

CLINICAL DRUG INVESTIGATION

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

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SUPPLEMENTARY MATERIAL

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Supplementary table S1. Read codes to identify tendon ruptures diagnoses in THIN.

Read code	Description
Nyu9200	[X]Spontaneous rupture of other tendons
N226200	Biceps tendon rupture
S922000	Complete division extensor tendon hand
S912300	Complete division extensor tendon wrist
S922100	Complete division flexor tendon hand
S912400	Complete division flexor tendon wrist
S902500	Complete division, biceps tendon
S932200	Complete division, both flexor tendons
S932300	Complete division, extensor digitorum tendon
S932600	Complete division, extensor pollicis longus tendon
SA22100	Complete division, extensor tendon, foot
S932100	Complete division, flexor digitorum profundus tendon
S932000	Complete division, flexor digitorum superficialis tendon
S932500	Complete division, flexor pollicis longus tendon
SA22000	Complete division, flexor tendon, foot
SA02300	Complete division, hamstring tendon
S902400	Complete division, long head of biceps tendon
SA12300	Complete division, patellar tendon
SA02200	Complete division, quadriceps tendon
SA12400	Complete division, tendocalcaneus (Achilles tendon)
S902600	Complete division, triceps tendon
N226D00	Flexor digitorum profundus tendon rupture
N226C00	Flexor digitorum sublimis tendon rupture
N226E00	Flexor pollicis longus tendon rupture
N226300	Hand and wrist extensor tendon rupture
N226400	Hand and wrist flexor tendon rupture
N226700	Nontraumatic rupture of Achilles tendon
N226600	Nontraumatic rupture of patellar tendon
N226.12	Nontraumatic tendon dislocation
N226.00	Nontraumatic tendon rupture
N226000	Nontraumatic tendon rupture, unspecified
N226y00	Other foot and ankle tendon rupture
N226z00	Other nontraumatic tendon rupture
S5W..00	Other specified tendon rupture
S932A00	Partial division both flexor tendons
S922200	Partial division extensor tendon hand
S912500	Partial division extensor tendon wrist
S922300	Partial division flexor tendon hand
S912600	Partial division flexor tendon wrist
S902800	Partial division, biceps tendon
S932B00	Partial division, extensor digitorum tendon
S932D00	Partial division, extensor pollicis longus tendon

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SA22300	Partial division, extensor tendon of foot
S932900	Partial division, flexor digitorum profundus tendon
S932800	Partial division, flexor digitorum superficialis tendon
S932C00	Partial division, flexor pollicis longus tendon
SA22200	Partial division, flexor tendon of foot
SA02500	Partial division, hamstring tendon
S902700	Partial division, long head of biceps tendon
SA12500	Partial division, patellar tendon
SA02400	Partial division, quadriceps tendon
SA12600	Partial division, tendocalcaneus (Achilles tendon)
S902900	Partial division, triceps tendon
N226500	Quadriceps tendon rupture
S5V0.00	Rupture Achilles tendon
S5Q4.00	Rupture biceps tendon
S5T2.00	Rupture extensor digitorum tendon
S5T1.00	Rupture flexor digitorum profundus tendon
S5T0.00	Rupture flexor digitorum superficialis tendon
S5V3.00	Rupture foot extensor tendon
S5V2.00	Rupture foot flexor tendon
S5U1.00	Rupture hamstring tendon
S5Q0.00	Rupture infraspinatus tendon
S5Q3.00	Rupture long head biceps tendon
S5U2.00	Rupture patellar tendon
S5V1.00	Rupture plantaris tendon
S5U0.00	Rupture quadriceps tendon
S5Q1.00	Rupture subscapularis tendon
S5Q2.00	Rupture supraspinatus tendon
S5R..00	Rupture tendon forearm or wrist
S5Rz.00	Rupture tendon hand or wrist NOS
S5V..00	Rupture tendon leg or foot
S5Vz.00	Rupture tendon leg or foot NOS
S5T..00	Rupture tendon of finger
S5Tz.00	Rupture tendon of finger NOS
S5S..00	Rupture tendon of thumb
S5U..00	Rupture tendon thigh
S5Sz.00	Rupture tendon thumb NOS
S5Q..00	Rupture tendon upper arm
S5Qz.00	Rupture tendon upper arm NOS
S5Q5.00	Rupture triceps tendon
S5Uz.00	Rupture upper leg tendon NOS
S550411	Ruptured Achilles tendon - traumatic
N226N00	Spontaneous rupture of extensor tendons
N226M00	Spontaneous rupture of flexor tendons
S5z..15	Tendon rupture NOS
S550412	Torn Achilles tendon
S50x.11	Traumatic rupture of biceps tendon

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Supplementary table S2. Incident rate ratios for the association between any tendon rupture and cumulative systemic fluoroquinolone and co-amoxiclav exposure within the current exposure risk window.

	Crude IRR	Adjusted IRR	Adjusted p-value
<i>Any tendon rupture</i>			
▪ Days of fluoroquinolone exposure	1.00 (0.999-1.001)	1.03 (1.01-1.05)	0.001
▪ Days of co-amoxiclav exposure	1.00 (0.998-1.002)	0.99 (0.97-1.02)	0.551
<i>Achilles tendon rupture</i>			
▪ Days of fluoroquinolone exposure	1.00 (0.999-1.001)	1.06 (1.03-1.09)	<0.001
▪ Days of co-amoxiclav exposure	1.02 (0.98-1.06)	0.99 (0.94-1.04)	0.653

Total number of days exposure measured on a continuous scale. Adjusted for exact age, body mass index, Charlson comorbidity score, hypothyroidism, hyperthyroidism, smoking status, oral and injectable corticosteroid exposure, and prior history of tendon rupture. IRR = Incidence rate ratio.

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Supplementary table S3. Sensitivity analyses for the association between tendon rupture and current systemic fluoroquinolone and current co-amoxiclav exposure.

Sensitivity analysis	Fluoroquinolone aIRR (95%CI)	Co-amoxiclav aIRR (95%CI)
<i><u>Any tendon rupture</u></i>		
Risk window using 60 days	1.45 (1.19-1.78)	1.09 (0.90-1.33)
Risk window using 90 days	1.19 (0.99-1.41)	1.05 (0.88-1.16)
Modelling individual Charlson comorbidities	1.63 (1.26-2.10)	1.02 (0.79-1.31)
Excluding traumatic tendon ruptures	1.63 (1.26-2.11)	1.02 (0.79-1.31)
Excluding people with prior tendon rupture	1.64 (1.27-2.12)	0.99 (0.76-1.27)
Complete case analysis	1.63 (1.23-2.16)	1.03 (0.79-1.34)
<i><u>Achilles tendon rupture</u></i>		
Risk window using 60 days	2.95 (2.12-4.11)	1.16 (0.82-1.64)
Risk window using 90 days	2.21 (1.65-2.96)	1.12 (0.84-1.51)
Modelling individual Charlson comorbidities	3.16 (2.11-4.74)	1.01 (0.64-1.59)
Excluding traumatic tendon ruptures	3.14 (2.11-4.66)	1.00 (0.64-1.57)
Excluding people with prior tendon rupture	3.08 (2.07-4.57)	0.97 (0.62-1.53)
Complete case analysis	3.28 (2.13-5.06)	1.02 (0.64-1.63)

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