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The association between oral fluoroquinolone use and the development of retinal detachment: a systematic review and meta-analysis of observational studies

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Abstract

Background: Several observational studies were published investigating the association between oral fluoroquinolone use and the development of retinal detachment; however, the findings are not concordant. This study is a meta-analysis of the existing literature and estimates the overall absolute risk of such an event.

Methods: Electronic databases were searched for observational studies on the association between oral fluoroquinolone and retinal detachment up to August 2014. Studies that did not meet the criteria for meta-analysis were narratively reviewed. Cases of retinal detachment during current fluoroquinolone use were also extracted for absolute risk calculation.

Results: Seven observational studies were included. Three (case-control and self-controlled case series studies) were eligible for meta-analysis and four (cohort studies) were narratively reviewed. The rate ratio of the case-control studies was 1.82 (95% CI 0.67-4.93), I^2=96% and the incidence rate ratio of the self-controlled case series was 1.03 (95% CI 0.84-1.27), I^2=36%. Three of the four cohort studies found no significant association between oral fluoroquinolone use and the development of retinal detachment. The pooled absolute risk of retinal detachment whilst on current oral fluoroquinolone treatment is estimated to be 4.85 per 1,000,000 prescriptions (95% CI 0.78 – 8.91).

Conclusion: The findings of this systematic review and meta-analysis do not support an association between oral fluoroquinolone use and the development of retinal detachment. Given the low absolute risk, such an event would be rare if there were an association. The current prescribing practice for fluoroquinolones should not be altered because of a previously suggested potential risk of retinal detachment.

Introduction

Etminan *et al.*[1] reported a significant association between the current use of oral fluoroquinolones (FQ) and the development of retinal detachment (RD) (i.e. an RD event occurring within the prescription period of FQ). This study caused the US, Canadian and European regulatory authorities to place FQ on their alert list[2-4] and since then more observational studies have been published. This systematic review and meta-analysis evaluates these observational studies and the potential for increased risk of RD with oral FQ use.

Method

A systematic literature search was conducted using keywords, MeSH and Emtree terms. Records were retrieved from databases including Pubmed, CINAHL and EMBASE in August 2014.The search terms included were fluoroquinolones AND (retinal detachment OR retinal*). This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[5] and the Meta-analysis of Observational Studies in Epidemiology[6] to ensure clear and comprehensive reporting.

Inclusion and exclusion criteria

Observational studies that investigated the association between FQ use and the development of RD were included. Animal studies were excluded.

Quality assessment

The included studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) as recommended by the Cochrane Collaboration.[7] CSLC and LYLW

independently reviewed and scored each of the studies. Study quality is indicated by the number of stars with a maximum allocation of 9 stars.

Data extraction

Data on the outcome of interest, which is the risk or odds of developing RD whilst on FQ treatment, were extracted for analysis. Statistics presenting the period up to 10 days from the first day of prescription were selected. Studies where such statistics could not be extracted or included in the meta-analysis were summarised in the narrative review.

Statistical analysis

A random-effects model[8] was used in the meta-analysis to account for heterogeneity between studies. Statistical analyses were conducted using Review Manager 5.2 (Cochrane Collaboration, 2012).

The number of RD cases that occurred whilst on FQ treatment was extracted from the original list of articles and the absolute risk was estimated using a method previously described.[9] The 95% CI was calculated using the Wilson score interval.[10] The analysis was performed using SAS 9.3 (SAS Inc, USA).

Results

A total of 695 citations were retrieved from the literature search. CSLC and LYLW screened and reviewed relevant articles independently. Seven observational studies were relevant (Figure 1). The quality of the methodology was assessed and the results are presented in Table 1 and 2.

