-amoxiclav antibiotics. The relative and absolute risk of tendon rupture with fluoroquinolone exposure was calculated.

Results

Current fluoroquinolone exposure was associated with an increased risk of any tendon rupture (adjusted incidence rate ratio [aIRR] 1.60, 95%CI 1.23-2.07) and Achilles tendon rupture (aIRR 3.15, 95%CI 2.12-4.67) that persisted for 60 days. Risk increased with cumulative exposure and was greatest when co-prescribed with oral corticosteroids (aIRR 19.73, 95%CI 7.93-49.11 for Achilles tendon rupture). The adjusted rate difference (aRD) with fluoroquinolone exposure was 2.9 and 2.1 per 10000 patients for any and Achilles tendon rupture respectively, and was greatest in people aged ≥60 years prescribed concomitant oral corticosteroid therapy (aDR 19.6 for any tendon and 6.6 Achilles tendon rupture per 10000). No association was seen with co-amoxiclav or statin exposure, or with biceps or other tendon ruptures.

Conclusions

Risk of tendon rupture with fluoroquinolones depends on timing, cumulative dose and concomitant exposure to oral corticosteroids. Absolute risk significantly varied by age and concomitant corticosteroid exposure, affecting elderly patients the greatest.

Introduction

Fluoroquinolone antibiotics are widely used to treat a broad range of infections, including those of the urinary respiratory and gastrointestinal systems, with variation in the prevalence of prescribing and indications for use within different health systems.[1] However, fluoroquinolones cause important side effects as listed in their Summary of Product Characteristics (SPC), which include tendon ruptures that are listed as occurring very rarely with a frequency of less than 1 per 10000 patients.[2,3] Tendon ruptures manifest as complete or partial rupture of the tendon and are an important cause of morbidity, affecting both functional ability and quality of life with treatment often involving invasive surgery.[4,5] The incidence of tendon rupture in the general population varies according to tendon site, with estimates ranging from 4.7 to 55.2 per 100000 person-years for Achilles tendon rupture, and 2.6 to 5.4 per 100000 person-years for biceps tendon rupture.[6-8] The mechanism for fluroquinolone-induced tendon rupture remains uncertain but has been linked to changes in collagen fibrils following alterations in the regulation of matric metalloproteinases associated with non-traumatic rupture.[9] Although some risk factors for tendon rupture have been identified such as increasing age, male gender, obesity, diabetes, corticosteroid therapy and recreational sports, [10-12] a further understanding of risk factors is needed to identify at-risk individuals and minimize unintended harm.

In 1995, the U.S. Food and Drug Administration (FDA) updated fluoroquinolone product labelling with a warning about the possibility of tendon rupture, followed by a black box warning in 2008.[13,14] In May 2016, the FDA conducted a review of disabling and potentially irreversible serious side effects of fluoroquinolones resulting in a restriction of their use in less severe infections of acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections when other treatment options are available.[15] The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) is also reviewing the persistence of fluoroquinolones adverse reactions to help determine the need for any restriction in indication, and requires further data to characterise the risk of such reactions.[16] Whilst the risk of tendon rupture is recognized, there is inconsistency in its reported size with relative risk ranging between 1.9 and 5.3-fold increased risk, with limited information on absolute risk.[10,17-22] The aim of this study was to quantify the relative and absolute risk of tendon rupture with fluoroquinolone exposure, and to investigate factors influencing this risk.

Methods

Data source

The THIN database contains electronic patient records extracted from >500 general practices across the UK covering approximately 6% of the UK population. Data is representative of the UK population in terms of age, gender, deprivation status, and geographical distribution.[23] Data is linked via an anonymous ID number allowing patients to be followed longitudinally over time. THIN contains diagnostic, prescription, and lifestyle information. Diagnoses, symptoms, procedures, and other relevant health information are coded using the Read Code clinical classification system. The Read code system has been the standard approach to recording patient data in UK primary care since 1990, and is a hierarchical classification system, linked to the International Classification of Diseases.[24] Data quality control measures available in THIN include The Acceptable Mortality Reporting (AMR) date specific to each practice and defines the date from which computerised recording of mortality data has reached an acceptable standard.[25]

