Arthritis as a risk factor for carpal tunnel syndrome: a meta-analysis

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Objectives: The effects of inflammatory and degenerative arthritis on carpal tunnel syndrome (CTS) are not well known. This systematic review and meta-analysis aimed to assess whether rheumatoid arthritis (RA) and osteoarthritis (OA) increase the risk of CTS.

Method: Literature searches were conducted in PubMed, Embase, Web of Science, Scopus, Google Scholar, and ResearchGate until January 2015. Twenty-three (five cohort, 10 case control, and eight cross sectional) studies qualified for the meta-analyses. A random-effects meta-analysis was used and heterogeneity and publication bias were assessed.

Results: Both RA and OA were associated with CTS. Pooled unadjusted odds ratios (ORs) were 1.91 [95% confidence interval (CI) 1.33–2.75, I² = 55.2%, nine studies, n = 10 688] for arthritis (either inflammatory or degenerative), 2.91 (95% CI 2.33–3.62, I² = 22.3%, 11 studies, n = 74 730) for RA, and 2.13 (95% CI 1.65–2.76, I² = 39.2%, five studies, n = 20 574) for OA of any joint. Pooled confounder-adjusted ORs were 1.96 (95% CI 1.21–3.18, I² = 73.1%, six studies, n = 11 542) for arthritis, 1.96 (95% CI 1.57–2.44, I² = 32.2%, eight studies, n = 72 212) for RA, and 1.87 (95% CI 1.64–2.13, I² = 0%, two studies, n = 19 480) for OA. There was no evidence of publication bias, and excluding cross-sectional studies or studies appraised as having a high risk of selection bias did not change the magnitude of the associations.

Conclusions: The findings of this systematic review and meta-analysis suggest that both RA and OA increase the risk of CTS. Further prospective studies on the effect of wrist OA on CTS are needed.

Carpal tunnel syndrome (CTS) is a common upper extremity disorder (1, 2) and carpal tunnel release is one of the commonly performed upper extremity orthopaedic procedures (3). However, the contribution of chronic medical conditions to the aetiology of CTS is not well known. Some chronic medical conditions such as obesity (4), diabetes mellitus (5), rheumatoid arthritis (RA) (6), and hypothyroidism (6, 7) have been suggested as possible risk factors for CTS.

The carpal tunnel consists of the carpal bones and transverse carpal ligament. In the carpal tunnel, in addition to the median nerve there are nine flexor tendons (8). Each flexor tendon is covered by a synovial sheath. RA can cause tenosynovitis, swelling and oedema of the synovial sheaths of the flexor tendons in the carpal tunnel (9). RA patients with flexor tenosynovitis of the hand are reported to have a higher prevalence of CTS than RA patients without tenosynovitis (10). A long duration of RA can lead to histopathological changes in the tendons of the wrist such as synovial proliferation or tendon damage (11).

To date, only one meta-analysis has been conducted on the association between RA and CTS (6). That meta-analysis included seven studies published between 1984 and 2002 and found a twofold increased risk of CTS in RA patients. However, of the seven primary studies included in the meta-analysis, two (12, 13) were conducted in CTS patients but there was no control group, and two (14, 15) estimated the effect of any arthritis. The aim of the current systematic review and meta-analysis was to assess whether RA and osteoarthritis (OA) increase the risk of CTS.

Method

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to develop the review protocol and to report the results of this meta-analysis (16). Literature searches were systematically conducted in PubMed, Embase, Web of Science, Scopus, Google Scholar, and ResearchGate up to
January 2015. The following predefined keywords were used: [carpal tunnel syndrome OR median neuropathy OR median nerve OR carpal tunnel (text word only) OR carpal canal (text word only) OR CTS (text word only)] AND [rheumatoid arthritis OR arthritis OR joint diseases OR rheumatic diseases OR rheumatism OR osteoarthritis OR antirheumatic agents OR chronic disease]. Both MeSH terms and text words were used in PubMed, and Emtree terms and text words were used in Embase. The reference lists of the included reports and the full text of studies on other risk factors for CTS, such as smoking (17), obesity (4), diabetes (5), thyroid disease (7), hand anthropometric measurements (18), and computer use (19), were looked at for additional studies on the relationship between arthritis and CTS.