Case-control

Two case-control studies were included in the meta-analysis. Etminan *et al.*[1] reported a positive association between FQ use and the development of RD in a cohort, nested among patients who had visited an ophthalmologist, using The British Columbia Linked Health Database.[11] Cases were defined as those with an RD-related procedure 14 days after the diagnosis date. Cases in FQ users and non-FQ users were compared and the rate ratio (RR) was adjusted for sex, previous history of cataract surgery, myopia, diabetes, number of visits to ophthalmologist, and number of prescription drugs used. In an attempt to replicate the study of Etminan *et al.*, Fife *et al.*[12] conducted a similar analysis in the US using the MarketScan Commercial Claims and Encounters and the Optum ClinFormatics database. The results are presented as Fife 2014 (CCAE-CC) and Fife 2014 (Optum-CC) respectively in the meta-analysis. Meta-analysis of the three databases did not show a significant association with an odds ratio (OR) of 1.82(95% CI 0.67-4.93), I^2=96% (Figure 2). There was no significant change to the RR [1.25(95%CI 0.95-1.65)], I^2 of 0%, following removal of Etminan *et al.* study from the sensitivity analysis.

Self-controlled case series

Two studies using four different databases were included in this meta-analysis. Neither study found a significant association between oral FQ use and the development of RD. Of these, one study[9] was done using the Hong Kong Clinical Data Analysis and Reporting System (CDARS) and Taiwan National Health Insurance Research Database (NHIRD). The incident RR (IRR) was adjusted for age, history of diabetes and cataract surgery. The meta-analysis results of Hong Kong and Taiwan database are presented as Chui 2014 (HK) and Chui 2014 (TW),

respectively. Fife *et al.*[12] also conducted a self-controlled case series study in the US. Unlike the case-control analysis, ophthalmology visits were not an inclusion criterion. Cases were defined as those with RD 30 days after the beginning of FQ exposure. The RRs are presented as Fife 2014 (CCAE-SCCS) and Fife 2014 (Optum-SCCS). Meta-analysis of the four databases gave a statistically non-significant IRR of 1.03(95% CI 0.84-1.27), I^2=36% (Figure 3).

Narrative review

Four cohort studies[13-16] were also included in this review. However, their study designs were very different and therefore, are not appropriate for meta-analysis.

Pasternak *et al.*[13] used the Central Person Register to identify adults living in Denmark from 1997 to 2011. RD cases were defined as incident diagnosis of RD with a related procedure performed within 14 days of the diagnosis date. They reported 5 cases of RD among current FQ users (1-10 days post first day of treatment) with a corresponding RR of 1.29(95% CI 0.53-3.13) compared to non-FQ use. RR for recent use (11-30 days) was 0.97(95%CI 0.46-2.05), past use (31-60 days) was 1.37(95% CI 0.80-2.35) and distant use (61-180 days) was 1.27(95% CI 0.93-1.75). The crude incidence rate was 25.3 cases per 100,000 person-years in current users. The authors concluded that oral FQ use was not associated with an increased risk of RD.

Kuo *et al.*[14] identified FQ and amoxicillin users from the NHIRD between 1998 and 2010. They compared FQ users with amoxicillin users and estimated an adjusted hazard ratio (HR) of 2.07(95% CI 1.45-2.96) in a 90 day follow-up period. The adjusted HR was 10.68(95% CI 3.28-34.82) for ciprofloxacin, 2.41(95% CI 0.76-7.68) for levofloxacin, 2.00(95% CI 1.06-3.79) for norfloxacin, 1.17(95% CI 0.59-2.31) for ofloxacin and 1.48(95% CI 0.25-8.84) for lomefloxacin. The median interval between the beginning of the FQ prescription and the index date of RD

diagnosis was 35.5 days. RD cases were defined as diagnosis with RD within 90 days of the follow-up period. The authors concluded that oral FQ was associated with subsequent occurrence of RD. The FQ risk was independent of age, sex, diabetes, indications for antimicrobials, and underlying ophthalmic conditions.

