The relationship between rheumatoid arthritis and diabetes mellitus: a systematic review and meta-analysis

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Objective **This systematic review/meta-analysis was conducted to investigate the relationship between rheumatoid arthritis and the incidence of diabetes mellitus.**

Methods **A comprehensive search was conducted up to 10 March 2020 in Medline (via Ovid), Embase (via Ovid) and Web of Science core collection to identify cohort studies comparing the risk of diabetes mellitus incidence in people with rheumatoid arthritis with the general population. The I2 statistic was used to test heterogeneity. Pooled relative risks were calculated using random-effects models. Publication bias was assessed using Egger's test and Begg's test.**

Results **The initial search provided 3669 articles. Of those, five journal articles/two conference abstracts comprising 1 629 854 participants were included in this study. The funnel plot showed potential publication bias, proven by Egger's test (−3.15, $P < 0.01$), but not Begg's test (−0.05, $P = 1.00$). Heterogeneity was observed in I2 test ($I2 = 96\%$, $P < 0.01$). We found that rheumatoid arthritis was associated with a higher risk of diabetes mellitus incidence (pooled relative risk, 1.23; 95% confidence interval, 1.07–1.40). Exploration of potential sources of heterogeneity found significant heterogeneity in different countries/regions ($P = 0.002$), but heterogeneity was NS in different study designs ($P = 0.30$). Sensitivity analyses confirmed that the association between rheumatoid arthritis and diabetes mellitus incidence was robust.**

Conclusion **Rheumatoid arthritis is associated with an increased risk of diabetes mellitus incidence. This finding supports the notion that inflammatory pathways are involved in the pathogenesis of diabetes. More intensive interventions targeting diabetes risk factors should be considered in people with rheumatoid arthritis.** ***Cardiovasc Endocrinol Metab*** **10: 125–131**

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Keywords: diabetes mellitus, incidence, inflammation, meta-analysis, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disorder characterized by persistent synovial inflammation resulting in damage to cartilage and underlying bone [1]. The prevalence of this disease is 0.5–1.0% of adults in developed countries [2]. Accumulating evidence showed that inflammation emerges as a key factor in the onset and progression of diabetes [3]. Systemic inflammation associated with RA might contribute to the risk of developing diabetes in the future. Markers of active inflammation, such as CRP, are associated with an increased risk of diabetes in people with RA. Other traditional risk factors for type 2 diabetes mellitus (T2DM) are also highly prevalent among people with RA [4] and may contribute to the higher risk of diabetes. The prevalence of metabolic syndrome in people with RA is high [5]. As a result of chronic pain, swelling and stiffness of the joints, physical inactivity is common in people with RA, which in turn contributes to T2DM [6] through decreased calorie burning.

In summary, inflammation is implicated in the development of diabetes. Some traditional risk factors of T2DM are also highly prevalent among people with RA. Therefore, the incidence of diabetes could be higher in people with RA. Several observational studies investigated the relationship between RA and DM incidence; however, results have been conflicting [7,8]. A previous meta-analysis reviewed cohort studies (five eligible studies) before January 2014 and found that people with RA had a statistically significant increased risk of diabetes [relative risks (RR), 1.24; 95% confidence intervals (CI),

