



Fluoroquinolones and the risk of tendon injury: a systematic review and meta-analysis

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Abstract

Purpose Tendinopathy is a known adverse reaction associated to fluoroquinolones, but a meta-analysis was not yet published. The aim of this study was to conduct a systematic review and a meta-analysis of the scientific evidence evaluating the risk of tendon injury associated with fluoroquinolones.

Methods A literature search was conducted to identify observational studies which reported results on the risk of Achilles tendon rupture (ATR), risk of Achilles tendinitis (AT), or risk of any tendon disorders (ATD). A meta-analysis was performed by pooling odds ratios (ORs) with their 95% confidence intervals (CIs).

Results Fifteen studies were included in the meta-analysis. Treatment with fluoroquinolones was associated with an increased risk of ATR (OR 2.52 (95% CI 1.81–3.52), $p < 0.001$, $I^2 = 76.7\%$), an increased risk of AT (OR 3.95 (95% CI 3.11–5.01), $p < 0.001$, $I^2 = 0\%$), and increased risk of ATD (OR 1.98 (95% CI 1.62–2.43), $p < 0.001$, $I^2 = 84.5\%$). The initial risk estimates remained statistically significant among patients aged ≥ 60 years old. Risk estimates did not significantly change after depending on the concomitant use of corticosteroids or studies methodological quality assessment. The analysis according to the type of fluoroquinolones was only possible for ATR, which were ofloxacin and norfloxacin were found to increase the risk of this outcome, but not ciprofloxacin and levofloxacin.

Conclusions The results of this meta-analysis confirm the risk of tendon injuries associated with fluoroquinolones. Older age and concomitant use of corticosteroids seem to be additional risk factors for tendinopathy.

Keywords Fluoroquinolones · Tendinopathy · Pharmacovigilance · Risk assessment · Meta-analysis

Introduction

Systemic fluoroquinolones are commonly used antibiotics, presenting excellent potency in vitro against most Enterobacteriaceae, fastidious gram-negative bacilli including species of *Haemophilus* and gram-negative cocci [1]. When administered orally, fluoroquinolones have good

bioavailability and are generally well tolerated [2]. However, over the years, the use of fluoroquinolones has been associated with serious adverse reactions, leading to the market withdrawal of some of these antibiotics, such as temafloxacin (severe hemolytic–uremic syndrome), trovafloxacin (hepatotoxicity), grepafloxacin (QT interval lengthening), and gatifloxacin (dysglycemia) [2–4].

Although rare, tendon injury is a serious adverse effect of systemic fluoroquinolones. In 1995, the US Food and Drug Administration (US FDA) recommended an update of the labeling of all marketed systemic fluoroquinolones to include a warning about the possibility of tendon rupture [5]. In 2008, a boxed warning citing an increased risk of tendinitis and tendon rupture was added to the labeling of systemic fluoroquinolones, based on evidence from post-marketing spontaneous reports and observational studies [6]. The risk of such adverse effects is further increased in patients aged over 60, in transplant recipients, and among individuals on steroid therapy [7].

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In 2016, the US FDA reinforced warnings about the risk of tendinopathies associated with the use of systemic fluoroquinolones [6]. Since the risk of these serious adverse effects may outweigh the benefits of systemic fluoroquinolones in the treatment of minor infections, these antibiotics should be reserved for use when no alternative treatment options can be considered [6]. In 2018, the European Medicines Agency (EMA) also recommended new restrictions on the use of systemic fluoroquinolones after reviewing safety information about disabling and potentially long-lasting adverse effects, including tendon injuries [8, 9].

Some systematic reviews of studies evaluating the risk of tendinopathies associated with the use of systematic fluoroquinolones have been carried out [2, 10–12]. However, important limitations seem to characterize those works. Not all the observational studies available in the scientific literature were conducted in the previous systematic reviews, particularly the most recently published evidence [9, 13–15]. Moreover, although a meta-analysis has been conducted, the results were not stratified according to the different outcomes assessed in the epidemiological studies, different risk windows, studies methodological quality, or type of comparators used [12].

Since fluoroquinolones are essential medicines, it is important, from a public health perspective, to evaluate the consistency of the results from observational studies assessing the risk of tendinopathies. Although meta-analyses may have some limitations, quantitative synthesis is usually preferred over qualitative analysis of the results of a set of studies [16]. Moreover, conducting a meta-analysis may allow assessing the consistency of the results and understanding the influence of risk factors and additional variables in the risk of tendinopathies associated with the use of fluoroquinolones [17, 18].

The aim of this systematic review and meta-analysis is to assess the risk of tendon injuries associated with the use of systemic fluoroquinolones, as well as to explore risk variations due to risk factors, study designs, and methodological quality of included studies.

Methods

The current systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19].

Literature search

PUBMED, EMBASE, and Cochrane Library were searched from its inception until November 2018 in order to identify relevant studies evaluating the risk for tendon injury

associated with systemic fluoroquinolones. MeSH and Emtree terms, the MedDRA dictionary (v.21.0), and the International Nonproprietary Names (INN) of fluoroquinolones were used in the search equation [20–22]. Only the literature published in the English language was considered for inclusion. Bibliographic references list of all relevant studies, meta-analyses, and systematic reviews were hand searched in order to identify additional eligible articles. We did not seek to identify safety data of fluoroquinolones beyond published studies. The electronic databases search strategy is available in Supplemental Table 1.

Study selection, data extraction, and quality assessment

The titles and abstracts of all retrieved citations were screened by two independent reviewers (C.A. and D.M.) to identify potentially relevant publications. Full texts were retrieved for relevant citations. Discrepancies were resolved by majority decision (two out of three) involving a third investigator (F.B.M.). Studies would be included if they fulfilled the following criteria: 1, being a comparative observational study (case-control or cohort studies); 2, included patients of all ages and genders; 3, compared fluoroquinolones with a placebo (or non-use) or active control; and 4, have provided risk estimates (relative risk (RR), odds ratio (OR), or hazard ratio (HR)) or data allowing to calculate such risk estimates. Only peer-reviewed full papers were considered. Basic science studies, reviews, case reports, and studies without a comparison group were excluded.