Study Population

The study population consisted of adults ≥18 years identified in THIN between 01/01/1999 and 31/12/2015 who were issued at least one prescription of co-amoxiclav or fluoroquinolone antibiotic with a systemic route of administration. Co-amoxiclav was chosen so that controls were sampled from a more representative population prescribed antibiotics to circumvent problems related to confounding by indication and by severity. Cohort entry was defined as the date of the first co-amoxiclav or fluoroquinolone prescription for systemic administration after the latest of the following criteria: start of the study period (01/01/1999); the practices AMR date; the patient's 18th birthday; date of registration with a general practice + one year. In this regard, all participants were required to have at least one year of observation prior to cohort entry. Cohort exit was defined by the earliest of the following criteria: occurrence of the outcome; deregistration from the general practice; death; date of last data collection from the general practice; end of the study period (31/12/2015).

Study design and outcomes

A nested case control study was used to efficiently account for time-varying confounders and time-varying exposure to prescribed medicines.[26] The date of the first event occurring after cohort entry was the index date for case subjects. Tendon ruptures were first evaluated as any tendon ruptures and were then grouped according to their incidence: Achilles tendon; biceps tendon; and other tendon

ruptures (consisting of triceps, hand/wrist, hamstrings/quadriceps, foot, shoulder, and non-specifically coded tendon ruptures) (see supplementary table S1)

Control selection

Up to 4 controls were randomly selected and matched to each case on age decile, gender, general practice and calendar year of cohort entry using incidence density sampling.[26] The risk-set date for controls was the index date for cases. With incidence density sampling, 'controls' are a selection of person-moments from individuals who have not experienced the event at the index date. In this regard, controls may be selected more than once, and people who subsequently become cases may be selected as controls at earlier time points. 82 cases of tendon rupture (1.7%) were unmatched to controls following the first round of matching criteria, and were subsequently included matched on age decile, gender and calendar year of cohort entry only, with sensitivity analyses conducted excluding these risk sets from the analysis.

Exposures

Systemic fluoroquinolone (ciprofloxacin, moxifloxacin, levofloxacin, norfloxacin and ofloxacin) and co-amoxiclav antibiotic exposure was measured by identifying prescriptions issued within a pre-specified risk window prior to the index date. Fluoroquinolone and co-amoxiclav exposure was primarily defined as current exposure when one or more prescriptions were issued in a 30 day exposure risk window prior to the index date. Exposure risk windows 31-60 days, 61-90 days and 91-180 days prior to the index date were then examined for systemic fluoroquinolone exposure to assess past exposure. Cumulative fluoroquinolone and co-amoxiclav exposure was measured as the total number of days of systemic fluoroquinolone or systemic co-amoxiclav exposure prescribed within each risk window. Cumulative days exposure was calculated by dividing the prescription quantity information by the standard administration schedule for each type of antibiotic as follows: oral co-amoxiclav three times a days; oral levofloxacin, moxifloxacin and norfloxacin once a day; ciprofloxacin and ofloxacin twice a day.[27] Prescriptions for oral suspension formulations were similarly calculated taking into account quantity information recorded in milliliters. Cumulative exposure was examined as a continuous variable predicting the increased risk associated with each additional day of therapy during the risk window and also modelled with a categorical variable using the median days of exposure and interquartile range.

Confounders

Analyses were adjusted for exact age, sex and practice-level socioeconomic deprivation (inherent in the matching criteria), smoking status, body mass index (BMI), exposure to oral and injectable corticosteroid therapy and statin therapy (defined as by prescriptions issued within 90 days of the index date), and prior history of tendon rupture. Comorbidity was accounted by adjusting for a history of hypothyroidism, hyperparathyroidism and the Charlson comorbidity index, and then by modelling individual conditions in the Charlson comorbidity index as a sensitivity analysis. The Charlson comorbidity index is defined using the following clinical conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, peptic ulcer, chronic liver disease, diabetes, hemiplegia, moderate or severe kidney disease, diabetes with complications, liver disease, cancer, cancer with metastasis, and AIDS.[28]

Data analysis

Conditional logistic regression was used to calculate odds ratios for the association between tendon rupture and fluoroquinolone exposure and co-amoxiclav exposure. Using an incidence density sampling approach, odds ratios calculated in this way are estimators of incidence rate ratios (IRR). Interaction between fluoroquinolone exposure and oral corticosteroid exposure was tested on the multiplicative scale. This was not done for statins as there was no statistically significant independent association with exposure. Adjusted rate differences (per 10000) were calculated for significant associations providing an absolute measure of effect.[29] Risk of exposure was presented for any tendon rupture and by type of tendon rupture.

