Review

Diabetes mellitus risk factors in rheumatoid arthritis: a systematic review and meta-analysis

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ABSTRACT

Objective. *The aim of this study was to investigate the relationship between rheumatoid arthritis (RA) and the occurrence of diabetes mellitus (DM).*

Methods. *A meta-analysis was conducted to explore the risk of DM in RA patients. All relevant studies were identified by searching PUBMED, EMBASE and MEDLINE database prior to 1 January 2014. Pooled risk estimates were calculated with random-effects models using STATA 11.0.*

Results. *A total of 11 case-control studies and 8 cohort studies were included in the final analysis. The pooled risk estimate of 11 case-control studies showed a statistically significant increased risk of DM prevalence among RA individuals (OR=1.40, 95% CI: 1.34–1.47). The pooled risk estimate of 8 cohort studies also showed a statistically significant increasing risk of DM (RR=1.43, 95%CI: 1.38–1.47). In a subgroup analysis for case-control studies, the pooled risk estimate of individuals with RA increased the incidence of T1DM (type 1 diabetes mellitus) and the incidence of T2DM (type 2 diabetes mellitus) (OR, 4.78 vs. 1.41). In a subgroup analysis for cohort studies, RA was also found to have a statistically significant increasing risk of T2DM (RR=1.24, 95%CI: 1.14–1.35). Begg funnel plot and Egger test showed no evidence of publication bias.*

Conclusion. *RA is associated with increased risk of DM, including T1DM and T2DM.*

Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic systemic inflammatory disease of unknown aetiology that affects approximately 1% of the adult general population (1, 2). People with RA not only contribute an increased burden of chronic disease (3, 4), but also may increase the risk of cardiovascular morbidity and mortality compared with persons without RA (2, 5, 6). Diabetes mellitus (DM) is one of the most common cardiovascular disease risk factors, but the association between RA and DM morbidity still remains unclear.

Several case-control studies have suggested that RA plays a major role in diabetes mellitus development (7-9), however, in contrast, other studies have revealed that no significant associations were found between diabetes mellitus and RA (10, 11). Therefore, in the present study, we performed a systematic review of the literature and a meta-analysis to clarify the associations between RA and DM.

Methods

Literature collection

Two reviewers independently searched PUBMED, EMBASE and MEDLINE databases prior to 1 January 2014 for English-language studies. The MeSH (Medical Subject Heading) search headings were all combinations of index terms: "diabetes mellitus" or "DM" or "diabetes" and "arthritis, rheumatoid". We also reviewed the reference lists of retrieved articles to search more relevant studies.

Inclusion and exclusion criteria

Studies were eligible for inclusion into the meta-analysis as follows:

1. case control or cohort study;
2. the exposure of interest was RA;
3. the outcome was diabetes mellitus incidence;
4. studies reporting risk estimates with 95% confidence interval (CI) or providing available information to calculate risk estimates.

Abstracts, letters, reviews, case reports, studies lacking control groups and studies that did not provide sufficient

data to calculate risk estimates were excluded. If there was more than one publication from the same study population, only the study from the most recent publication was included. Two investigators independently selected studies and resolved any discrepancies by consensus.

Most studies used the American College of Rheumatology 1987 criteria to define RA; diabetes mellitus met the World Health Organization 1998 diagnostic criteria, with two determinations of fasting plasma glucose ≥126 mg/dl (7.0mmol/l) or a 2-h plasma glucose ≥200 mg/dl (11.1mmol/l).

Data extraction

For each eligible study, the following parameters were extracted independently by two researchers:

1. first author's last name, date of study publication and the country where the study was conducted;
2. study design;
3. type of control;
4. number of exposures in cases and controls;
5. risk estimates and 95%CI;
6. adjustments and other information.

The present meta-analysis included different measures of risk estimates (odds ratio, incidence rate ratio, standardised incidence ratio and hazard ratio). In fact, the different measures yielded a very similar risk estimate due to the scarce occurrence of DM in RA patients.