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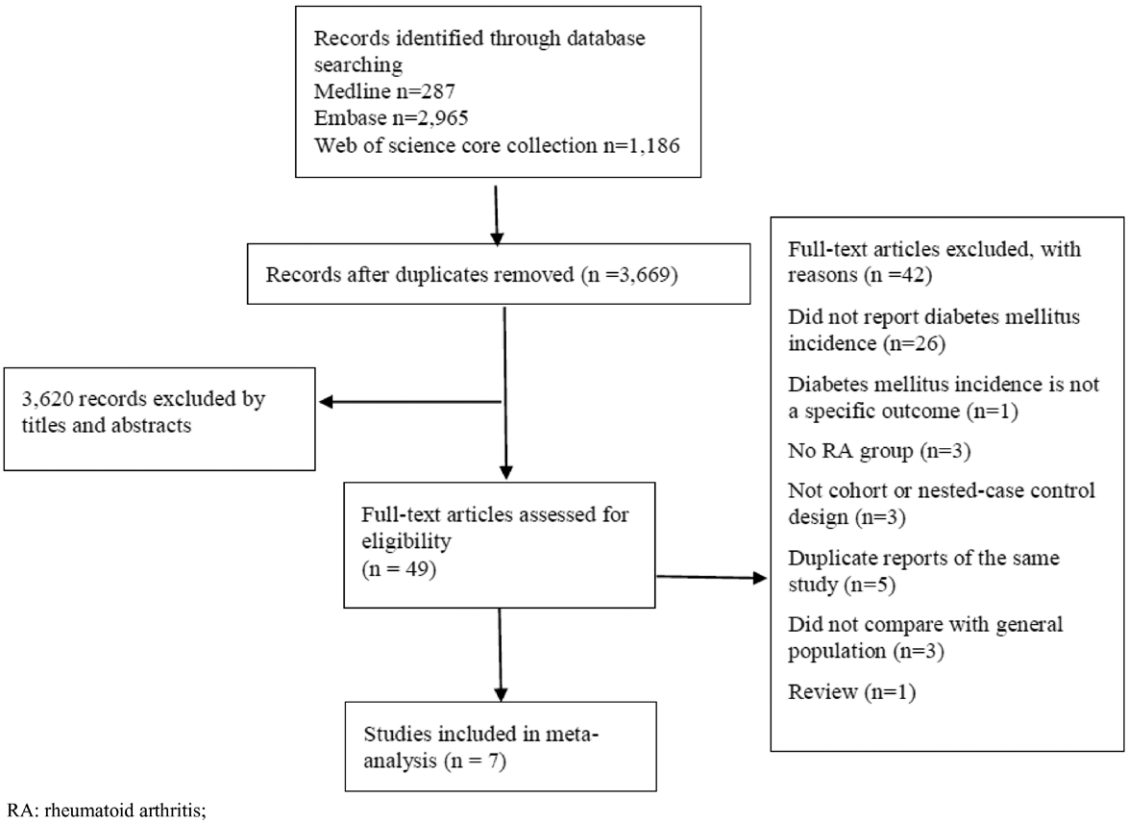
Fig. 1



Flowchart of study selection. RA, rheumatoid arthritis.

1.14–1.35] [9]. Since then, three further cohort studies have been published [10–12]. We aim to update the systematic review and meta-analysis.

Method

The meta-analysis was conducted according to the report Meta-analysis of Observational Studies in Epidemiology [13], and the protocol was registered with PROSPERO (CRD42020172084).

Search terms and strategy

The PICO/S tool was deployed to define the scope of the literature. We included cohort studies and nested case-control studies in adult humans (population) and compared the incidence of diabetes (outcome) between people with RA (intervention/exposure) and the general population (control).

A comprehensive search was conducted in Medline (via Ovid), Embase (via Ovid) and Web of Science core collection from inception to 10 March 2020. The search was limited to English language and human studies. The search terms were a combination of thesaurus terms and free-text terms, including RA, diabetes, cohort study or nested case-control study, and human. These were based on the search strategy developed for Medline but revised appropriately for the other two databases (Supplementary Contents 1–3, Supplemental digital content 1, *http://links.lww.com/CAEN/A29*). Search alerts were created in the databases to notify new studies according to the outlined search strategy. We also manually checked reference lists of the identified studies for potentially missing eligible studies. For eligible conference abstracts, we further searched the author to find if there were related full texts.

Inclusion and exclusion criteria

Two independent reviewers (A.H. and Z.T.) assessed the eligibility of studies according to the inclusion and exclusion criteria below. Disagreements were resolved by a third independent investigator (J.M.).

Inclusion: (1) cohort studies or nested case-control studies; (2) to compare general population with people with RA (case-control design); (3) to provide enough data to calculate RR and CIs; (4) to consider the incidence of diabetes mellitus as a specific outcome event.

Exclusion: (1) review studies, editorials/letters, case reports; (2) studies with the main outcome as gestational diabetes mellitus. If there was more than one publication