The following data from the studies was extracted: design, characteristics of participants, treatments under evaluation, risk-window length, and estimated effect measures.

Studies' methodological quality was assessed through Newcastle–Ottawa scale, which considers the following characteristics: selection of the study groups, comparability of the groups, ascertainment of either the exposure (for case-control studies), or outcome of interest (for cohort studies) [23]. A maximum of one point for each item within the “Selection” and “Exposure/Outcome” categories could be awarded. For “Comparability” category, a maximum of two points could be awarded. The summary score equals the number of points earned by each study, totaling a maximum of 9 points. Studies scoring ≥ 8 points were considered to be of good quality, those scoring < 8 and ≥ 6 points were of moderate quality, and those scoring < 6 points were considered to have poor quality. Two independent reviewers assessed the methodological quality of the studies (C.A. and D.M.). A third investigator (F.B.M.) helped to resolve discrepancies by majority decision. When more than one reference was found for the same study, the methodological quality evaluation was based on the total set of information.

Outcomes assessed

The following outcomes were assessed in this meta-analysis: risk of Achilles tendon rupture (ATR), risk of Achilles tendinitis (AT), and risk of any tendon disorders (ATD). The outcomes selected for this systematic review and meta-analysis were the same as those considered in a previous systematic review [10]. The ATR and AT are the most frequently evaluated tendon injury outcomes in published studies. The ATD is a composite outcome of any tendon rupture and/or any tendinitis.

Statistical analysis

A meta-analysis was performed by pooling odds ratios (ORs) with their 95% confidence intervals (CIs), using the DerSimonian and Laird random-effects model [24]. This model was chosen since the validity of tests of heterogeneity can be limited with a small number of component studies and it is more conservative than a fixed effect model in the presence of between-studies heterogeneity. If the studies presented more than one risk estimate, the most adjusted one would be used. The effect size estimates available for the shortest time intervals between fluoroquinolones prescription and tendon injury diagnosis or treatment were used in the overall risk estimate. The I^2 statistic test was used to assess heterogeneity between studies. An I^2 estimate > 50% was considered indicative of substantial heterogeneity [25]. The publication bias was visually examined by a funnel plot and statistically evaluated by Egger's regression asymmetry test [26].

A sensitivity analysis was conducted to explore the influence of the following variables on the summary estimates: study designs, studies' methodological quality scores, risk windows defined in included studies, age (≥ 60 vs. < 60 years old), type of fluoroquinolone, corticosteroid use, kidney disease, and comparator (fluoroquinolone non-users vs. active comparator). Risk window is the period of time considered after the end of fluoroquinolone treatment course during which patients are at risk of suffering tendon injuries. The influence of each individual study in overall risk estimate was assessed using the "one-study removed" analysis. All reported p values are 2-sided with significance being set as less than 0.05. Stata (version 13.1) was used to perform statistics.

Results

Figure 1 presents the flow of the search strategy criteria. The electronic databases searched returned 1612 references. After excluding duplicates and other studies with inadequate design, 15 studies were included in this meta-

analysis comprising seven cohort studies [15, 27–32] and eight case-control studies [9, 13, 14, 33–37].

Studies characteristics

The main characteristics of the studies are presented in Table 1. Study design, participants' demographic characteristics, drugs under evaluation, and a number of subjects evaluated were described. Patients' mean age varied from 43.5 to 65.0 years and the proportion of female patients included in the studies ranged from 22.1 to 71.4%. Most of the studies elected the population sample from either prescription dispensing data, health administrative data, or general practice data, although one study examined a post-transplant population (heart) and one study evaluated patients with end-stage renal disease [30, 32]. Only one study used propensity score to match participants [31], while the remaining adjusted the analyses for several variables. Five studies compared the risk of tendon injuries in fluoroquinolone users with active controls (other antibiotics), while the remaining compared fluoroquinolone users with non-users [15, 27–29, 31]. Thirteen studies defined a risk window of 30 days between fluoroquinolone exposure and outcome development. Two studies adopted a 90-days risk period and the other two did not report the length of time during which the outcome was assessed. Nine studies assessed the risk of ATR, three the risk of AT, and eight the risk of ATD.

The results of the assessment of studies' methodological quality are also presented in Table 1. The methodological quality was assessed as "good" for three studies, "moderate" for nine, and "poor" for three. Lack of information on confounding variables used to adjust risk estimates was the main methodological impairment found among these studies.

Risk for tendon injuries

The treatment with fluoroquinolones was associated with an increased risk of ATR (9 studies, OR 2.52 (95% CI 1.81–3.52), $p < 0.001$, $I^2 = 76.7\%$) (Fig. 2; Table 2). Fluoroquinolones were also associated with an increased risk of AT (3 studies, OR 3.95 (95% CI 3.11–5.01), $p < 0.001$, $I^2 = 0\%$) and of ATD (8 studies, OR 1.98 (95% CI 1.62–2.43), $p < 0.001$, $I^2 = 84.5\%$) (Fig. 3 and Fig. 4, respectively). The risk estimates did not significantly change when the analysis was stratified according to different study designs, with the exception of the risk of AT among cohort studies (1 study, OR 3.70 (95% CI 0.90–15.16), $p = 0.069$). The increased risk of all three outcomes remained statistically increased among older patients (aged ≥ 60 years) when the analysis was stratified by age. The risks estimated for any of the three outcomes did not significantly change irrespective of the concomitant use of corticosteroids and fluoroquinolones.