Quality score assessment

The quality of included studies was assessed based on the Newcastle-Ottawa Scale (NOS) (12). The NOS uses a 'star' rating system (range from 0 star to 9 stars) to judge quality. Studies with a score of 5 stars or greater were considered to be of reliable study quality.

Statistical analysis

A pooled risk estimate was calculated with a random-effects model, considering both intra-study and inter-study variance. Statistical heterogeneity was evaluated using the Q and I^2 statistics. For the Q statistic, $p<0.10$ was used as an indication of the existence of heterogeneity. To explore potential heterogeneity among studies, subgroup analysis was performed. Publication bias was assessed by using Begg funnel plot and the Egger test. A p-value of <0.10 was considered as an indicator of publication bias (13, 14). All statistical analyses were conducted using STATA11.0 for Windows (Stata, College Station, TX, USA).

Results

Search results

The literature search identified 2978 articles. With strict screening, a total of 11 case-control studies (8, 9, 15-23) and 8 cohort studies (6, 11, 24-29) were ultimately included in the present study (Fig. 1). Six case-control studies and three cohort sudies that did not report risk estimates were also included because they provided enough data to calculate the risk estimates (9, 11, 15, 17-19, 22, 24, 28). The main features of these studies are shown in Table I and Table II.

Characteristics of case-control studies

As listed in Table I, we identified 11 case-control studies from 2001 to 2012. Six studies were from the United States (8, 9, 15, 16, 22, 23), two from Austria (18, 19), one from Italy (17), one from Sweden (21) and one from the UK (20). A total of 30847 patients with RA were reported in these case-control studies. Among these cases, 3134 patients with DM, including 20 T1DM and 2976 T2DM, were reported. Regarding the remaining 138 patients with DM, the respective studies did not distinguish between T1DM and T2DM.

Among 121067 control subjects, a total of 9537 subjects with DM were reported. Controls recruited originated from hospital-based (17-19) or general population-based groups (8, 9, 15, 16, 20-23). Hospital-based control subjects were selected the same department as those without RA (17-19). Four studies found a statistically significant positive association between RA and DM (OR=1.4–3.08) (8, 16, 21, 23). One study did not find a positive association between RA and DM (20), whereas six studies did not report the risk estimates (9, 15, 17-19, 22). The NOS results showed that the average score of the 11 case-control studies was 6.1 (range 5–8), indicating that the methodological quality was satisfactory.

Characteristics of cohort studies

As listed in Table II, we identified 8 cohort studies reporting an association between RA and the risk of DM (6, 11, 24-29). Six cohort studies were from the United States (6, 11, 24, 27-29), one from the Netherlands (25), and one from Taiwan, China (26). More than 1309383 participants were included in the present meta-analysis study. The median follow-up period ranged from 2.0 to 17 years. Compared with non-RA patients, risk for DM with RA patients was significantly increased (RR=1.12–2.28) (6, 25-27, 29). The remaining three studies did not report the risk estimates (11, 24, 28). Su *et al*. reported that compared with non-RA patients, risk for T2DM with RA patients was 1.68-fold in men, 1.46-fold in women. The NOS results showed that the average score of the 8 cohort studies was 8 (range 7–9), indicating that the methodological quality was good.

Analysis for case-control studies

The meta-analysis for 11 case-control studies showed a statistically significant positive association between RA and diabetes incidence (OR=1.40, 95%CI 1.34–1.46, $p<0.001$) (Fig. 2). However, we found significant heterogeneity among these studies (I^2= 84.9%, $p<0.001$). In order to explore potential heterogeneity, we conducted subgroup analyses by geographic region, sources and type of diabetes (Table III). In the subgroup analyses, the pooled risk estimates were 1.42 (95%CI 1.36–1.49) for studies with population-based controls and 0.27 (95%CI 0.16–0.45) with hospital-based controls. The heterogeneity for subgroups with hospitalised controls was more significant than that for studies with population-based controls ($p<0.05$). The pooled OR of North American studies (OR=1.42, 95%CI 1.36–1.49) was higher than that of European studies (OR=0.30, 95%CI 0.18–0.49). Only 1 case-control study reported case incidence by T1DM (8) and 2 studies reported case incidence by T2DM (8, 16). The remaining stuies did not distinguish between T1DM and T2DM (9, 15, 17-23). The OR of