Table 1 Characteristics of eligible studies

Reference	Country/ region	Sample size	Study period	Percent of female, %	Mean age, years	Data source	Crude or age/ sex-adjusted risk	Adjusted risk	Adjustment
Solomon *et al.* [7]	Canada	RA 48 718 non-RA 442 033	1996–2006	RA 68 non-RA 60	RA 58 ± 16 non-RA 53 ± 17	Insurance programme of British Columbia	NR	HR, 1.5 (1.4–1.5)	Age, sex, doctor visits, number of drugs, prior use of oral glucocorticoids, prior use of systemic immunosuppressive agents, prior use of topical glucocorticoids and comorbidity index
Schmidt *et al.* [12]	Canada	RA 26 013 non-RA 25 823	1996–2006–2010	RA 67 non-RA 67	RA 58.6 ± 17.2 non-RA 58.1 ± 17.1	Administrative health data	NR	HR 1.62 (1.49–1.76)	Age, sex and comorbidity index (excluding DM).
Su *et al.* [17]	Taiwan	RA 3839 non-RA 596 497	1998–2009	RA 70.6 non-RA 49.9	>20[a]	Taiwan national health insurance	HR, 2.37 (2.15–2.60)	HR, 2.40 (2.18–2.63)	NR
Jafri *et al.* [10]	UK	48 639 RA 364 988 non-RA	1994–2014	RA: 70.3 non-RA: 55.9	RA 60.73 ± 15.41 non-RA 51.33 ± 17.93	The health improvement network	HR, 1.16 (1.12–1.21)	HR, 1.21 (1.15–1.26)	Age, sex, hypertension, hyperlipidaemia, smoking, BMI, heart disease, comorbidity index and healthcare utilization
Wilson *et al.* [11]	UK	RA 31 330 non-RA 31 464	1995–2015	RA 70.5 non-RA 70.5	RA 56.2 ± 16.0 non-RA 56.2 ± 16.0	UK Clinical Practice Research Datalink	RR, 1.20 (1.11–1.29)	NR	NR
Gonzalez *et al.* [8]	USA	RA 559 non-RA 562	RA 15 non-RA 17[b]	RA 73 non-RA 73	RA 58 ± NA non-RA 58 ± NA	Rochester Epidemiology Project	RR, 0.78 (0.57–1.06)	NR	NR
Mathew *et al.* [16]	USA	RA 1502 non-RA 7887	2001–2012	RA 70 non-RA 60	RA 55 ± NA non-RA 55 ± ±NA	Electronic medical record database	RR, 1.32 (1.13–1.54)	HR, 1.14 (0.94–1.38)	Age, sex, race, BMI, hypertension, hyperlipidaemia, ESR, number of office visits, number of drug classes, glucocorticoid and immunosuppressive agent and statin use in the year prior to cohort entry

DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HR, hazard ratio; NR, not reported; RA, rheumatoid arthritis; RR, risk ratio.
[a]Age range.
[b]Mean year of follow-up, years.

from the same study population, only the study from the most recent publication was included.

Data extraction and quality assessment

For each eligible study, two researchers (A.H. and Z.T.) independently extracted the following items: (1) the first author, the year of publication, the country or region where the subjects lived; (2) characteristics of the participants, including sample size, sex and age; (3) study design and data source; (4) diagnosis criteria of RA and DM; (5) the number of outcomes in exposed and non-exposed cohorts; (6) crude and adjusted risk estimates, 95% CI; (7) adjustments. The quality of the included studies was assessed by the Newcastle–Ottawa scale [14], in which a study was judged based on section (four items, one star each), comparability (one item, up to two stars) and outcome (three items, one star each). In this meta-analysis, we graded quality as good (≥7 stars), fair (4–6 stars) and poor (<4 stars) [15]. We evaluated comparability by whether the studies had adequately adjusted for potential confounders (one star for age, one star for at least three of five confounders including a family history of diabetes, BMI or other measures of overweight/obesity, comorbidity, the use of glucocorticoids and ethnicity). The item 'was follow-up long enough for outcomes to occur' was evaluated by whether the study period was above 5 years.

Outcome measures

T2DM was defined when the subjects were described as having adult-onset, type II or noninsulin-dependent DM. DM is defined when the subjects were described as DM or composite DM.

Statistical analysis

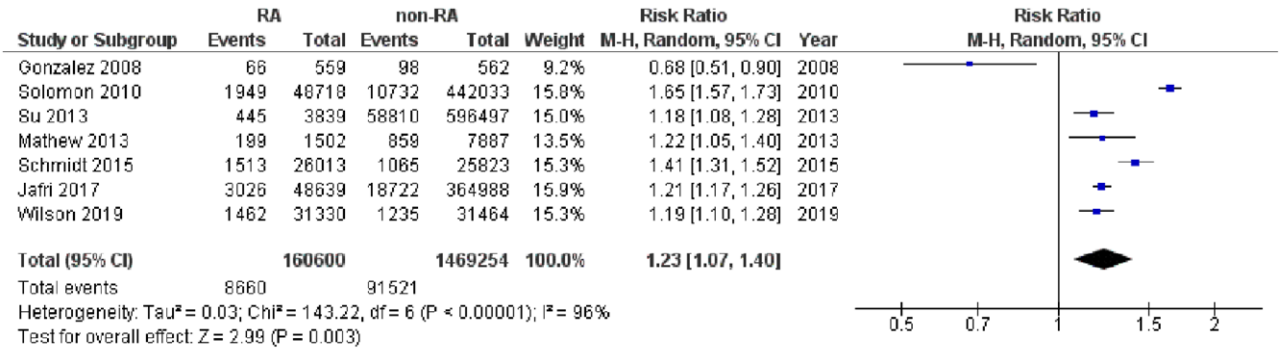
The random-effects models were used to estimate the pooled RR according to heterogeneity. The I^2 statistic and Q-test were used to test heterogeneity. $P_{\text{Q statistic}} \geq 0.10$ was considered to indicate no significant heterogeneity among the included studies. Publication bias was assessed using funnel plot, Egger's test and Begg's test. Sensitivity analyses were conducted by excluding one study at a time. Subgroup analyses were conducted based on the countries (or regions) of subjects and study designs (age and sex-matched or not). All analyses were performed using R, version 3.6.2 64 bit (R Core Team. R Foundation for Statistical Computing, Vienna, Austria) and Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