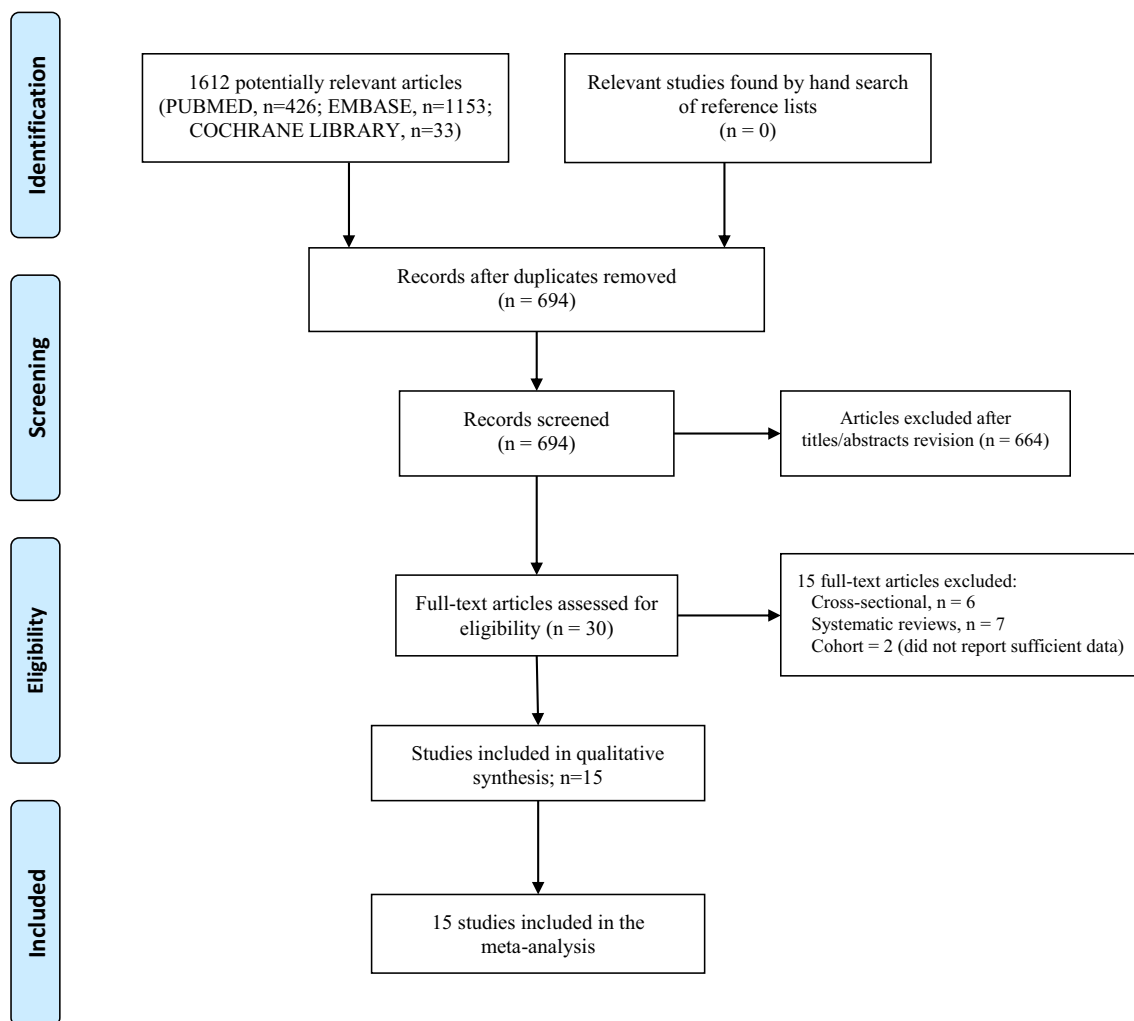


Fig. 1 PRISMA flow diagram

It was not possible to stratify the results according to renal failure status, since only two studies assessed the risk of tendinopathy associated with fluoroquinolones in patients with renal insufficiency, one considering a different outcome from the other (ATR vs. AT) [30, 35]. One identified an increased risk of AT (OR 20.0, 95% CI 2.7–149) and the other increased risk of ATR (RR 1.65, 95% CI 1.32–1.84) [30, 35].

The risk of AT did not significantly change when the analysis was conducted according to the methodological quality of the studies (Table 2). The risk of ATR remained increased, with statistical significance, among the studies with “moderate” methodological quality. Among the studies with “good” methodological quality, the risk of ATR became statistically non-significant but associated with high heterogeneity (OR 1.94, 95% CI 0.76–4.99, $p = 0.147$, $I^2 = 91.0\%$). The risk of ATD became statistically non-significant when only studies with “poor” methodological quality were considered (OR 3.04, 95% CI 0.68–13.52, $p = 0.144$, $I^2 = 72.0\%$).

No statistically significant result was identified among the studies evaluating the risk of ATR more than 30 days after the fluoroquinolone prescription (OR 1.72, 95% CI 0.70–4.25, $p = 0.238$, $I^2 = 18.2\%$) (Table 2). The initial ATR risk estimate did not significantly change among the studies considering a 30-day at-risk window after the fluoroquinolone prescription.

When comparing fluoroquinolone users with non-users, the initial increased risk estimates remained statistically significant (Table 2). Only one study compared fluoroquinolones with an active comparator for both ATR and AT risk analyses (Table 2). The initial ATD risk estimate did not significantly change when the analysis was stratified by different comparators.

The stratification of the risk estimates according to the types of fluoroquinolones was only possible for the outcome ATR (Table 2). Ofloxacin and norfloxacin were associated with an increased risk of ATR, but not ciprofloxacin and levofloxacin. For AT and ATD, no sufficient data was available to stratify the results according to the type of fluoroquinolone.