Kapoor *et al.*[15] examined whether there was an associated increase in subsequent RD and symptomatic retinal breaks and oral FQ. They included adult residents of Olmsted County, Minnesota, who were prescribed oral FQ from 2003 to 2011, from the Rochester Epidemiology Project. Patients prescribed oral FQ were compared to those prescribed oral macrolide and β-lactam antibiotics. Cases were defined as procedures recorded within 1 year of the first prescription. RD repair procedures were performed within 365 days of the first prescription in 0.03% (95% CI 0.01-0.06) of the FQ group, 0.02% (95% CI 0.01-0.03) of the macrolide group, and 0.03% (95% CI, 0.02-0.05) of the β-lactam group (P>0.05). There were no significant differences in treatment rates within 7, 30, and 90 days of the first prescription between the groups. Kapoor *et al.*[15] concluded that oral FQ use was not associated with an increased risk of RD or symptomatic retinal breaks in their study.

Eftekhari *et al.*[16] investigated whether oral FQ use would increase the risk of RD and retinal tear in the UK using The Health Improvement Network database (THIN). Patients prescribed FQ between 1994 and 2012 were compared with those prescribed β-lactam. Cases were defined as those with a procedure related to retinal break during the observation period. No case was observed 7 days after the prescription among FQ users; therefore it was not possible to estimate the HR. The adjusted HR was 0.78 (95% CI 0.02-4.74) 30 days after prescription, 1.26 (95% CI 0.40-3.06) at 90 days, and 1.35 (95% CI 0.85-2.06) at 365 days. A sensitivity analysis included only cases with a retinal break diagnosis within 30 days of the procedure with no

findings of increased risk. Eftekhari *et al.*[16] concluded that no increased risk of retinal break was observed using the THIN database.

Absolute risk of RD whilst on current FQ treatment

The absolute risks of developing RD whilst on current FQ treatment among the included studies are presented in Table 2. No RD cases in current FQ users were reported in Kapoor *et al.*[15] and Eftekhari *et al.*[16] The total number of FQ prescriptions was not reported by Etminan *et al.*[1] and Fife *et al.*;[12] therefore the absolute risk cannot be estimated. The pooled absolute risk of the five database analyses is estimated to be 4.85 per 1,000,000 prescriptions (95% CI 0.78–8.91) (Figure 4).

Discussion

The results of this meta-analysis do not support an association between oral FQ use and the development of RD. Three of the four cohort studies[13, 15, 16] in the narrative review do not support an association either. Although two studies[1, 14] reported significant results, they do not concur. Etminan *et al.*[1] reported that the effect of FQ on RD is of an acute nature, i.e. current FQ users. However, Kuo *et al.*[14] report that the median interval between the prescription and the index date of RD diagnosis was 35.5 days, i.e. not acute.

Farioli and Kriebel[17] estimated the incidence rate of RD in the study of Kuo *et al.*[14] to be 218.5 per 100,000 patient-years with a mean age of 47 years. The incidence of RD is age-dependent with <19–27 cases per 100,000 person-years in the sixth decade of life[18]. They questioned the validity of the findings of Kuo *et al.*since the study's incidence rate was much higher with a lower mean age. This discrepancy may be explained by significant differences in

the RD case definition in the study of Kuo *et al.*,[14] where procedure codes were not required to confirm RD cases.

It is worth noting that the RR reported by Etminan *et al.*[1] was much higher than that reported by other included studies. Fife *et al.*[12] replicated the analysis using two datasets from two databases and estimated an OR of almost 1. Since both studies had similar settings, it is unclear why this discrepancy occurred. However, differences in clinical practice and the coding system may account for this. Fife *et al.*[12] validated their results with additional analyses; however, they did not find a significant association, which concurs with the findings of this meta-analysis.

The meta-analysis for self-controlled case series gave an RR of almost 1 [1.03(95% CI 0.84-1.27)] with moderate variability among the studies from different countries (I^2=36%). With such a narrow confidence interval around 1, the results clearly reject an association between the use of FQ and RD. Finally, it is important to note that the pooled absolute risk of developing RD whilst on FQ treatment was minimal (Figure 4). Such an event would be very rare if there were an association.