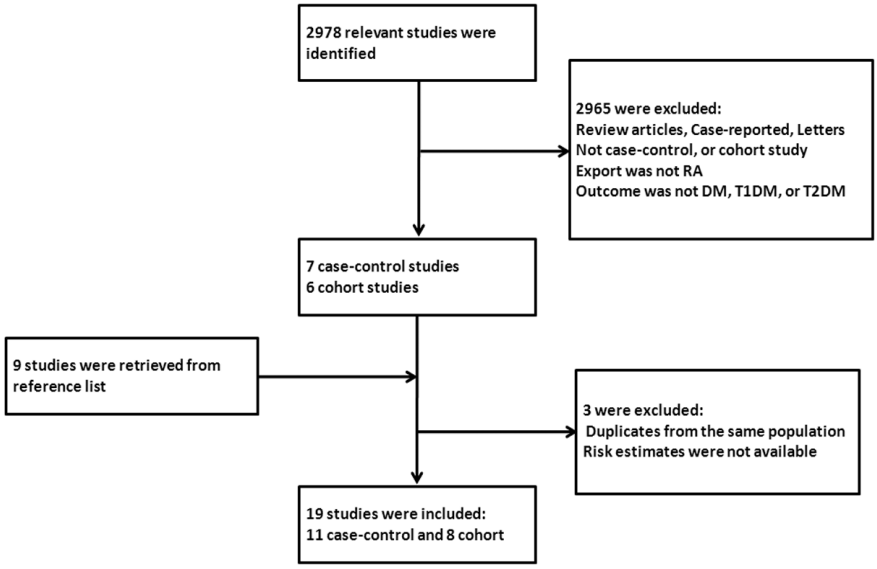

Fig. 1. Flow chart of selection and disposition of studies. A total of 2978 relevant studies were identified during the initial search and 19 studies remained after careful screening.

the T1DM study (OR=4.78, 95%CI 1.79–12.78) was higher than that of the T2DM studies (OR=1.41, 95%CI 1.35–1.47) and DM studies (OR=1.18, 95%CI 0.96–1.46).

Analysis for cohort studies

The meta-analysis for 8 cohort studies showed a statistically significant positive association between RA and diabetes incidence (RR=1.43, 95%CI 1.38–1.47, $p<0.001$) (Fig. 3). The heterogeneity among the studies was significant ($I^2=88.3\%$, $p<0.001$). The subgroup analysis by type of diabetes showed statistical significance between RA and the risk of T2DM (RR=1.24, 95%CI 1.14–1.35) or the risk of DM (RR=1.46, 95%CI 1.41–1.50). We still found that the pooled RR of the European study was higher than that of North America studies and Asian studies (2.02 *vs*. 1.46 *vs*. 1.18) (Table III).

Publication bias

Funnel plots showed no publication bias concerning case-control studies and cohort studies (Fig. 4-5). *p*-values for Begg's adjusted rank correlation test were positive ($p>0.05$), suggesting that publication bias had little effect on summary estimates.

Discussion

Diabetes mellitus is an important cardiac risk factor and it is on the rise. It is reported that over 240 million people globally have DM, and that 439 million people will be affected by DM in 2030. The most common cause of death among patients with diabetes is cardiovascular disease (30). The risk of increased cardiovascular morbidity and mortality among patients with diabetes has been recognised for years. Similarly, the most frequent cause of death in RA is cardiovascular disease. Moreover, cardiovascular disease mortality in persons with RA occurs in excess of what would normally be expected in people without RA (31). However, it is not clear if a higher-than-normal frequency of DM is attributable to RA. Although many researchers have focused on the association between RA and the risk of DM, the findings of these studies were not in agreement due to the differences between geographic regions, study design, sample size and controls. To date, no meta-analysis has focused on the association between RA and the risk of DM.

In the present study, NOS demonstrated high quality for cohort studies (7.9 score) and case-control studies (6.1 score). We found that the prevalence of

Table I. Characteristics of case-control studies of RA and the risk of DM.