Table 1 Characteristics of the studies included

Study	Study design	Population	Studied interventions	
			Intervention/cases	Control
van der Linden et al. 1999	Retrospective cohort study	Patients, aged at least 15 years old, living in The Netherlands, whose data was collected from 41 general practices in the period from January 1, 1995 until December 31, 1996. All individuals treated with either fluoroquinolones, amoxicillin, trimethoprim, cotrimoxazole, or nitrofurantoin were followed from the first day of treatment until the outcome of interest, death, transfer to another practice, or end of the study period, whichever came first.	Fluoroquinolone	Reference group: amoxicillin, trimethoprim, cotrimoxazole, or nitrofurantoin
Sode et al. 2007	Retrospective cohort study	Patients living at Funen County, Denmark, with data on Achilles tendon ruptures and fluoroquinolones, tetracyclines, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycosides, and glycopeptides use retrieved from three population-based databases which included information on residents in primary and secondary care during the period 1991–1999.	Fluoroquinolone	Reference group: tetracyclines, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycosides, or glycopeptides
Barge-Caballero et al. 2008	Retrospective cohort study	Adult patients, aged at least 18 years old, submitted to heart transplantation in a Spanish hospital and prescribed with fluoroquinolones, with data collected from August 1995 to September 2006	Levofloxacin	Levofloxacin non-use
Hori et al. 2012	Retrospective cohort study	Patients prescribed with fluoroquinolones or cephalosporins in Japan from April 1996 to December 2009 were identified and considered for inclusion in the study. Diagnosis of tendon disorder after fluoroquinolone or cephalosporin administration was identified by an automatic search of the hospital medical records.	Fluoroquinolone	Cephalosporin
Daneman et al. 2015	Retrospective cohort study	The Ontario Registered Persons Database was used to identify adult patients from Ontario, Canada, turning age 65 between April 1, 1997, and March 31, 2012 were followed until primary outcome, death or end of follow-up course.	Fluoroquinolone	Amoxicillin
Humbyrd et al. 2018	Retrospective cohort study	Patients with end-stage renal disease (ESRD) using Medicare parts A and B (USA) as their primary health insurance between January 1, 1999, and December 31, 2013. All patients were studied from their development of ESRD until death, end of Medicare primary coverage, or end of the study.	Fluoroquinolone	Fluoroquinolone non-use
Jupiter et al. 2018	Retrospective cohort study	Adult patients aged 18 to 90 years with at least one index prescription of fluoroquinolone between January 1, 2009, and June 30, 2014. Data was retrieved from Clinformatics DataMart, USA. Propensity scores were used to match fluoroquinolone users with other antibiotic users and antibiotic non-users.	Fluoroquinolone	Fluoroquinolone non-use
van der Linden et al. 2002	Case-control study	Patients aged 18 years or over who had received a fluoroquinolone and had clinical data on IMS Health database, UK (July 1, 1992 to June 30, 1998). Potential cases were identified by reviewing patient profiles and clinical data and excluded tendon disorders due to direct trauma. A group of 10,000 control patients from the study cohort was randomly selected.	Diagnosis of ATR, AT, and ATD	–
van der Linden et al. 2003	Case-control study	Data was retrieved from the General Practice Research Database, UK, considering a period from 1988 to 1998. Cases were defined as all persons who had an Achilles tendon rupture and who had at least 18 months of valid medical history before the index date. A group of	Diagnosis of ATR	–

Table 1 (continued)

Study	Risk period (days)	Age mean (years)	Female (%)	Patients (n, ID/C)	Outcomes/fluoroquinolone use (n, ID/C)*	M.Q.
Seeger et al. 2006	Case-control study	50,000 randomly selected patients with at least 18 months of valid history who were assigned a random date as index date was included as control.		Study included data from patients registered at the Ingenix Research Database, USA. Cases were persons with both a diagnosis and procedure (either surgical or non-surgical) related to ATR occurring between January 1, 1997, and June 30, 2001. Controls were randomly sampled persons by calendar day with replacement in a ratio of 20:1.	Diagnosis of ATR and a procedure for ATR.	–
Corrao et al. 2006	Case-control study	Study was performed by retrieving data from automated health databases from the Region of Lombardia, Italy. Cases were defined as patients aged 18 years or over who had a hospital discharge diagnosis of non-traumatic tendinitis in 2002–2003. Controls were randomly selected among those eligible for inclusion in the study in a ratio of 5:1.			Diagnosis of ATR and ATD	–
Wise et al. 2012	Case-control study	Data was retrieved from The Health Improvement Network (THIN) database, UK. All subjects who had a first-time diagnosis of Achilles tendinitis between January 1, 1986, and November 31, 2009 were identified. For each subject, a case period as the 30 days immediately before the diagnosis date, and a control period as the 30 days 1 year before the diagnosis date were defined.			Diagnosis of AT	–
Nyyssönen et al. 2018	Case-control study	Data was collected from the Finnish Hospital Discharge Register. Cases were defined as patients admitted in hospital with Achilles tendon rupture during the years 1998–1999. Randomly selected age- and sex-matched controls from the Finnish population registry were used for comparison.			Diagnosis of ATR	–
Morales et al. 2018	Nested case-control study	Adults aged at least 18 years or over identified in THIN database, UK, between January 1, 1999, and December 31, 2015. The date of the first event occurring after cohort entry was the index date for case subjects. Controls were randomly selected and matched to cases in a ratio of 4:1.			Diagnosis of ATR	–
Persson and Jick, 2019	Nested case-control study	The study included all patients who were registered in the UK Clinical Practice Research Datalink (CPRD) Gold, between 1990 and 2015. Cases were patients with a diagnosis of tendon rupture identified using Read codes. Up to 4 controls were matched to each case.			Diagnosis of ATR	–
van der Linden et al. 1999	30 days	Fluo 53.0 Ref 45.0	Fluo 63.9 Ref 71.4	1841/9406	AT 4/4	7
Sode et al. 2007	90 days	44.2	25.0	28,262/401080	ATR 5/21	6
Barge-Caballero et al. 2008	30 days	58.8	22.1	149	ATD 14	3
Hori et al. 2012	30 days	NR	NR	17,147/38517	ATD 14/5	4
Daneman et al. 2015	30 days	Fluo 65 Amox 65	Fluo 51.4 Amox 51.1	657,950/1,086,410	ATD 23028/14123	6
Humbyrd et al. 2018	NR	NR	55.0	NR	ATR: NR	5
Jupiter et al. 2018	30 days	Fluo 43.5 Non-U 43.8 Ref 43.7	Fluo 52.4 Non-U 52.3 Ref NR	576,318/576,318/631304*	ATD 550/323/551*	8