Strength and limitation

Disease codes such as ICD-9 were used to identify cases among the included studies. Although the case definitions varied, all (except Kuo *et al.*[14]) included a procedure code to confirm the RD case. The codes of the included databases have been validated in other settings,[19-21] thus ensuring the quality of the analysed data. In addition, the study designs of all the included studies are of satisfactory quality, obtaining more than 6 of 9 stars from the NOS quality assessment.

The results of this meta-analysis are compiled from available observational studies and attempts to draw a conclusion on the potential for increased risk of RD with oral FQ use. Variability may have an effect on heterogeneity, which is demonstrated in the meta-analysis of the case-control studies. However, the result remains non-significant in the sensitivity analysis with reduced heterogeneity. Furthermore, the heterogeneity of the self-controlled case series studies analyses was not significant and supports the validity of the conclusion.

Conclusion

The results of the meta-analysis do not support an association between oral FQ use and the development RD. However, if there were an association, such events would be rare given the small absolute risk estimated in the available literature. Based on the evidence from this meta-analysis, the use of oral FQ should not be precluded.

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Author contributions: CSLC, EWC, LYLW and ICKW had the original idea for this study and contributed to the development of the idea and the study design. CSLC and LYLW

209 independently conducted a systematic review and reviewed the literature for relevance. CSLC,
210 EWC and ICKW undertook the primary analysis. CSLC, EWC and ICKW contributed to the
211 interpretation of the analysis. CSLC, EWC and LYLW wrote the first draft of the paper. EWC,
212 LYLW and ICKW critically reviewed the paper. EWC and ICKW provided oversight of all
213 aspects of this project. CSLC and ICKW are the guarantors. All authors had full access to all the
214 data in the study and take responsibility for the integrity of the data and the accuracy of data
215 analysis.

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Table 1. Study characteristics and quality

Study	Data Source	Study period	Region	Study design	Inclusion criteria	Exclusion criteria	Outcome definition	Newcastle-Ottawa Scale[a,b]		
								Selection	Comparability	Exposure/ Outcome
Etminan 2012[1]	British Columbia Linked Health Database	01/2000-12/2007	Canada	CC	Had an ophthalmologist visit	History of RD diagnosis or procedures; endophthalmitis; intravitreal injection or vitreous biopsy	RD procedure (British Columbia procedure codes) received within 14 days after RD diagnosis (ICD-9)	*	**	***
Kuo 2013[14]	NHIRD	1998-2010	Taiwan	C	Aged >18 years; prescribed >3 consecutive doses of oral FQ/amoxicillin	Treated with FQ or amoxicillin during the prior 90 days; hospitalised 90 days prior to enrollment; history of RD diagnosis or procedure; blindness; procedure for encleation or evisceration of eyes	RD diagnosis (ICD-9) within 90 days of follow-up	***	**	***
Pasternak 2013[13]	Central Person Register, The National Prescription Registry, The Danish National Patient Registry	1/1/1997-31/12/2011	Denmark	C	Aged ≥18 years; prescribed FQ; no history of RD or retinal break; did not use FQ in the last 180 days; had lived in Denmark for minimum of 2 years; had filled at least 1 prescription for	History of endophthalmitis, intravitreal injection, or choroidal; retinal or vitreal biopsy; cataract surgery; major eye surgery or eye trauma 30 days before RD	RD procedure received within 14 days after RD diagnosis	****	**	***

					any medication in the last year; no history of hospitalisation in the last 30 days					
Chui 2014[9]	CDARS, NHIRD	HK: 1/1/2001-31/12/2012 Taiwan: 1/1/2000-31/12/2010	HK, Taiwan	SCCS	Prescribed FQ	Head or eye injury 30 days before RD; history of endophthalmitis, RD diagnosis or procedure.	RD procedure during FQ prescription (ICD-9)	***	**	***
Eftekhari 2014[16]	THIN	06/1994-01/2012	UK	C	Had prescription for FQ or β-lactam; registered with GP for at least 365 consecutive days prior prescription date	History of RD or retinal tear; FQ and β-lactam prescribed on the same day; history of intraocular surgery or diagnosis of endophthalmitis within 90 days of prescription.	RD or retinal tear procedure (Medcodes) within 7, 30, 90 and 365 days after the FQ prescription	****	*	***
Fife 2014[12c]	CCAE, Optum	CCAE: 1/1/2000-31/1/2012 Optum: 1/9/2005-31/3/2012	USA	CC	Had an ophthalmologist visit and at least 1 year in the cohort	History of RD diagnosis or procedure; endophthalmitis or related procedures such as vitreous biopsy or intravitreal injection; RD event happened during hospitalisation or within 10 days after being discharged	RD procedure received within 14 days after RD diagnosis	*	**	***