Multiple imputation was used to impute missing data on body mass index (9.5% missing) and smoking status (2.1% missing). The imputation model included all variables relating to clinical characteristics, outcomes, medications, and fluoroquinolone and co-amoxiclav exposure. Multiple imputation used fully conditional specification, with linear regression for continuous variables (BMI) and logistic regression for categorical variables (smoking status) with five imputations and analysed using Rubin's rules.[30] Sensitivity analyses were conducted varying the exposure risk window duration to 60 and 90 days, modelling individual Charlson comorbidities, excluding traumatic tendon ruptures, excluding people with prior history of tendon rupture, and undertaking a complete case analysis. Analysis was carried out using SAS Enterprise Guidev7.1 and STATAv15. The study was approved by the THIN Scientific Review Committee (17THIN087).

Results

The cohort contained 1351780 adult patients prescribed ≥1 prescription for fluoroquinolone (34.3%) or co-amoxiclav (65.7%) antibiotics (mean age of cohort 52.8 years, 57.0% female). Overall, 4,836 tendon rupture events were identified during cohort follow-up (incidence of any tendon rupture 5.9 per 10,000 person-years (pyrs) and of Achilles tendon rupture 1.9 per 10000 pyrs) that were matched to 18356 controls (table 1). Cases and controls were well matched on age, sex and duration of follow-up. The most common types of tendon rupture were: Achilles tendon (32.4%); biceps tendon (27.5%); shoulder tendons (16.6%); hand/wrist tendons (7.4%); hamstring/quadriceps/patellar tendons (7.0%); foot/ankle tendons (0.8%) and triceps tendon (0.5%). Unspecified tendon ruptures accounted for 8.3% of all cases. The mean duration of cumulative fluroquinolone exposure was 10.6 days (standard deviation, SD 8.9 days) and for co-amoxiclav was 8.6 days (SD 7.4 days).

Risk of tendon rupture with fluoroquinolone exposure

The relative incidence of any tendon rupture was significantly elevated with current systemic fluoroquinolone exposure (adjusted IRR [aIRR] 1.61, 95%CI 1.25-2.09). When stratified by type of tendon rupture, current fluoroquinolone exposure was associated with a significantly elevated rate of Achilles tendon rupture (aIRR 3.14, 95%CI 2.11-4.65) but not biceps tendon rupture (aIRR 1.07, 95%CI 0.61-1.89) or other tendon ruptures (aIRR 0.82, 95%CI 0.50-1.35) (table 2). In contrast, the relative incidence of tendon ruptures was not significantly elevated with current co-amoxiclav exposure (table 2).

Increasing cumulative days of systemic fluoroquinolone exposure was significantly associated with in increased risk of Achilles tendon rupture (IRR 1.06, 95%CI 1.03-1.09). In contrast, no significant association was observed with cumulative co-amoxiclav exposure (supplementary table S2). The relative incidence of Achilles tendon rupture was significantly increased with systemic fluoroquinolone exposure within 1-30 days (aIRR 2.97, 95%CI 1.98-4.43) and 31-60 days (aIRR 2.11, 95%CI 1.30-3.41) of the index date but not with systemic fluoroquinolone exposure occurring further in the past (aIRR 0.69, 95%CI 0.41-1.16 for 61-90 days and aIRR 1.23, 95%CI 0.88-1.71 for 91-180 days prior to the index date).