Table 1 (continued)

van der Linden et al. 2002	30 days	Cases 56.0 Controls: NR	Cases 61.0 Controls: NR	742/10,000	ATR 3/124 AT 43/298 ATD 49/298 ATR 14/100	7
van der Linden et al. 2003	30 days	Cases 48 Controls 47 NR	Cases 30.6 Controls 52.0 NR	1367/50,000	ATR 29/448 ATR 6/10 ATD 160/432 AT 267/77	7
Seeger et al. 2006	90 days	Cases 55.9 Controls: NR	Cases 63.5 Controls: NR	947/18,940		8
Corrao et al. 2006	30 days	Cases 46.5 Controls: NR	Cases 63.5 Controls: NR	22,194/104,906		7
Wise et al. 2012	30 days	Cases 44.1 Controls: NR	Cases 46.5 Controls: NR	28,907/28,907		7
Nyyssönen et al. 2018	NR	Cases 61.6 Controls 61.3 NR	21.0 Cases 38.8 Controls 39.0 Cases 35.9 Controls 36.3	1118/1118 4836/18356 3802/14002	ATR 42/21 ATR 67/82 ATD 111/236 ATR 41/19 ATD 85/178	6
Morales et al. 2018	30 days					8
Persson and Jick, 2019	30 days					7

ID, intervention drug; *C*, control; *M.Q.*, methodological quality assessment; *ATD*, any tendon disorder; *AT*, Achilles tendinitis; *ATR*, Achilles tendon rupture; *F.luo*, fluoroquinolone; *Ref.*, reference group; *Amox*, amoxicillin; *NR*, not reported; *ESRD*, end-stage renal disease; *USA*, United States of America; *UK*, United Kingdom; *THIN*, The Health Improvement Network; *CPRD*, Clinical Practice Research Datalink

Among the results identified for the three outcomes, the “one-study removed” analysis indicates that the overall risk estimates did not significantly change when each study was individually removed from the meta-analysis (Supplemental Figs. 1, 2, and 3).

Publication bias

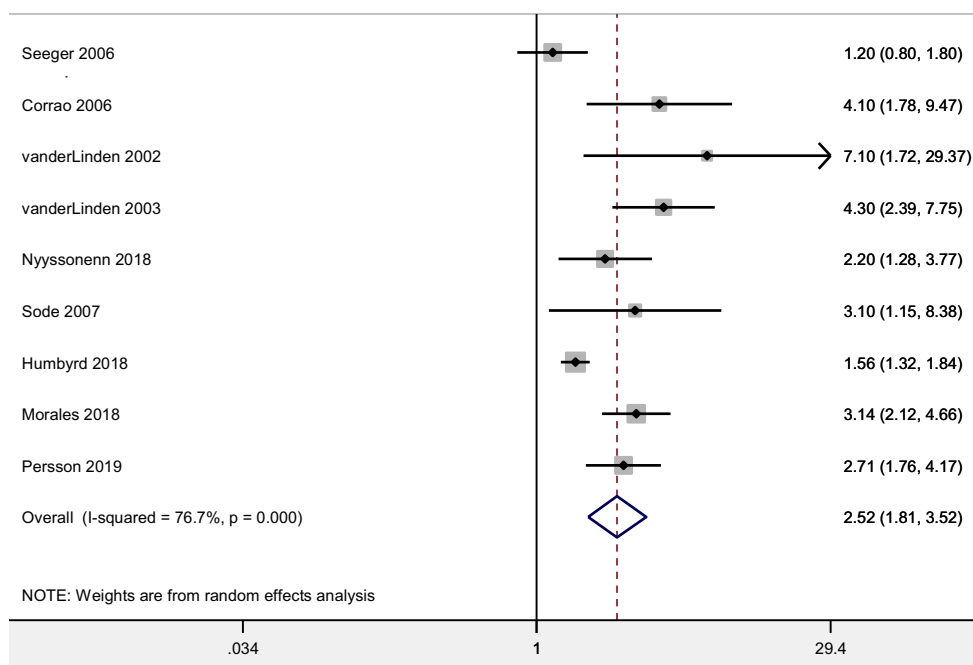
Egger’s asymmetry test was not statistically significant for the outcomes AT and ATD. Evidence of small-study effects was identified among the studies assessing the risk of ATR ($p = 0.024$). Subjective evaluation of publication bias was based on the visual inspection of the funnel plot. Most studies did identify increased risk estimates for the three outcomes, although studies with less precise risk estimates have been identified as well (Supplemental Figs. 4, 5, and 6).

Discussion

The benefits of antibiotic therapy with systemically administered fluoroquinolones are well recognized. However, the use of this class of antibiotics is associated with rare but serious adverse effects that may result in significant impairment of patients, namely tendinitis and tendon rupture, particularly of the Achilles tendon. Despite being known for some time, the risk of tendon injuries associated with fluoroquinolones has been continuously investigated by the scientific community, mainly through the conduction of several pharmacoepidemiological studies [9, 13, 15]. Moreover, EMA and US FDA have recently recommended reinforcing the restriction of the use of fluoroquinolones due to their disabling and potentially permanent adverse effects involving muscles, tendons or joints, and the nervous system [6, 8, 9]. This systematic review and meta-analysis identified increased risks of ATR, AT, and ATD associated with fluoroquinolones. The findings are in line with the current knowledge about the safety profile of these drugs.

The mechanism of tendon injury associated with fluoroquinolones is not well clarified but appears to be multifactorial and may result from direct toxicity and degenerative changes in collagen fibers [10, 28]. It was demonstrated that fluoroquinolones can enhance matrix metalloproteinase expression and the inhibition of both fibroblasts proliferation and the synthesis of the matrix, which can result in the development of tendinopathies [38, 39]. A study conducted in dogs assessed the hypothesis of fluoroquinolones having chelate properties [40]. The findings suggested that fluoroquinolone-induced toxic effects on connective tissues may be due to the magnesium-antagonistic effects of these antibiotics [40]. Additionally, there is evidence supporting that fluoroquinolone-associated tendinopathy may result from oxidative stress induction [41].