The initial search provided 3669 articles. Forty-nine studies were included after a screen of titles and abstracts. Ultimately, five journal articles and two conference abstracts comprising 1 629 854 participants were included in our study (Fig. 1).

Most eligible studies were population-based, whereas one was hospital-based [16]. All the eligible studies were retrospective cohort in design. Sample sizes ranged from 1121 to 600 336, with a female predominance. The studies were conducted in diverse settings, including large electronic medical record databases [10–12,16], insurance claims [7,17] or a population-based RA inception cohort with a medical records linkage system [8]. Most of these studies used International Classification of Disease codes (ICD-9-CM 714.0) [7,16,17], diagnosis codes [10–12] and/or prescription of antirheumatic drugs [10,17] to identify people with RA. One study further reviewed RA cases identified by medical records based on the American Rheumatism Association 1987 classification criteria [8]. International Classification of Disease codes [7,12,16,17], diagnosis codes [10,11] and/or DM-specific

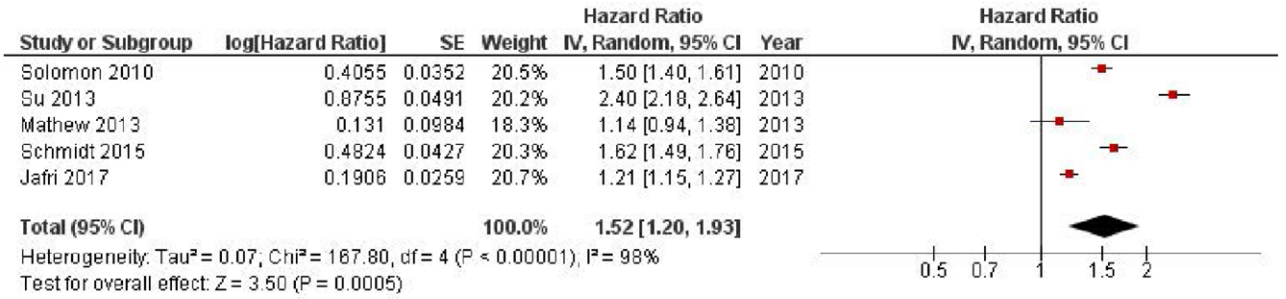
Fig. 2



RA: rheumatoid arthritis; CI: confidence interval; M-H Random: Mantel-Haenszel Random

Incidence of diabetes in people with rheumatoid arthritis compared with controls, calculated from a 2 × 2 table. RA, rheumatoid arthritis; CI, confidence interval; M–H random, Mantel–Haenszel random

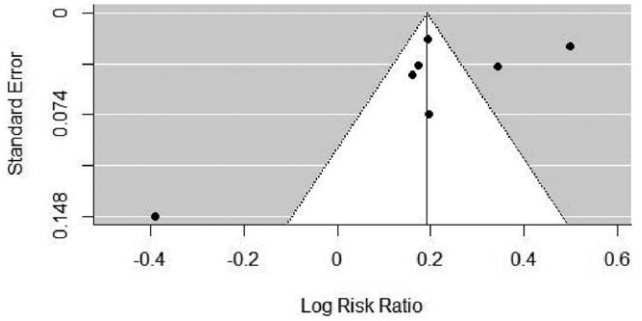
Fig. 3



RA: rheumatoid arthritis; CI: confidence interval; M-H Random: Mantel-Haenszel Random

Incidence of diabetes in people with rheumatoid arthritis compared with controls, generic inverse variance method. RA, rheumatoid arthritis; CI, confidence interval; M–H random, Mantel–Haenszel random.

Fig. 4



Publication bias in meta-analysis with funnel plot.

drug [7,11,12,16] were used to identify the DM. Two studies also used blood glucose to define the incidence of DM during follow-up (Table 1) [8,16]. The quality of the studies was good (7–8 stars, Supplementary Content 4, Supplemental digital content 1, *http://links.lww.com/CAEN/A29*).