Relationship with other risk factors

The adjusted relative incidence of tendon rupture was significantly elevated in people with a history of prior tendon rupture, in those with oral corticosteroid therapy, and with increasing BMI (table 3). The risk of tendon rupture was not significantly associated with statin therapy or comorbidity score whilst smoking was associated with a reduced relative incidence of tendon rupture. A large significant interaction was observed with concomitant systemic fluoroquinolone and oral corticosteroid exposure (aIRR 6.88, 95%CI 3.94-12.03 and aIRR 19.36, 95%CI 7.78-48.19, for any tendon rupture and Achilles tendon rupture respectively, table 4).

Absolute risk

Adjusted rate differences for any tendon rupture and Achilles tendon rupture are presented overall and for age and sex (table 5). Fluoroquinolone exposure caused an estimated 2.9 tendon ruptures and 2.1 Achilles tendon ruptures per 10000 patients per year and was greatest in patients aged 60 and over. Concomitant oral corticosteroid exposure had a large impact on absolute risk with the highest rates of tendon rupture associated with concomitant fluoroquinolone and corticosteroid exposure in males and in patients aged 60 years and over.

Sensitivity analyses

The relative incidence was elevated using 60 day and 90 day risk windows but was smaller in size with increasing risk-window duration, whilst the results of all other sensitivity analyse were similar to those in the main analysis (supplementary table S3).

Discussion

Fluoroquinolone exposure significantly increased the risk of tendon rupture which appeared to last up to 60 days following exposure for Achilles tendon rupture. Risk was also estimated to increase by ~6% with each additional day exposed to fluoroquinolones within the current risk window and was increased markedly with concomitant exposure to oral corticosteroids. In contrast, co-amoxiclav exposure, which was chosen as a negative control, was not associated with an increased relative risk of any tendon rupture. Absolute risk of tendon rupture from fluoroquinolone exposure was greater than currently highlighted by product information and varied markedly according to age and concomitant exposure to oral corticosteroids.

Observational studies have previously investigated the risk of tendon rupture with fluoroquinolones with results varying in the size and precision of estimates. One case-control study consisting of only 38 cases of Achilles tendon rupture, reported a relative risk with current exposure to fluoroquinolone antibiotics of 1.9 (95%CI 1.3-2.6), whilst a larger case control study from Italy reported an 30% increased risk of any tendon rupture and a larger but less precise risk of Achilles tendon rupture (OR 4.1, 95%CI 1.8-9.6 for Achilles tendon rupture).[17,19] Meanwhile, a small cohort study from Denmark has reported an age-standardized incidence ratio of Achilles tendon rupture of 3.1 (95%CI 1.0-7.3) within 90 days of incident fluoroquinolone exposure whilst a further case-control study reported a larger risk of Achilles tendon rupture (OR 5.3, 95%CI 1.8-15.2).[18,20] However, these studies did not include an antibiotics-treated comparator in their design to help assess the presence of residual confounding.

One case-crossover study, whereby the patient acts as their own control, reported a smaller association with Achilles tendon rupture (OR 2.0, 95%CI 1.2-3.3) and used a composite of nitrofurantoin, amoxicillin and trimethoprim exposure as a negative control with no significant association being observed.[10] This comparator group consisted of medications weighted towards the treatment of milder urinary tract infections. In contrast, a cohort study from Canada reporting an increased risk of tendon rupture with fluoroquinolones did use an active comparator of amoxicillin exposure that was also significantly associated with tendon rupture, suggesting the presence of residual confounding can affect the validity and size of the relative risk.[21] We used co-amoxiclav as a negative control because in the UK, co-amoxiclav is a similar broader-spectrum antibiotic reserved for more severe types of infection and may be less subject to unmeasured confounding compared to amoxicillin, nitrofurantoin and trimethoprim. Similar to fluoroquinolones, co-amoxiclav is also associated with an increased risk of *Clostridium difficile* infection, which has resulted in similar changes to UK antibiotic prescribing guidelines during the study period.