				SCCS	Ophthalmologist visit not required	Exclusion criteria in CC; history of inflammatory, infectious, or traumatic retinitis; index date of RD event happened during current or recent use of multiple antibiotic prescription (FQ and/or β-lactam); hospitalisation between cohort entry and event date	Restricted to codes associated with rheumatogenous retinal detachment and within 30 days after the beginning of FQ prescription	***	**	***
Kapoor 2014[15]	REP	1/1/2003-30/6/2011	USA	C	Prescribed FQ, macrolides or β-lactam	History of endophthalmitis, necrotising retinitis, ipsilateral intraocular surgery; severe ocular/head trauma within 90 days of RD; treated with serous/ exudative retinal detachment or diabetic retinopathy-related tractional RD.	RD procedure (Current Procedure Terminology) within 7, 30, 90 and 365 days after the FQ prescription	****	*	***

Abbreviations: CC=Case-control study; RD=retinal detachment; ICD-9= International Classification of Diseases, Ninth Revision; NHIRD=National Health Insurance Research Database; C=Cohort study; FQ=fluoroquinolones; CDARS=Clinical Data Analysis and Reporting System; HK=Hong Kong; SCCS=Self-controlled case series; THIN=The Health Improvement Network; UK=United Kingdom;

CCAE=MarketScan Commercial Claims and Encounter database; Optum=Optum ClinFormatics database; USA=United States of America; REP=Rochester Epidemiology Project.

[a] Quality assessment of the methodology of the included studies. The assessment guideline for case-control studies was used for self-controlled case series studies.
[b] Study quality was indicated by a higher number of stars. Each study could be allocated a maximum of 9 stars.

[c] Replication case-control and self-controlled case series analyses.

Table 2. Summary of the results of included studies and estimated absolute risk

Study	Sample size	Closest "Current use" definition	Number of cases in "current FQ use"	Result of current FQ use	Absolute risk of RD whilst on FQ treatment (up to 10 days from the first day of prescription)[a]
Etminan 2012[1]	RD case: 4,384 Control: 43,840	Within prescription period	145	Rate Ratio: 4.50(95% CI 3.56-5.70)	Data not available
Kuo 2013[14]	FQ prescriptions: 178,179 AMX prescriptions: 178,179	Patients were followed up for 90 days after they entered the cohort	96	Hazard Ratio: 2.07(95% CI 1.45-2.96)	Data not available
Pasternak 2013[13]	FQ episodes: 748,792 Control episodes: 5,520,446	1-10 days starting from the first day of prescription	5	Rate Ratio: 1.29(95% CI 0.53-3.13)	5 cases out of 748,792 prescriptions =6.7 per 1,000,000 prescriptions
Chui 2014[9]	FQ prescriptions[b]: HK: 260,198 TW: 1,098,086	Within prescription period	HK: 2[b] TW: 7[b]	Incidence rate ratio: HK: 0.82(95% CI 0.20-3.36) TW: 1.45(95% CI 0.68-3.10)	HK: 2 cases out of 260,198 prescriptions =7.7 per 1,000,000 prescriptions TW: 7 cases out of 1,098,086 prescriptions =6.4 per 1,000,000 prescriptions
Eftekhari 2014[16]	FQ prescriptions: 290,393 β-lactam prescriptions: 6,314,030	1-7 days after the prescription	0	Data not available	0 case out of 290,393 prescriptions
Fife 2014[12c]	Case control: CCAE: RD case: 7,844 Control: 77,654 Optum: RD case: 3,059 Control: 30,230 Self-controlled case series (case only): CCAE: 19,101 Optum: 6,896	Case control: Within prescription period Self-controlled case series: 30 days after start of FQ prescription	Case control: CCAE: 66 Optum: 13 Self-controlled case series: CCAE: 74 Optum: 18	Odds ratio (Case control): CCAE: 1.33(95% CI 0.99-1.80) Optum: 0.93(95% CI 0.48-1.81) Rate Ratio (Self-controlled case series): CCAE: 1.13(95% CI 0.99-1.29) Optum: 0.85(95% CI 0.66-1.09)	Data not available