Inclusion and exclusion criteria

Cross-sectional studies, both population-based and hospital-based case–control studies, and cohort studies were included in the systematic review. There was no restriction on language. Studies that reported a quantitative result for the association between any inflammatory or degenerative arthritis and CTS were eligible to be included in the review. The CTS case definition required symptoms consistent with CTS plus a nerve conduction study and/or physical examination finding(s) consistent with CTS. Carpal tunnel release surgery was also considered to meet the CTS case definition.

Published studies that were conducted among CTS patients with no control group, studies on arthritis patients lacking a control group, and studies with insufficient quantitative results were excluded from the review. In addition, studies on the symptoms of CTS that were not verified by a clinical diagnosis or a nerve conduction study were excluded from the meta-analysis.

Quality assessment

The quality of included studies was appraised using the criteria adapted from the Effective Public Health Practice Project (EPHPP) tool for observational studies (20). Five sources of bias were assessed: selection bias, performance bias, detection bias, confounding, and attrition bias (Supplementary Table S1).

Meta-analysis

A crude prevalence ratio for cross-sectional studies (2, 21–24), a crude odds ratio (OR) for case–control studies (14, 25–27), and a crude risk ratio (RR) for a cohort study (28) were estimated. Woolf confidence intervals (CIs) were calculated for the estimated ORs (29). All of the included studies, except three, reported adjusted ORs. As the risk of CTS is less than 5%, the ORs are similar to the RRs. A prevalence ratio or RR was not therefore converted to an OR. Zero-cell correction was used for studies (27, 30, 31) with a zero-cell count using the Mantel-Haenszel fixed effect. Some studies reported two or more risk estimates for the associations of different types of arthritis with CTS. To obtain an overall risk estimate for arthritis (either inflammatory or degenerative) or OA of any joint, a method (32) suggested for combining multiple outcomes within a single study was used to correct the variance of the pooled estimate.

A random-effects meta-analysis was used to combine the estimates of the studies (33). The presence of heterogeneity across the studies was assessed by the I² statistic (34). The influence of each study on the summary estimate and heterogeneity was examined by repeating the meta-analysis with one study removed at a time. Sensitivity analyses were performed with regard to study design and risk of bias in the included studies. Publication bias was assessed by a funnel plot. The Egger test was used to examine funnel plot asymmetry and the trim-and-fill method was used to explore the number of missing studies attributed to publication bias (35, 36). Statistical significance for publication bias was based on a p-value < 0.10 (32). Stata version 13 (Stata Corp, College Station, TX, USA) was used for the meta-analysis.

Results

Study selection

The study selection process is presented in Supplementary Figure S1. The searches initially identified 2612 abstracts. Fifty-two relevant studies were then identified. Twenty-nine studies were excluded from the meta-analysis: seven studies on CTS patients lacking a control group, 17 studies on patients with arthritis lacking a control group, four studies defining CTS by a nerve conduction study only, and one study not providing quantitative results. Finally, 23 (five cohort, 10 case control, and eight cross sectional) studies qualified for the meta-analyses. The sample size of the included studies ranged between 65 and 47 406 individuals (Table 1 and Supplementary Table S2). Twelve studies controlled their risk estimates for some potential confounders including age and sex. Only a few studies controlled their estimates for occupational factors, body mass index (BMI), or diabetes.

Arthritis and CTS

Eleven (two cohort, four case–control, and five cross-sectional) studies explored the association between any inflammatory or degenerative arthritis and CTS (Table 1 and Supplementary Table S2). The symptoms of CTS were confirmed by a nerve conduction study in seven studies and by a clinical diagnosis in two studies. Moreover, the assessment of CTS was based on medical
Table 1. Studies included in the meta-analysis on the association between arthritis and carpal tunnel syndrome (CTS) or carpal tunnel release (CTR).