Study	Country	RA (n)	Control (n)	Sources	Demographics Age (years)	Sex (% F)	DM Type	DM%	OR (95%CI)	Adjustment	Score
Liao (2009)[8]	USA	1419	1674	Population-based	18-70	71%	DM	4.4%	1.4(1.0-2.0)	age, sex, location of residence	8
					(range)		T1DM	1.4%	4.9(1.8-3.1)		
							T2DM	3.0%	1.1(0.7-1.5)		
Del Rincon (2003)[9]	USA	204	102	Population-based	59.6	89%	DM	18%	NR	NR	7
Han (2006)[16]	USA	28208	112832	Population-based	51.9	76.2%	T2DM	10.4%	1.4(1.3-1.4)	NR	7
Gerli (2005)[17]	Italy	101	75	Hospital-based	63	73%	DM	6.9%	NR	NR	5
Pieringer (2012)[18]	Austria	203	208	Hospital-based	56.3	83.7%	DM	3.4%	NR	NR	5
Brady (2009)[19]	Austria	50	150	Hospital-based	64.9	76%	DM	8.0%	NR	NR	6
McEntegart (2001)[20]	UK	76	641	Population-based	57	82.9%	DM	1.0%	0.44(0.06-0.31)	NR	6
Jonsson (2001)[21]	Sweden	39	39	Population-based	51.6	76.9%	DM	2.6%	3.08(0.12-77.91)	NR	7
Del Rincon (2005)[22]	USA	234	102	Population-based	59	89.7%	DM	16.7%	NR	NR	5
Rho (2009)[15]	USA	169	92	Population-based	54.2	69.2%	DM	11.2%	NR	NR	6
Simard (2007)[23]	USA	144	5152	Population-based	72.9	59%	DM	16.7%	1.3 (0.68–2.3)	NR	5

n: number; RA: rheumatoid arthritis; DM: diabetes mellitus; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; F: Female; CI: confidence interval; OR: odds ratio; NR: not reported.

Table II. Characteristics of cohort studies of RA and the risk of DM.

Study	Country	RA (n)	Non-RA (n)	Sources	Demographics Age (years)	Sex (% F)	follow-up (years)	DM Type	DM%	RR (95%CI)	Adjustment	Score
Doran (2002)[24]	USA	609	609	Population-based	58.0	73.1%	12.7	DM	4.1%	NR	NR	7
Solomon (2010)[27]	USA	48718	442033	Population-based	58.0	68.0%	0–11 (range)	DM	4.0%	1.5 (1.4–1.5)	Age and sex	8
Gonzalez (2008)[11]	USA	603	603	Population-based	58.0	73.0%	15	DM	7.3%	NR	NR	8
Peters (2009)[25]	Netherlands	312	1850	Population-based	63.0	65.0%	2.7	T2DM	7.0%	2.04 (1.12–3.67)	Age and sex	8
Del Rincon (2001)[6]	USA	236	4635	Population-based	22-80 (range)	62.3%	7–16 (range)	T2DM	16.1%	2.28 (1.65–3.12)	Age and sex	9
Su (2013)[26]	TaiWan, China	3839	596497	Population-based	>20	70.6%	0–12 (range)	T2DM	3.9% (Men) 7.7% (Women)	1.68(1.53–1.84) (Men) 1.46 (1.39–1.54) (Women)	NR	8
Solomon (2004)[28]	USA	287	87019	Population-based	56.1	100%	12	DM	4.8%	NR	NR	7
Dubreuil (2014)[29]	USA	11158	110375	Population-based	58.0	68%	5.5	DM	3.4%	1.12 (1.01–1.25)	Age-, sex- and entry time-matched	9

n: number; RA: rheumatoid arthritis; DM: diabetes mellitus; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; F: female; CI: confidence interval; RR: risk ratio; NR: not reported.

diabetes mellitus was increased in RA patients whether in case-control studies or cohort studies. Insulin resistance, an essential feature in the metabolic syndrome, is frequently observed in patients with RA, in particular in those with severe and active disease (32). On the other hand, impaired beta cell function is also found in these patients (33). Interestingly, anti-TNF-alpha therapy yields to beneficial effects on insulin resistance and insulin sensitivity in pa-