Kapoor 2014[15]	FQ prescriptions: 92,130 Macrolide prescriptions: 107,086 β-lactam prescriptions: 178,352	Within 7 days after the prescription	0	0%(95% CI 0-0.01)	0 case out of 92,130 prescriptions
Overall absolute risk					4.85 case out of 1,000,000 prescriptions (95% CI 0.78-8.91)

Abbreviations: FQ=fluoroquinolones; RD=retinal detachment; AMX=Amoxicillin; HK=Hong Kong; TW=Taiwan; CCAE=MarketScan Commercial Claims and Encounters database; Optum=OptumClinFormatics database.

[a] Absolute risk of RD whilst on FQ treatment = number of RD cases whilst on FQ treatment divided by total number of FQ prescriptions included in the study

[b] Unpublished data, requested from authors

[c] Replication case-control analysis

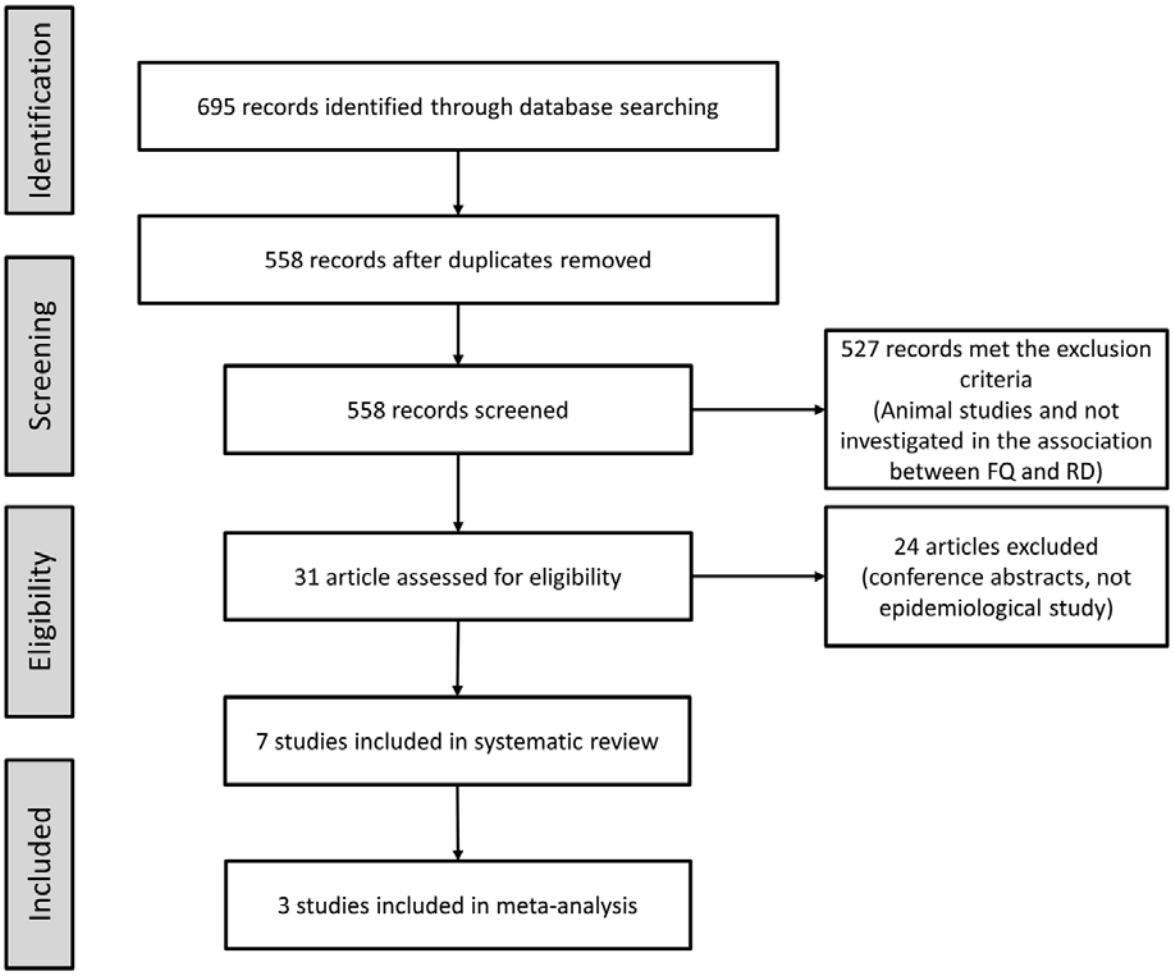
Figure legend:

Figure 1. PRISMA flowchart

Figure 2. Meta-analysis of case-control studies

Figure 3. Meta-analysis of self-controlled case series studies

Figure 4. Meta-analysis of absolute risk of retinal detachment whilst on oral fluoroquinolone treatment



Abbreviations: FQ=oral fluoroquinolones; RD=retinal detachment.

Figure 1. PRISMA flowchart

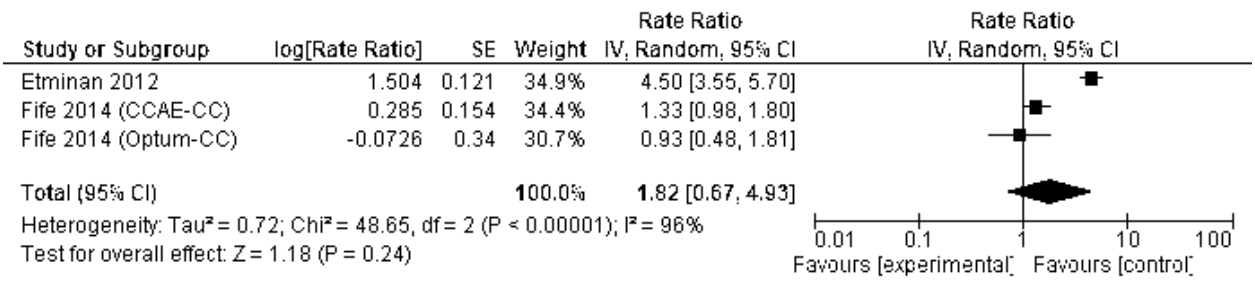


Figure 2. Meta-analysis of case-control studies