| First author, year (ref.) | Country | Design            | Population                          | Mean age; age range (years) | Gender | Sample size | Arthritis | Outcome | Adjustment |
|---------------------------|---------|-------------------|-------------------------------------|-----------------------------|--------|-------------|-----------|---------|------------|
| Evanoff 2013 (28)         | USA     | Prospective cohort | Occupational population             | 31                          | Both   | 711         | Arthritis | CTS     | Unadjusted |
| Harris-Adamson 2013 (37)  | USA     | Prospective cohort | Occupational population             | 31; ≥ 18                    | Both   | 3375        | RA        | CTS     | Adjusted   |
| Garg 2012 (38)            | USA     | Prospective cohort | Occupational population             | 41; 19–68                   | Both   | 429         | Arthritis, OA | CTS     | Adjusted   |
| Gell 2006 (39)            | USA     | Prospective cohort | Occupational population             | 39 (cases), 38 (controls); 19–69 | Both   | 432         | RA        | CTS     | Unadjusted |
| Werner 2005 (31)          | USA     | Prospective cohort | Occupational population             | 48                          | Both   | 189         | RA        | CTS     | Unadjusted |
| Coggon 2013 (40)          | UK      | Case–control      | CTS patients + patient controls     | 20–64                       | Both   | 1230        | Arthritis, RA | CTS     | Adjusted   |
| Karadag 2012 (26)         | Turkey  | Case–control      | RA patients + healthy controls      | 51 (cases), 47 (controls); 24–76 | Both   | 145         | RA        | CTS     | Unadjusted |
| Tseng 2012 (41)           | Taiwan  | Case–control      | National insurance claim population | 20% ≤ 19, 69% 20–59, 11% ≥ 60 | Both   | 47 406      | RA        | CTS     | Adjusted   |
| Mattioli 2009 (42)        | Italy   | Case–control      | CTS patients + patient controls     | 18–65                       | Both   | 476         | RA        | CTR     | Adjusted   |
| Geoghegan 2004 (43)       | UK      | Case–control      | General practice population         | 46 (cases); 16–96           | Both   | 16 995      | RA, OA    | CTS, CTR | Adjusted   |
| Ferry 2000 (44)           | UK      | Case–control      | General practice population         | 42                          | Female | 2528        | Arthritis, RA, OA | CTS     | Adjusted   |
| Solomon 1999 (15)         | USA     | Case–control      | Medicare or Medicaid population     | ≥ 45                        | Both   | 4244        | Arthritis | CTR     | Adjusted   |
| de Krom 1990 (14)         | Netherlands | Case–control | CTS patients + healthy controls     | 25–74                       | Both   | 629         | Arthritis | CTS     | Unadjusted |
| Wieslander 1989 (25)      | Sweden  | Case–control      | CTS patients + healthy and patient controls | 20–66                       | Male   | 177         | RA        | CTR     | Adjusted   |
| Barnes 1987 (27)          | UK      | Case–control      | RA patients + patient controls      | Not reported                | Both   | 65          | RA        | CTS     | Adjusted   |
| Eleferthou 2012 (45)      | Greece  | Cross-sectional   | Occupational population             | 45                          | Both   | 461         | RA        | CTS     | Unadjusted |
| Shin 2012 (23)            | South Korea | Cross-sectional | Elderly population                  | 75, 66–96                   | Both   | 368         | OA        | CTS     | Unadjusted |
| Burt 2011 (22)            | USA     | Cross-sectional   | Occupational population             | 41; 19–68                   | Both   | 455         | Arthritis | CTS     | Adjusted   |
| Raighani 2009 (24)        | Iran    | Cross-sectional   | Patients with upper extremity disorders | Not reported                | Both | 1000        | Arthritis | CTS     | Unadjusted |
| Majhsoudipour 2008 (30)   | Iran    | Cross-sectional   | Occupational population             | 30 (cases), 28 (controls)   | Both   | 395         | Arthritis | CTS     | Unadjusted |
| Melchior 2006 (46)        | France  | Cross-sectional   | Occupational population             | 38, 20–59                   | Both   | 2656        | Arthritis | CTS     | Adjusted   |
| Atrashi 1999 (3)          | Sweden  | Cross-sectional   | General population                  | 25–74                       | Both   | 2466        | RA        | CTS     | Unadjusted |
| Atchison 1998 (21)        | USA     | Cross-sectional   | Patients with upper extremity disorders | 25–54                       | Both   | 297         | Arthritis, RA, OA | CTS     | Unadjusted |

RA, Rheumatoid arthritis; OA, osteoarthritis.
records in two studies. Four studies qualified as having a high risk of selection bias.