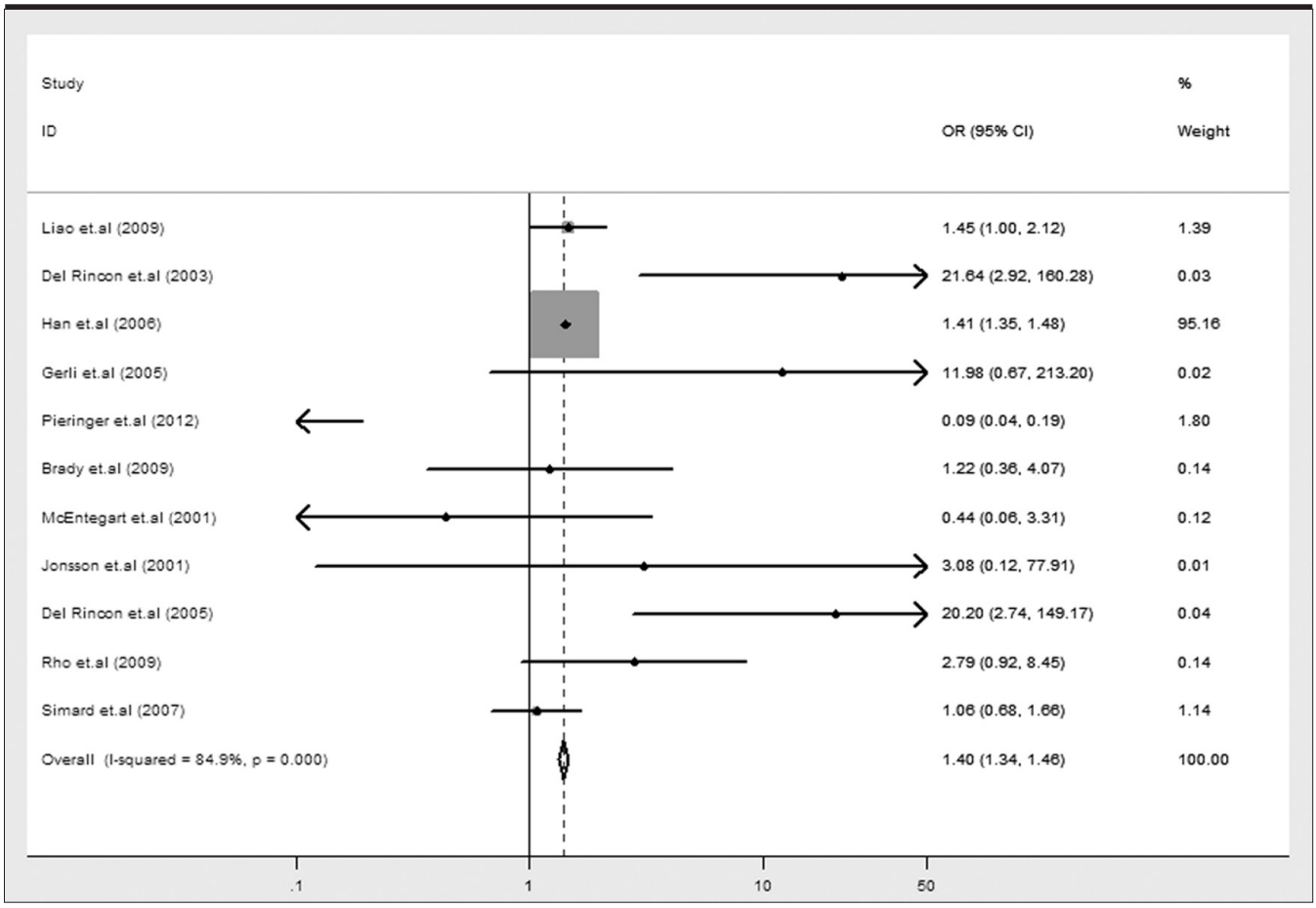

Fig. 2. Forest plot of DM risk associated with RA in 11 case-control studies. A statistically significant positive association was found between RA and DM incidence (OR=1.40, 95%CI: 1.34-1.46, $p<0.001$) in a random-effects model.