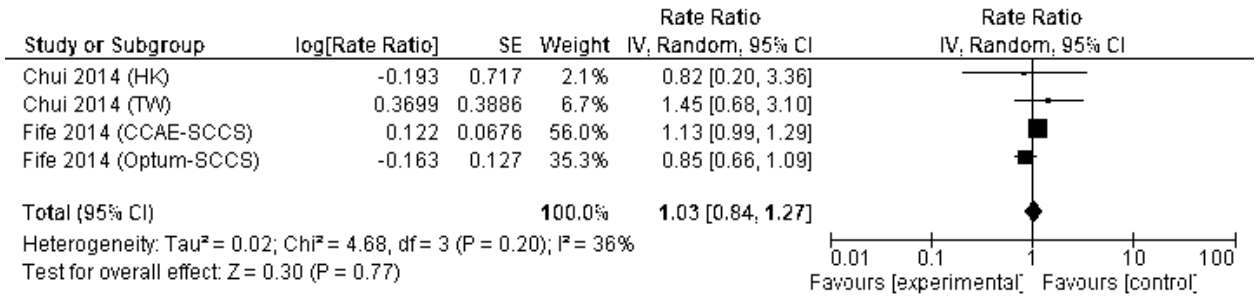


Figure 3. Meta-analysis of self-controlled case series studies

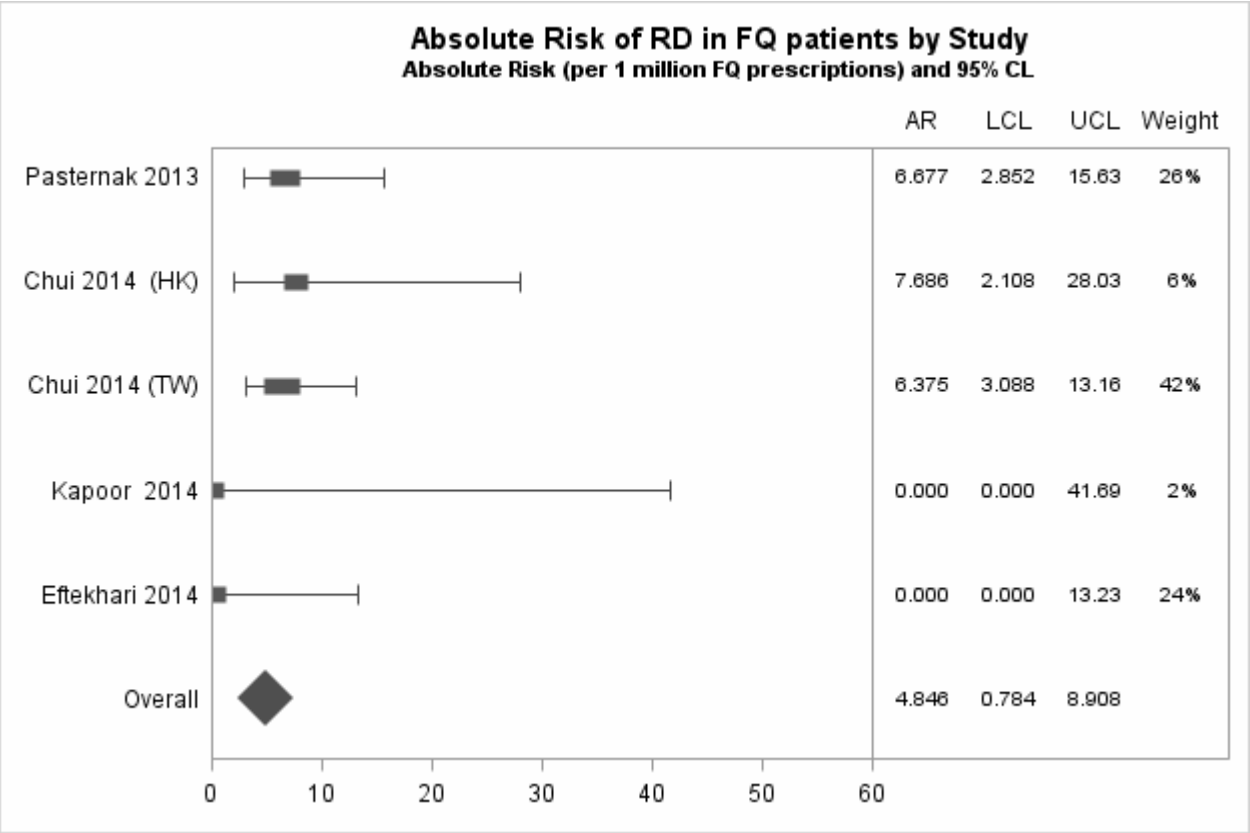


Figure 4. Meta-analysis of absolute risk of retinal detachment whilst on oral fluoroquinolone treatment

Abbreviations: RD=retinal detachment; FQ=oral fluoroquinolones; CL=confidence Limit; AR=absolute risk; LCL=Lower 95% Confident Limit; UCL=Upper 95% Confident Limit; HK=Hong Kong; TW=Taiwan.