Fig. 2 Forest plot of the risk of ATR associated with fluoroquinolones



According to this meta-analysis, patients aged ≥ 60 years old are at an increased risk for ATR and AT. These results are in line with previous warnings issued by regulatory authorities, which recommended that fluoroquinolones should be used with special caution in older patients [6, 8]. The influence of concomitant use of corticosteroids on the risk of tendon injury in patients treated with fluoroquinolones was also evaluated in some pharmacoepidemiological studies. According to the sensitivity analysis, it was observed an increase in risk sizes between 4.68-fold (ATD) and 14.72-fold (ATR) for the three outcomes among patients simultaneously using fluoroquinolones and corticosteroids, compared with the initial estimates. Therefore, the combination of these drugs should be avoided, as previously recommended by drug regulatory agencies [6, 8].

The observational studies included in this meta-analysis presented varying demographic characteristics and methodologies. Two cohort studies investigating the risk of tendon injuries associated with fluoroquinolones included heart transplanted patients and end-stage renal disease patients [30, 32]. It has been suggested that individuals submitted to organ transplant and patients with renal insufficiency are at greater risk of suffering tendon injuries, particularly Achilles tendon ruptures and tendinitis [30, 32]. Gender distribution of the population samples was significantly different among the studies. There is conflicting evidence regarding the influence of patients' sex in the risk of tendon injuries. There are studies suggesting that one specific gender, male or female, may be a risk factor for tendon injury, while others have not [33–35]. Although renal impairment is a known risk factor for tendon injury, it was not possible to conduct a sensitivity analysis due

to the scarcity of data. Only two studies assessed the risk of tendinopathy associated with fluoroquinolones in patients suffering from renal insufficiency, but considered two different outcomes (ATR vs. AT), precluding a quantitative synthesis of the results [30, 35].

Most of the studies assessing the risk of ATR due to fluoroquinolones included in this meta-analysis considered risk-window periods of 30 days. Yet, two studies assumed risk-window periods of 90 days and two other studies did not report the length of time during which patients were considered to be at risk. The sensitivity analysis demonstrated that the risk of ATR remained statistically increased when the analysis was restricted to studies considering a 30-day risk window, but not among those considering a risk period of 90 days. A systematic review of case reports concluded that 40% of the cases of tendon rupture were diagnosed within the first 6 days after treatment initiation, while the mean time to onset was estimated at 26 days [2]. Additionally, half of the cases of tendinitis occurred within the first 6 days of treatment and the mean time to onset of symptoms after the initiation of fluoroquinolone therapy was 18 days [2]. The studies included in this meta-analysis assessed the risk of AT and ATD within a risk period of 30 days.

The control groups used by the observational studies included in this meta-analysis differed as well. Although non-use of fluoroquinolones was the most common comparator group, four cohort studies used active controls [15, 27–29]. Noteworthy, it is possible that observational studies using fluoroquinolone non-users as control groups may have been affected by confounding-by-indication, namely if the infections were causally related to the tendon injuries

Table 2 Odds ratios (OR) and 95% CIs of tendon injury associated with fluoroquinolones

	Studies <i>n</i>	Odds ratio (OR)		Heterogeneity <i>I</i> ²
		95% CI	<i>p</i>	
Outcome				
Achilles tendon rupture	9	2.52 (1.81–3.52)	< 0.001	76.7%
Achilles tendinitis	3	3.95 (3.11–5.01)	< 0.001	0.0%
Any tendon disorders	8	1.98 (1.62–2.43)	< 0.001	84.5%
Age				
Achilles tendon rupture				
< 60 years	3	1.71 (0.92–3.17)	0.088	16.0%
≥ 60 years	4	3.61 (1.21–10.79)	0.022	83.8%
Achilles tendinitis				
< 60 years	2	1.35 (0.87–2.10)	0.180	31.8%
≥ 60 years	2	5.08 (1.93–13.33)	0.001	89.9%
Any tendon disorders				
< 60 years	4	1.28 (1.11–1.49)	0.001	47.4%
≥ 60 years	4	2.17 (1.48–3.20)	< 0.001	94.6%
Corticosteroid use				
Achilles tendon rupture				
Yes	5	14.72 (8.83–24.53)	< 0.001	0.0%
No	4	2.27 (1.21–4.27)	0.011	59.2%
Achilles tendinitis				
Yes	1	9.10 (4.60–18.00)	< 0.001	–
No	1	3.20 (2.31–4.43)	< 0.001	–
Any tendon disorders				
Yes	4	4.68 (2.32–9.45)	< 0.001	84.1%
No	2	1.56 (1.22–1.99)	< 0.001	54.8%
Study designs				
Achilles tendon rupture				
Case controls	7	2.76 (1.86–4.08)	< 0.001	71.3%
Cohorts	2	1.83 (1.04–3.24)	0.037	43.9%
Achilles tendinitis				
Case controls	2	3.85 (2.75–5.37)	< 0.001	41.6%
Cohorts	1	3.70 (0.90–15.16)	0.069	–
Any tendon disorders				
Case controls	4	1.83 (1.46–2.30)	< 0.001	65.6%
Cohorts	4	2.18 (1.57–3.02)	< 0.001	87.4%
Methodological quality assessment				
Achilles tendon rupture				
Good methodological quality	2	1.94 (0.76–4.99)	0.167	91.0%
Moderate methodological quality	6	3.07 (2.36–3.98)	< 0.001	0.0%
Poor methodological quality	1	1.56 (1.32–1.84)	–	–
Achilles tendinitis				
Good methodological quality	0	–	–	–
Moderate methodological quality	3	3.95 (3.11–5.01)	< 0.001	0.0%
Poor methodological quality	0	–	–	–
Any tendon disorder				
Good methodological quality	2	1.68 (1.49–1.90)	< 0.001	0.0%
Moderate methodological quality	4	2.08 (1.60–2.70)	< 0.001	86.1%
Poor methodological quality	2	3.04 (0.68–13.52)	0.144	72.0%