Table III. Summary of subgroup analyses for case-control and cohort studies.

Study	Number of studies	RR (OR) (95%CI)	I^2 (%)
In case-control studies	11	1.40 (1.34–1.46)	84.9
Control sources			
Population-based control	8	1.42 (1.36–1.49)	62.3%
Hospital-based control	3	0.27 (0.16–0.45)	90.1%
Geographic region			
North America	6	1.42 (1.36–1.49)	70.7%
Europe	5	0.30 (0.18–0.49)	82.4
Type of diabetes			
DM	10	1.18 (0.96–1.46)	85.8
T1DM	1	4.78 (1.79–12.78)	0
T2DM	2	1.41 (1.35–1.47)	28.0
In cohort studies	8	1.43 (1.38–1.47)	88.3
Type of diabetes			
DM	5	1.46 (1.41–1.50)	86.6
T2DM	3	1.24 (1.14–1.35)	89.0
Geographic region			
North America	6	1.46 (1.42–1.51)	86.6
Europe	1	2.02 (1.12–3.69)	0
East Asia	1	1.18 (1.08–1.28)	0

DM: diabetes mellitus; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; RR: risk ratio; CI: confidence interval.

tients with RA (34). Compared to people without RA, patients with RA had more than 1.40-fold increased risk of developing DM, which reached statistical significance ($p<0.05$). Several reasons may explain this result. A study conducted by Dessein *et al*. demonstrated that the insulin resistance reported in RA could be linked to DM (35). Chung *et al*. even found that insulin resistance might place patients at a higher risk for DM (36). Because both chronic systemic inflammation and glucocorticoid use can affect glucose metabolism, rheumatologists in clinical practice need to have a higher level of awareness of RA patients with DM and provide more aggressive intervention.

In order to explore the heterogeneity of studies, we conducted subgroup analysis in the case-control studies. We found that RA could increase the incidence of T1DM (OR=4.78) and T2DM (OR=1.41) or DM (OR=1.18) in studies that did not distinguish between T1DM and T2DM. In subgroup analysis of geographic regions regarding RA and the risk of DM, the pooled OR in studies from Europe were not statistically significant (OR=0.30). This might be due to three case-control studies that had selected hospitalised patients as controls rather than population-based controls. Hospitalised patients had more chances to be exposed to the risk of DM than the