The pooled OR of CTS for any inflammatory or degenerative arthritis was 1.91 (95% CI 1.33–2.75, $I^2 = 55.2\%$) in the meta-analysis of nine studies consisting of 10 688 individuals that reported estimates not controlled for any confounder (Figure 1). Excluding one study (15) on carpal tunnel release from the meta-analysis decreased the value of $I^2$ to 24.5% and the pooled OR to 1.71 (95% CI 1.21–2.40). Excluding studies with a high risk of selection bias did not change the result (pooled unadjusted OR 1.83, 95% CI 1.22–2.75, $I^2 = 61.4\%$).

The pooled OR was the same (1.96, 95% CI 1.21–3.18, $I^2 = 73.1\%$) in the meta-analysis of six studies (n = 11 542 individuals) that reported estimates controlled for some potential confounders. The $I^2$ value fell to 37.3% and the pooled OR to 1.59 (95% CI 1.06–2.38) after excluding one study (15) on carpal tunnel release. The $I^2$ value dropped further to 0% (pooled OR 1.89, 95% CI 1.27–2.80) after also excluding another study (40). Excluding studies with a high risk of selection bias did not change the result (pooled adjusted OR 2.21, 95% CI 1.44–3.41, $I^2 = 46.7\%$).

RA and CTS

Fourteen (three cohort, eight case–control, and three cross-sectional) studies assessed the association between RA and CTS (Table 1 and Supplementary Table S2). The symptoms of CTS were confirmed by a nerve conduction study in nine studies and by a clinical diagnosis in two studies. ICD codes were used for the assessment of CTS in three studies. The risk of selection bias was high for four studies.

Ten studies consisting of 74 254 individuals reported unadjusted estimates for the association between RA and CTS (pooled OR 2.88, 95% CI 2.25–3.69, $I^2 = 25.9\%$; Figure 2). Only one study reported an unadjusted estimate for carpal tunnel release. The pooled OR was 2.91 (95% CI 2.33–3.62, $I^2 = 22.3\%$, n = 74 730) for CTS and carpal tunnel release combined.

First author and year of publication

Unadjusted estimates

| First author and year of publication | OR (95% CI) | Weight, % |
|-------------------------------------|------------|-----------|
| Evanoff 2013                         | 1.04 (0.26, 4.12) | 5.44 |
| Garg 2012                            | 3.80 (1.47, 9.79) | 9.29 |
| Burt 2011                            | 1.98 (1.20, 3.26) | 17.07 |
| Raigani 2009                         | 1.67 (0.56, 4.93) | 7.75 |
| Maghsoudipour 2008                   | 2.42 (0.10, 5.870) | 1.24 |
| Ferry 2000                           | 1.71 (1.01, 2.90) | 16.46 |
| Solomon 1999                         | 3.10 (2.40, 4.10) | 22.15 |
| Atcheson 1998                        | 1.75 (0.92, 3.31) | 14.15 |
| de Krom 1990                         | 0.38 (0.11, 1.30) | 6.46 |
| Subtotal (1$^2 = 55.2\%, P = 0.022$) | 1.91 (1.33, 2.75) | 100.00 |

Confounder-adjusted estimates

| First author and year of publication | OR (95% CI) | Weight, % |
|-------------------------------------|------------|-----------|
| Coggon 2013                         | 1.06 (0.70, 1.61) | 22.22 |
| Garg 2012                            | 3.66 (1.32, 10.16) | 12.20 |
| Burt 2011                            | 2.03 (1.02, 4.04) | 17.31 |
| Melchior 2006                        | 2.06 (0.29, 14.36) | 5.01 |
| Ferry 2000                           | 1.45 (0.82, 2.55) | 19.49 |
| Solomon 1999                         | 3.10 (2.20, 4.20) | 23.77 |
| Subtotal (1$^2 = 73.1\%, P = 0.002$) | 1.96 (1.21, 3.18) | 100.00 |

Figure 1. A meta-analysis of 11 studies on the association between arthritis and carpal tunnel syndrome (CTS) or carpal tunnel release. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CIs). OR, odds ratio.
The pooled confounder-adjusted OR was 1.88 (95% CI 1.43–2.49, I² = 51.5%) for CTS in the meta-analysis of six studies consisting of 71 559 individuals and 2.34 (95% CI 1.45–3.75, I² = 0%) for carpal tunnel release in the meta-analysis of three studies consisting of 17 608 individuals (Figure 2). The pooled adjusted OR was 1.96 (95% CI 1.57–2.44, I² = 32.2%, eight studies, n = 72 212) for CTS and carpal tunnel release combined. Excluding studies with a high risk of selection bias did not change the result (pooled adjusted OR 2.12, 95% CI 1.78–2.54, I² = 12.7%).