Our study extends knowledge by demonstrating that risk appears to be present up to 60 days following treatment and increases by ~6% with each days of current exposure. People with prior tendon rupture, comorbidity, those with increasing BMI and those prescribed oral corticosteroid exposure were at increased risk of tendon rupture, with a significant interaction detected between concomitant fluoroquinolone and oral corticosteroid therapy. This interaction has previously been reported but with variable precision, ranging from an odds ratio of 9.1 to 43.2.[10,17,20] Information on absolute risk is limited. van der Linden et al. report an excess absolute risk of Achilles tendon rupture of 3.2 cases per

1000 patient years, although the method used to calculate this was not reported.[17] In a related study, van der Linden et al. report the incidence of Achilles tendon rupture in people aged 60 and over as a population-attributable risk estimating that 2.2% of Achilles tendon rupture in patients age 60 to 79 years and 6.3% in patients aged 80 years and over are attributable to fluoroquinolone exposure.[18] This risk may be dependent on the prevalence of exposure in the population. Although low, we found that absolute risk in this population was greater than that listed in the product information for fluoroquinolones (which states less than 1 in 10000 patients). Although we estimate a population-average adjusted rate difference (akin to excess risk) of ~2.9 tendon ruptures per 10000 person years, absolute risk was greater is certain subgroups, significantly varying by age, concomitant corticosteroid exposure and to a lesser extent, by gender. Lastly, statin therapy has previously been linked to tendon disorders using spontaneous reports and pharmacovigilance databases.[31] Our study found no significant increased risk with statin use, in keeping with three other recent observational studies.[32-34]

Our study has strengths and limitations. We matched on general practice so that controls were more likely to have similar socio-economic deprivation status and health care physician prescribing behavior helping to reduce confounding by indication. Only small numbers of cases were included unmatched on general practice, with sensitivity analysis demonstrating this had negligible influence on the observed results. Despite adjustment for multiple confounders, risk of residual unmeasured confounding remains possible that may include channeling bias, although evaluating the risk of tendon rupture with co-amoxiclav exposure consistently showed no statistically significant association. Very few traumatic tendon ruptures were explicitly recorded and it is not possible to determine what proportion of other events may have been associated with trauma, if any. Antibiotic exposures were identified through prescriptions issued within general practice. Our study focuses on tendon rupture only and further investigation on the risk of tendinitis may be useful for clinical decision making. Similarly, we focus on fluoroquinolone as a class and risk associated with individual fluoroquinolone products requires further evaluation.

Antibiotic stewardship aimed at reducing fluoroquinolone exposure may prevent unnecessary harm but this may not be possible or appropriate for all patients. Despite the relatively large increase in risk associated with concomitant exposure to systemic fluoroquinolones and corticosteroids relatively little attention is given to this interaction among clinical guideline recommendations. This may have

implications for special patient groups such as for in the management of asthma, COPD, or bronchiectasis exacerbations which may require concomitant use of both antibiotics and oral corticosteroids regimens for example and commonly have other risk factors such as comorbidity.[35-37] This study was conducted to provide further information to quantify the risk of tendon ruptures associated with fluoroquinolone antibiotics to support a review of safety information at the EMA PRAC in order to aid regulatory decision making for the use of fluoroquinolones across Europe. In this regard, tendon rupture is only one potential adverse effect of fluoroquinolone exposure, with other potential adverse effects associated with peripheral neuropathy and aortic aneurysm having been reported.[38, 21, 39-41]

In conclusion, the risk of tendon rupture associated with fluoroquinolone therapy appears to depend on timing, dose and concomitant exposure to corticosteroids that affects elderly patients the greatest in absolute terms, which patients and healthcare professionals should be informed of.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interest

Daniel Morales has no conflicts of interest.

Jim Slattery has no conflicts of interest.

Luis Pinheiro has no conflicts of interest.

Xavier Kurz has no conflicts of interest.

Patricia McGettigan has no conflicts of interest.

Alexandra Pacurariu has no conflicts of interest.

Ethical approval

Approval to conduct the studies using anonymised data was granted by the Scientific Review Committees of The Health Improvement Network (protocol number 17THIN087).

Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be not be understood or quoted as reflecting the views of the EMA or one of its committees or working parties.

Contributions

All authors were involved in the study design and data collection. DM performed the analysis and is guarantor for the study. All authors contributed to the interpretation of results, writing the manuscript and approved the final draft.

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Table 1. Characteristics of matched cases and controls.