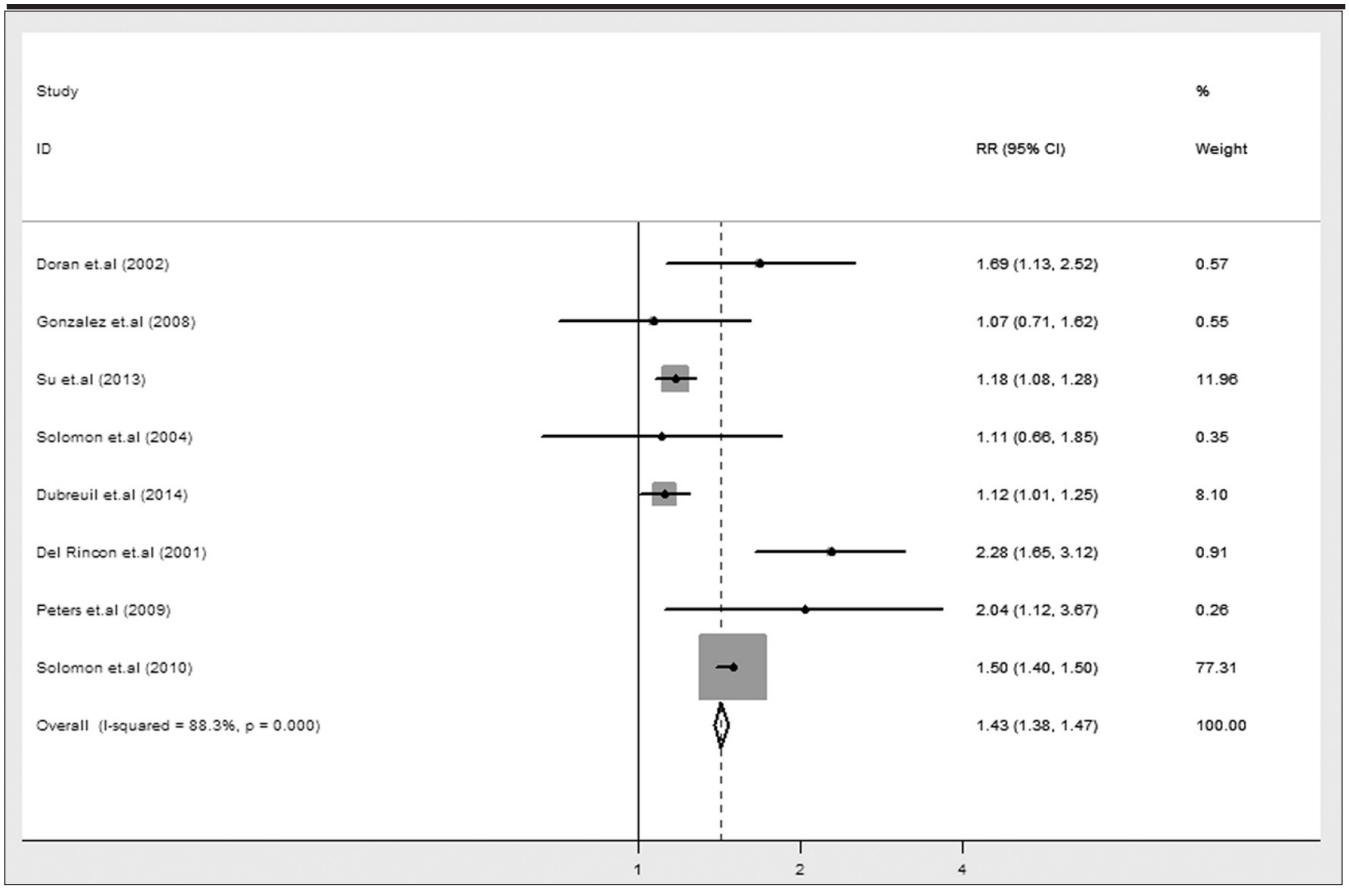

Fig. 3. Forest plot of DM risk associated with RA in 8 cohort studies. The pooled risk estimate was 1.43 (95%CI 1.38–1.47).

general population. In subgroup analysis of the cohort studies, the pooled RR was obviously higher in studies from North America and Europe than in those from Asia (1.46 *vs*. 2.02 *vs*. 1.18). This might be explained by the fact that diabetes has markedly higher prevalence in Europe and North America. Also, ethnic susceptibility to diabetes may be different in North America, Europe and Asia.

As for the type of diabetes, the incidence of RA-associated T1DM was higher than RA-associated T2DM (OR, 4.78 *vs*. 1.41). It has been reported that the association between T1DM and RA share the same genetic and environmental factors, for example, the presence or effect of the PTPN22 polymorphism (37-39). However, only one study included in the present meta-analysis reported the incidence of T1DM. Therefore, a larger sample of T1DM patients is needed to confirm results of the present study.

The mechanism of development of DM in patients with RA has not yet been clarified in detail. Inflammation in RA is characterised by increased levels of mediators and cytokines, including, for example, tumour necrosis factor-α and interleukin 6 (40-43). These cytokines appear to block the function of insulin, which may induce insulin resistance and ultimately result in development of DM. It also may be due to glucocorticoid use for the treatment of RA. Glucocorticoids deteriorate glucose tolerance due to multiple mechanisms, including augmentation of hepatic gluconeogenesis and inhibition of glucose uptake in adipose tissue (44).

This meta-analysis had several limitations that should be considered when explaining the results. First, this meta-analysis selected a small number of studies. This is a result of the strict prespecified criteria that were applied to the selection process, including study design, sex-and age-matched controls and validated criteria for RA and DM. Second, only one study reported the association between RA and T1DM, which influences the objective evaluation of associations between RA and T1DM. The third limitation of our work results from the statistical heterogeneity observed in our meta-analysis. This heterogeneity could be the result of disease duration or treatment disparities between the study populations (45, 46).