The pooled RR from random-effects analysis for the association between RA and the risk of DM incidence is shown in Fig. 2, which was 1.23 (95% CI, 1.07–1.40). There was considerable between-study heterogeneity (I^2 = 96%). Exploration of potential sources of heterogeneity found that there was no significant heterogeneity in different study designs (P = 0.30). However, there was significant heterogeneity in different countries or regions (P = 0.002). RA was not significantly associated DM in studies conducted in the United States of America (RR, 0.92, 95% CI, 0.52–1.63, Supplementary Content 5, Supplemental digital content 1, *http://links.lww.com/CAEN/A29*).

Sensitivity analyses showed that the heterogeneity ranged from 84 to 96%, and confirmed that the association between RA and DM incidence was robust. We further performed a sensitivity analysis with studies reporting adjusted HR (Fig. 3), where the DM incidence was still higher in people with RA (HR, 1.52, 95% CI, 1.20–1.93). The funnel plot showed potential publication bias (Fig. 4), proven by Egger's test (–3.15, P < 0.01), but not Begg's test (–0.05, P = 1.00).

Discussion

Using both, calculation of pooled RR from a 2 × 2 table and adjusted HRs from original studies, we have confirmed an association between RA and DM, which was consistent across five included studies. Our finding strengthens the potential role of inflammation in DM on the basis of an increased incidence of this disease in people with RA.

Most eligible studies provided no distinction between different types of diabetes. Therefore we could not exclude the possibility that the data provided could represent the sum of all types of diabetes. However, considering T2DM accounts for more than 90% of all diabetes worldwide [18], and that the mean age of subjects in eligible studies was above 50 years old, it is reasonable to conclude that the papers in our meta-analysis predominantly described the link between RA and incidence of T2DM.

Accumulating evidence showed that inflammation emerges as a key factor in the onset of diabetes. The β-cell has a high density of interleukin-1β (IL-1β) receptors [19], and is susceptible to the toxic effects of innate mediators [20]. IL-1β, which is abundantly expressed in RA [21], induces the production of various cytokines and chemokines, including interleukin 6 (IL-6), interleukin-8, interleukin-33 and tumour necrosis factor-alpha (TNF-α). These mediators attract macrophages and other immune cells to the islet leading to β cell dysfunction and apoptosis, relative and absolute insulin deficiency and eventually DM [1]. Key pathways in the pathophysiology of RA include overproduction and overexpression of TNF-α and IL-6 [1]. TNF-α and IL-6 have

a deleterious effect on insulin sensitivity in animal experiments, and are involved in inhibiting insulin signalling, thereby promoting insulin resistance [22], which links to T2DM.

Subgroup analysis showed heterogeneity was significant for the countries or regions of study. RA was not significantly associated with RA in studies conducted in the United States of America. The reason for this may due to a high incidence rate of DM in the control group in one study of this group [7].

Widdifield *et al*. [23] found only half of the people with RA were screened for diabetes risk factors, including lipid testing, glycosylated haemoglobin testing or BMI. The screening rates were similar between RA and non-RA groups. However, people with RA are at greater risk of developing DM. Thus we suggest that RA patients require enhanced screening to prevent and reduce diabetes morbidity.

We have found only two previous meta-analyses focused on the association between RA and DM [9,24]. The substudy of Boyer in 2011 included seven case-control or cross-sectional studies and found people with RA had a higher prevalence of DM (odds ratio, 1.74; 95% CI, 1.22–2.50). The second meta-analysis of Jiang, in 2015, compared the prevalence (11 studies) and incidence (five studies) of DM between people with RA and those without. Our meta-analysis has updated the relationship between RA and incidence of DM from three points as follows: (1) two of five eligible studies reporting incidence in Jiang's article were from the same study population [8,25], so we only kept the most recent one in this study [8]; (2) we replaced another included study in Jiang's with the study of Jafri *et al*. [10], which used the same data as the previous one; (3) our meta-analysis also included three new retrospective cohort studies; (4) we included both conference abstracts and full texts for potential publication bias.

Our study also has several limitations. We only included English articles. There were only seven eligible studies in our study, so the power of funnel plot and Egger test was too low to test publication bias. We could not perform further subgroup analyses to explore the heterogeneity due to the limited number of studies.

Conclusion

RA is associated with an increased risk of diabetes incidence. This finding supports the notion that inflammatory pathways are involved in the pathogenesis of diabetes. We suggest that more intensive screening and tighter management of DM risk factors should be considered in people with RA.

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Conflicts of interest

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