OA and CTS

There were five (one cohort, two case–control, and two cross-sectional) studies on the association between OA and CTS (Table 1 and Supplementary Table S2). The diagnosis of CTS was based on symptoms and a nerve conduction study in two studies, symptoms and a clinical diagnosis in one study, and medical records in two studies. Two studies qualified as having a high risk of selection bias.

In the meta-analysis of five studies consisting of 20 574 individuals, the pooled unadjusted OR of CTS for OA in any joint was 2.13 (95% CI 1.65–2.76, I² = 39.2%; Figure 3). The magnitude of association did not change after excluding two studies with a high risk of selection bias (pooled OR 2.30, 95% CI 1.78–2.99, I² = 39.8%) or after excluding two cross-sectional studies (pooled OR 2.55, 95% CI 2.25–2.89, I² = 0%).

The pooled confounder-adjusted OR of two studies consisting of 19 480 individuals was 1.87 (95% CI 0.25 – 10.68, P = 0.205)
1.64–2.13, $I^2 = 0\%$). These two studies were neither cross-sectional nor appraised as having a high risk of selection bias.

Publication bias

A funnel plot of 11 studies on arthritis (five unadjusted and six adjusted estimates) was symmetrical (p for the Egger test $= 0.39$) and the trim-and-fill method imputed no missing studies (Supplementary Figure S2). A funnel plot of 14 studies on RA showed no publication bias (p for the Egger test $= 0.57$, Supplementary Figure S3) and the trim-and-fill method did not impute any missing studies.

Discussion

This systematic review and meta-analysis found an increased risk of CTS in individuals who suffer from RA or OA. These results of an approximately twofold increased risk were relatively consistent for both types of arthritis regardless of which study inclusion method was used. The observed associations are most probably not due to selection bias, confounding factors, or publication bias.

RA and OA may not share similar mechanistic risks for CTS. CTS does not predict a new onset of arthritis (47) whereas it seems that arthritis does predict the development of CTS. RA may increase the risk of CTS by causing flexor tenosynovitis in the carpal tunnel (9). The symptoms and signs of CTS may be transient in RA patients and resolve within a year (48). Cervical or basal joint OA commonly coexists with idiopathic CTS (49). Osseous hypertrophy of the carpal bones can make the carpal canal smaller. Therefore, wrist OA may be one of the underlying causes of idiopathic CTS.

CTS and carpal tunnel release are more common in women than men (1). Of the studies included in this meta-analysis, only two that recruited both sexes performed a sex-specific analysis on the role of arthritis in CTS. One of these studies (46) had low statistical power and the other (41) showed a similar association between RA and CTS in both men and women. Women are also at higher risk of developing RA (50) and hand OA (51). RA and hand OA may explain a minor portion of the increased risk of CTS for women.

This systematic review and meta-analysis has some limitations. Many studies included in this meta-analysis did not control their risk estimates for potential confounding factors. Age and sex are known risk factors for RA, OA, and CTS.
The included studies that reported confounder-adjusted estimates controlled their risk estimates for both age and sex. Obesity is a known risk factor for CTS and a possible risk factor for RA (52, 53) and hand OA (54, 55). In the current meta-analysis, only a few primary studies adjusted their observed associations for BMI. The associations of RA and OA with CTS may therefore have been overestimated. Another limitation is that there were only a few prospective cohort studies, and all except one recruited a small population. Furthermore, some studies defined CTS based on symptoms and clinical diagnosis and did not use a nerve conduction study. More than half of the included studies assessed arthritis using self-reports. In addition, only a few studies explored the effect of wrist OA on CTS.

In summary, this meta-analysis suggests that RA and OA are possible risk factors for CTS. Further prospective studies on the effect of wrist OA on CTS are needed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Quality assessment of the included studies.

Supplementary Table S2. Studies included in the meta-analysis on the association between arthritis and carpal tunnel syndrome.

Supplementary Figure S1. Flow chart of the search strategy and selection of studies. CTS, carpal tunnel syndrome.

Supplementary Figure S2. Funnel plot for publication bias in 11 studies on arthritis.

Supplementary Figure S3. Funnel plot for publication bias in 14 studies on rheumatoid arthritis.

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