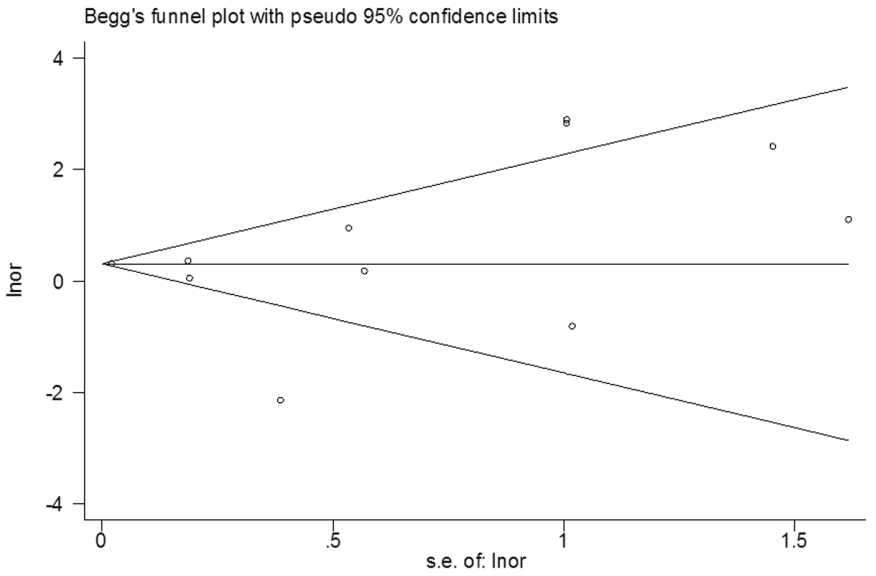

Fig. 4. Funnel plot of case-control studies. No publication bias was found in case-control studies (p=0.640) using Begg's adjusted rank correlation test.

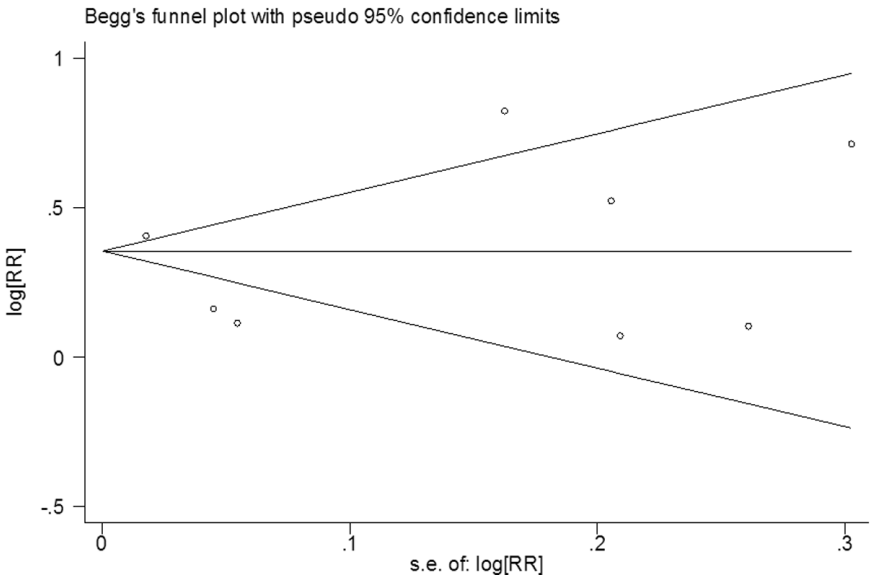

Fig. 5. Funnel plot of cohort studies. No publication bias was found in cohort studies (p=1.000) using Begg's adjusted rank correlation test.

Conclusion

In conclusion, despite these limitations of the study, our results have revealed that RA is associated with significantly increasing risk of DM. Further research is needed to understand the precise mechanism of increased DM in RA.

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