Table 2 (continued)

	Studies <i>n</i>	Odds ratio (OR)		Heterogeneity <i>I</i> ²
		95% CI	<i>p</i>	
Type of fluoroquinolone				
Achilles tendon rupture				
Ofloxacin	3	2.84 (1.31–6.19)	0.008	0.0%
Levofloxacin	1	0.60 (0.35–1.04)	0.069	–
Ciprofloxacin	3	1.34 (0.91–1.97)	0.138	0.0%
Norfloxacin	2	3.02 (1.32–6.93)	0.039	0.0%
Risk window				
Achilles tendon rupture				
≤ 30 days	5	3.32 (2.59–4.28)	< 0.001	0.0%
> 30 days	2	1.72 (0.70–4.25)	0.238	66.7%
NR	2	1.68 (1.27–2.21)	< 0.001	30.0%
Achilles tendinitis				
≤ 30 days	3	3.95 (3.11–5.01)	< 0.001	0.0%
> 30 days	0	–	–	–
NR	0	–	–	–
Any tendon disorder				
≤ 30 days	8	1.98 (1.62–2.43)	< 0.001	84.5%
> 30 days	0	–	–	–
NR	0	–	–	–
Comparator				
Achilles tendon rupture				
Fluoroquinolone non-users	8	1.58 (1.27–1.96)	< 0.001	0.0%
Active comparator	1	3.10 (0.13–72.34)	0.481	–
Achilles tendinitis				
Fluoroquinolone non-users	2	3.77 (1.48–9.57)	0.005	0.0%
Active comparator	1	3.70 (0.003–483.70)	0.718	–
Any tendon disorder*				
Fluoroquinolone non-users	7	1.88 (1.57–2.24)	< 0.001	41.4%
Active comparator	2	1.18 (1.03–1.35)	0.016	0.0%
Data source				
Achilles tendon rupture [#]	7	2.28 (1.57–3.30)	< 0.001	74.2%
Achilles tendinitis	3	3.95 (3.11–5.01)	< 0.001	0.0%
Any tendon disorders [§]	7	2.06 (1.65–2.56)	< 0.001	85.2%

*One study (Jupiter et al. 2018) assessed the risk of ATD associated with fluoroquinolones vs. non-users and vs. active comparator

[#] van der Linden et al. (2003) (MQ score 7) and Persson and Jick (MQ score 7) were removed from the analysis because their data source overlapped with van der Linden et al. (2002) (MQ score 7) and Morales et al. (2018) (MQ score 8), respectively (Note that although van der Linden et al. (2002) and van der Linden et al. (2003) both have the same MQ score, the 2003 publication was removed because it is the most recent one)

[§] Persson and Jick was removed from the analysis because the data source overlapped with Morales et al. (2018)

events [15]. Therefore, some authors established comparisons with active controls. Yet, the studies included in this meta-analysis used different antibiotics as active controls. Some compared fluoroquinolone users with a composite of multiple antibiotics, such as nitrofurantoin, amoxicillin, tetracyclines, and trimethoprim, which are mostly indicated to treat mild urinary tract infections [15, 27, 28]. Two

studies used antibiotics as negative controls in order to assess the specificity of the association between fluoroquinolones and tendinopathy [9, 15]. Nevertheless, the risk of tendon injuries seems to increase due to fluoroquinolones use, regardless of the chosen comparator.

Only three out of the 15 studies were assessed as having “good” methodological quality. Most of them did not take into

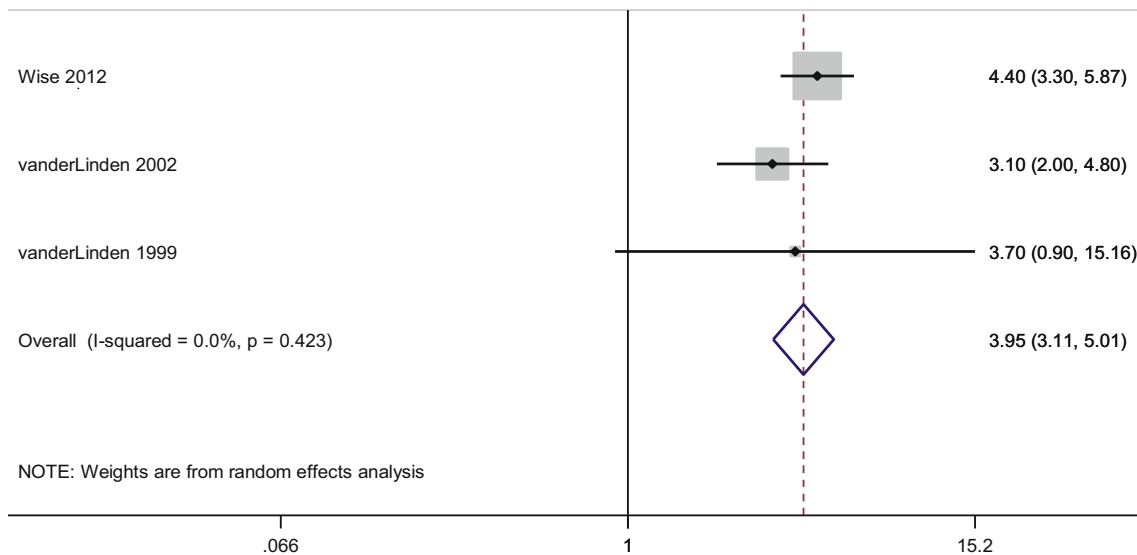


Fig. 3 Forest plot of the risk of AT associated with fluoroquinolones

account all the factors known to modify the risk of tendon injuries, such as trauma, transplant, obesity, diabetes mellitus, kidney failure, or recreational sports. The reduced risk of confounding was deemed to be important in order to attain higher methodological scores. These may have been the reason why previous systematic reviews using the same methodological quality assessment tool awarded higher scores to some of the

studies that were also included in this systematic review and meta-analysis [10, 12].