	Cases	Controls
Number of individuals	4836	18356
Female sex, no. (%)	1876 (38.8)	7164 (39.0)
Age (years), mean ± SD	61.6 (15.5)	61.3 (15.3)
Years of follow-up, mean ± SD	5.0 (3.7)	5.0 (3.7)
Body mass index, mean ± SD	28.1 (5.9)	27.7 (5.7)
Charlson comorbidity index, mean ± SD	1.32 (1.61)	1.27 (1.64)
Hypothyroidism, no. (%)	365 (7.6)	1296 (7.1)
Hyperparathyroidism, no. (%)	17 (0.3)	61 (0.3)
Current smokers, no. (%)	765 (16.1)	3371 (18.8)
Oral corticosteroid therapy[a], no. (%)	522 (10.8)	911 (5.0)
Injectable corticosteroid therapy[a], no. (%)	43 (0.9)	32 (0.2)
Statin therapy[a], no. (%)	326 (20.7)	1240 (20.6)
Current fluoroquinolone exposure, no. (%)	111 (2.3)	236 (1.3)
Current co-amoxiclav exposure, no. (%)	98 (2.0)	314 (1.7)
Prior history of tendon rupture, no. (%)	133 (2.8)	114 (0.6)

a = At least one prescription within 90 days of the index date. Current fluoroquinolone exposure=prescription within 30 days of the index date.

Table 2. Incidence rate ratios for the association between tendon rupture and current systemic fluoroquinolone and co-amoxiclav exposure.

Tendon rupture	Exposed cases/total	Exposed controls/total	Crude IRR	Adjusted IRR	Adjusted p-value
Any tendon rupture					
▪ Fluoroquinolones	111/4836	236/18356	1.79 (1.41-2.27)	1.61 (1.25-2.09)	<0.001
▪ Co-amoxiclav	98/4836	314/18356	1.15 (0.90-1.45)	1.02 (0.79-1.31)	0.900
Achilles tendon rupture					
▪ Fluoroquinolones	67/1577	82/6007	3.50 (2.45-5.02)	3.14 (2.11-4.65)	<0.001
▪ Co-amoxiclav	38/1577	114/6007	1.19 (0.81-1.77)	1.00 (0.64-1.57)	0.989
Biceps tendon rupture					
▪ Fluoroquinolones	20/1316	62/4946	1.19 (0.71-2.00)	1.07 (0.61-1.89)	0.804
▪ Co-amoxiclav	23/1316	74/4946	1.16 (0.72-1.88)	1.01 (0.61-1.66)	0.978
Other tendon rupture					
▪ Fluoroquinolones	24/1943	92/7403	0.94 (0.59-1.50)	0.82 (0.50-1.35)	0.439
▪ Co-amoxiclav	37/1943	126/7403	1.09 (0.75-1.60)	1.01 (0.68-1.50)	0.946

IRR=incidence rate ratio. Model adjusted for exact age, body mass index, Charlson comorbidity score, hypothyroidism, hyperparathyroidism, smoking status, oral and injectable corticosteroid therapy, statin therapy and prior history of tendon rupture.

Table 3. Association with any tendon rupture and Achilles tendon rupture and other potentially confounding variables and comorbidities.