The systematic review and meta-analysis conducted by Yu and colleagues (2019) have identified an increased risk of tendinopathy associated with fluoroquinolones as well [12]. However, some methodological approaches which could strengthen the analysis were not considered by the

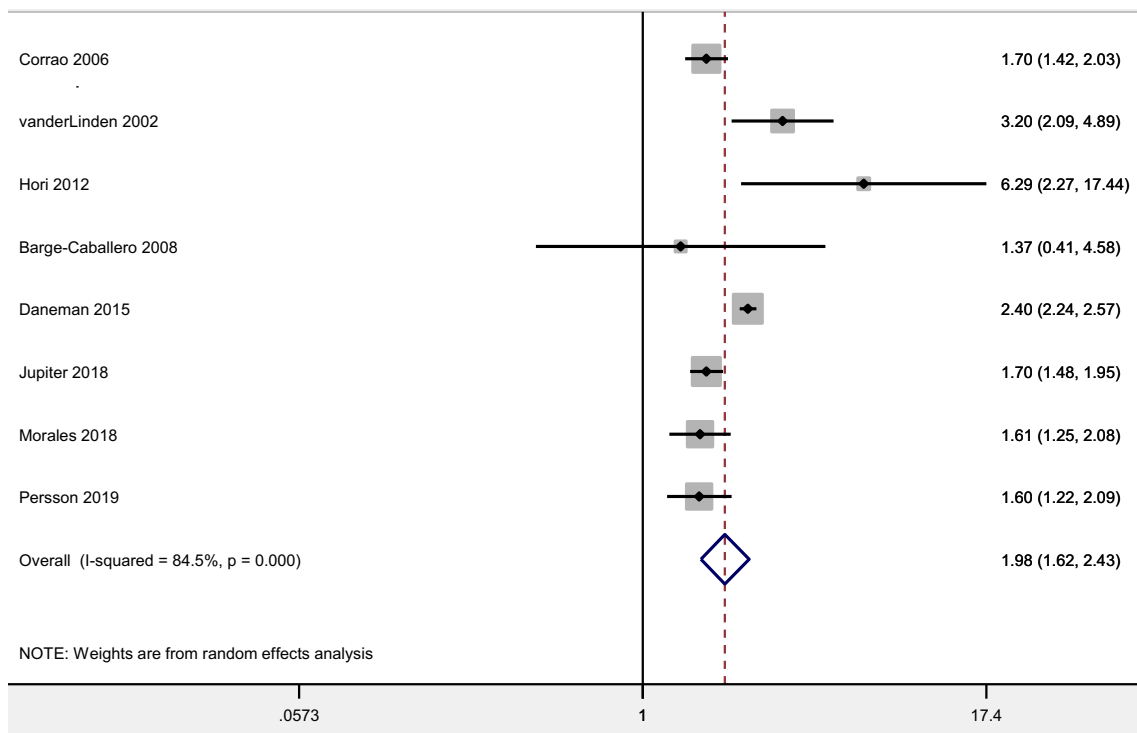


Fig. 4 Forest plot of the risk of ATD associated with fluoroquinolones

authors, namely the stratification of the results according to different outcomes (AT, ATR, or ATD), study designs and methodological quality scores and risk windows. Furthermore, some studies have not been included in the meta-analysis, and the results of a retrospective cohort study considering both tendon and joint disorders as an outcome were integrated into the risk estimate analysis, potentially increasing the confounding among the final results [12].

Systematic reviews and meta-analyses of non-experimental studies should be designed to explore eventual sources of heterogeneity among the risk estimates rather than to find evidence of causative associations [18]. With the exception of the subgroup analyses according to different comparators, all the risk estimates were associated with significant between-studies heterogeneity. These observational studies were conducted and published over two decades. Therefore, these results should be taken with precaution due to the inherent methodological limitations faced when comparing studies conducted from different databases and associated with varying size and precision [9]. Moreover, besides the different demographics previously described, there are additional methodological characteristics of the studies included in this meta-analysis which may not be entirely comparable, namely the endpoint' definition and methods of diagnosis of tendon injuries, the validation of fluoroquinolones' exposure, and the controlling for confounding variables.

There are additional limitations which should be addressed. Most of the studies did not detail the risk estimates by the type of fluoroquinolone and no sufficient data was provided in order to assess if there is a dose-response relationship associated with the development of tendon injuries. Future research should address these issues, since clinicians could benefit from such information in order to minimize and prevent the risk of these adverse effects [31]. Studies most frequently stratified their results according to patient's age and concomitant use of corticosteroids. However, additional risk factors for tendon injuries were not considered, precluding additional sensitivity analyses. Only three bibliographic databases were searched. Since tendon injuries have been associated with fluoroquinolones for so long, studies published in journals indexed elsewhere may not have been identified through this search strategy. A previous systematic review considered evidence from case series, cross-sectional, and surveillance pharmacovigilance studies using spontaneous reporting when assessing the risk of tendon injuries associated with fluoroquinolones. However, the methodological quality of such studies was considered to be very low by the authors [10]. Therefore, in order to reduce the risk of bias, other designs than case control and cohorts were not considered for inclusion in this meta-analysis.

Conclusion

The results of this systematic review and meta-analysis suggest that fluoroquinolones increase the risk of tendon injuries, which is in line with the current knowledge. The use of these antibiotics should be restricted since several subgroups of patients are at increased risk to develop serious tendon injuries, particularly older patients and individuals under concomitant treatment with corticosteroids. Moreover, patients should discontinue the treatment with fluoroquinolones and seek help from healthcare professionals when they start feeling tendon pain and inflammation.

Author contribution Carlos Alves conceived and designed the study, performed research, analyzed data, and wrote the paper. Diogo Mendes and Francisco Batel Marques conceived the study and wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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