Variable	Any tendon rupture		Achilles tendon rupture	
	Adjusted IRR	Adjusted p-value	Adjusted IRR	Adjusted p-value
Prior tendon rupture	4.60 (3.51-6.04)	<0.001	7.48 (4.53-12.35)	<0.001
Oral corticosteroid	2.25 (1.99-2.54)	<0.001	3.60 (2.89-4.48)	<0.001
Injectable corticosteroid	5.47 (3.36-8.91)	<0.001	1.82 (0.40-8.29)	0.435
Fluoroquinolone	1.61 (1.25-2.09)	<0.001	3.14 (2.11-4.65)	<0.001
Co-amoxicalv	1.02 (0.79-1.31)	0.900	1.00 (0.64-1.57)	0.989
Body Mass Index	1.01 (1.01-1.02)	<0.001	1.01 (1.00-1.03)	0.008
Statin therapy	1.06 (0.98-1.16)	0.129	0.96 (0.81-1.14)	0.650
Hypothyroidism	1.03 (0.90-1.17)	0.693	0.91 (0.70-1.18)	0.469
Hyperthyroidism	0.89 (0.51-1.55)	0.676	1.08 (0.41-2.89)	0.873
Charlson comorbidity	0.99 (0.97-1.01)	0.279	1.00 (0.96-1.05)	0.975
Connective tissue disease	2.03 (1.66-2.49)	<0.001	1.02 (0.63-1.65)	0.942
COPD	1.07 (0.99-1.17)	0.096	1.24 (1.08-1.44)	0.003
Cancer	0.97 (0.88-1.06)	0.473	0.98 (0.81-1.19)	0.854
Chronic kidney disease	0.96 (0.86-1.07)	0.452	1.02 (0.82-1.28)	0.865
Dementia	0.47 (0.34-0.66)	<0.001	0.34 (0.14-0.79)	<0.001
Diabetes	1.01 (0.91-1.11)	0.854	1.03 (0.85-1.25)	0.758
Heart failure	0.85 (0.71-1.01)	0.062	0.87 (0.64-1.25)	0.459
Liver disease	0.87 (0.56-1.34)	0.521	1.04 (0.49-2.23)	0.916
Myocardial infarction	1.07 (0.92-1.23)	0.404	0.96 (0.71-1.30)	0.796
Peptic ulcer disease	1.09 (0.94-1.27)	0.263	1.01 (0.76-1.36)	0.921
Peripheral vascular disease	0.90 (0.65-1.25)	0.543	0.85 (0.46-1.57)	0.606
Stroke	1.04 (0.90-1.21)	0.579	1.03 (0.75-1.41)	0.878
Smoking				
▪ Ex-smoker	1.04 (0.96-1.12)	0.360	0.85 (0.74-0.98)	0.029
▪ Current smoker	0.85 (0.78-0.94)	0.001	0.72 (0.61-0.85)	<0.001

IRR = incident rate ratio. Variables included separately in the model without interactions.

Table 4. Incidence rate ratios for the interaction between tendon rupture and current systemic fluoroquinolone and oral corticosteroid exposure

	Exposed cases/total	Exposed controls/total	Adjusted IRR	Adjusted p-value
Any tendon rupture				
▪ Oral corticosteroid alone	287/4836	443/18356	2.58 (2.19-3.03)	<0.001
▪ Oral corticosteroid plus fluoroquinolone exposure	36/4836	20/18356	6.88 (3.93-12.03)	<0.001
Achilles tendon rupture				
▪ Oral corticosteroid alone	148/1557	180/6007	4.59 (3.43-6.14)	<0.001
▪ Oral corticosteroid plus fluoroquinolone exposure	37/1557	10/6007	19.36 (7.78-48.19)	<0.001

Adjusted for exact age, body mass index, Charlson comorbidity score, hypothyroidism, hyperthyroidism, injectable corticosteroid therapy, smoking status, statin therapy and prior history of tendon rupture. IRR=incidence rate ratio.

Table 5. Adjusted rate differences in tendon rupture with fluoroquinolone exposure and concomitant oral corticosteroid exposure (per 10000 patients).

	Any tendon		Achilles tendon	
	ARD	**95%CI**	**ARD**	**95%CI**
Fluoroquinolone exposure				
▪ Overall	2.9	2.2-3.7	2.1	1.6-2.7
▪ Males	2.3	1.8-3.0	1.6	1.3-2.1
▪ Females	3.1	2.4-4.0	2.1	1.6-2.7
▪ Age <60 years	1.4	1.0-1.8	1.2	0.9-1.6
▪ Age ≥60 years	5.6	4.3-7.2	3.0	2.3-3.9
Fluoroquinolone plus prednisolone exposure				
▪ Overall	10.9	8.3-14.0	4.9	3.7-6.2
▪ Males	14.6	11.2-18.8	5.5	4.2-7.1
▪ Females	7.9	6.0-10.1	3.9	3.0-5.0
▪ Age <60 years	6.0	4.6-7.7	2.1	1.6-2.7
▪ Age ≥60 years	19.6	15.0-25.2	6.6	5.0-8.4

ADR=adjusted rate difference, the additional number of expected events per 10,000 patients per year.