Systematic Review and Meta-Analysis

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# Methotrexate can prevent cardiovascular events in patients with rheumatoid arthritis

## An updated meta-analysis

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**Abstract**

**Aims:** The incidence of cardiovascular events (CVEs) in patients with rheumatoid arthritis (RA) is higher than that in people without RA. This may be because inflammation promotes the progression of atherosclerosis. Anti-inflammatory drugs might reduce the occurrence of CVEs in patients with RA. Methotrexate (MTX) is a conventional synthetic anti-rheumatic drug that is widely used in the treatment of RA. We performed a meta-analysis to determine whether MTX can prevent CVEs in RA patients. Then, we discussed the possibility of using MTX to prevent recurred CVEs in patients with coronary heart disease (CHD).

**Methods:** We searched PubMed, Embase, Web of Science, and the Cochrane Library using the key words "methotrexate," "cardiovascular," "acute coronary syndrome," "coronary heart disease," "myocardial infarction," "angina pectoris," and "rheumatoid arthritis." The efficacy outcome was defined as a composite of CVEs, including stable angina, acute coronary syndrome, stroke, heart failure, and cardiac death.

**Results:** A total of 10 studies and 195,416 RA patients were included in our meta-analysis, and the effect size of relative risk (RR) was pooled using a fixed effect model. The results showed that MTX prevented CVEs in RA patients (RR: 0.798, 95% CI 0.726–0.876, $P = .001$, $I^2 = 27.9\%$).

**Conclusion:** MTX can prevent CVEs in RA patients, but there is not sufficient evidence for using MTX to treat patients with CHD.

**Abbreviations:** ACS = acute coronary syndrome, CHD = coronary heart disease, CVE = cardiovascular events, Hs-CRP = hypersensitive C-reactive protein, MTX = methotrexate, NOS = Newcastle-Ottawa Scale, RA = rheumatoid arthritis, RR = relative risk.

**Keywords:** cardiovascular events, meta-analysis, methotrexate, treatment

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by symmetrical polyarthritis, and inflammation promotes the development of atherosclerosis,[1] which is the core pathological change in coronary heart disease (CHD). Clinical studies have confirmed that patients with RA had an increased incidence of cardiovascular events (CVEs) compared to people without RA.[2,3] Therefore, it is possible that anti-inflammatory drugs may inhibit the inflammatory response in RA patients and reduce the incidence of CVEs.

Many anti-inflammatory drugs have been tested for their effects on atherosclerosis. For example, the CANTOS study found that the IL-1β monoclonal antibody (Canakinumab) reduced hypersensitive C-reactive protein (hs-CRP) and IL-6 levels as well as prevented CVEs.[4] In the COLCOT study, colchicine did not reduce hs-CRP levels but did prevent CVEs (HR = 0.77, 95% CI 0.79–1.16, $P = .02$).[5] Methotrexate (MTX) is a commonly used anti-inflammatory drug that can suppress inflammation by inhibiting dihydrofolitic reductase and causing the extracellular accumulation of adenosine.[6] However, the CIRT study found that MTX could not reduce the level of inflammatory factors or the incidence of CVEs in CHD patients.[7]

To fully interpret the results of the CIRT study, we re-retrieved studies related to MTX and CVEs, with the intention of summarizing the results of the existing studies by means of a meta-analysis. However, the vast majority of current studies discussing the role of MTX in CVEs prevention have primarily focused on rheumatic disease. Many observational studies have explored the effects of MTX on CVEs in RA patients[8–17]; however, the results are conflicting. For example, some studies suggested that MTX may prevent CVEs in RA patients,[12–14,17] while others found no statistically significant differences.[8–11,15,16] Previous meta-analyses summarized the results of these

Editor: Nicola Cosentino.

This work was supported by grants from the National Natural Science Fund of China (81871858).

The authors declare no conflict of interest.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Sun Kj, Liu Ll, Hu Jh, Chen Yy, Xu Dy. Methotrexate can prevent cardiovascular events in patients with rheumatoid arthritis: An updated meta-analysis. Medicine 2021;100:7(e24579).

Received: 27 September 2020 / Received in final form: 13 January 2021 / Accepted: 14 January 2021

http://dx.doi.org/10.1097/MD.0000000000024579

studies and concluded that MTX had a positive effect on preventing CVEs in RA patients.[18,19]

Nevertheless, the aforementioned meta-analysis[18,19] did not include studies published after 2015 nor did it discuss using MTX to treat patients with CHD. Therefore, we added newly published studies[16,17] to reassess the role of MTX in CVEs in RA patients. We also discussed the possibility of extending the application of MTX from RA patients to those with CHD.

## 2. Methods

### 2.1. Data sources

We searched multiple medical databases, including PubMed, Embase, Web of Science, and the Cochrane Library, using the key words "methotrexate," "cardiovascular," "acute coronary syndrome," "coronary heart disease," "myocardial infarction," "angina pectoris," and "rheumatoid arthritis." The search included publications available online up to September 2019. Article types were restricted to "clinical trials." The language the study was published in was not restricted. The literature search was performed according to the guidelines and recommendations expressed in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[20] Ethical approval was waived because this study did not involve individual patient data.

### 2.2. Inclusion criteria

Studies included must have patients diagnosed with RA with a duration of follow-up lasting at least 3 months. The intervention used must be MTX. The outcome was a composite of CVEs, including stable angina, acute coronary syndrome (ACS), stroke, heart failure, and cardiac death.

### 2.3. Data extraction

Two authors independently extracted data from each study. Extracted data included published year, study design, number of participants, number of events, inclusion criteria, duration of follow-up, assessment of disease severity, MTX exposure status, covariates adjusted in the regression models, adjusted risk estimates, and confidence intervals (95% CI). Any disagreements were resolved by consensus among the authors.

### 2.4. Assessment of the quality of the study

We used the Newcastle-Ottawa Scale (NOS) for quality assessment.[21] The studies were judged on 3 broad perspectives: the selection of the study groups (0–4 points); the comparability of the groups (0–2 points); and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies (0–3 points). In the cohort studies, a follow-up time of more than 3 years was considered sufficient for outcomes to occur and this was scored as 1 point on the NOS. Four confounders (demographic information, disease severity, cardiovascular risk factors, and anti-rheumatic medications) were adjusted in the analysis to ensure comparability between groups. If disease severity or the other 3 confounders were adjusted, this was scored as 1 point on the NOS. A maximum of 2 points were allotted on the NOS when determining the comparability between groups. Quality scores from 0 to 4 were considered low quality and from 5 to 9 were considered high quality. Low-quality studies were excluded in the sensitivity analysis.

### 2.5. Statistical analysis

The impact of MTX on the occurrence of CVEs was evaluated using relative risk (RR). We did not distinguish between the odds ratio, risk ratio, or hazard ratio. Pooled relative risk was obtained through the fixed effect (Inverse Variance) or random effect ($I$–$V$ heterogeneity) models. Heterogeneity was assessed using the $I^2$ statistic.[22] When the heterogeneity was low ($I^2 < 40\%$), we used a fixed effect model, otherwise we used a random effect model. The source of the heterogeneity was analyzed by subgroup analysis and meta regression. Possible confounding factors included study design, study location, follow-up time, MTX exposure status, adjusted factors in regression and NOS score. Publication bias for the efficacy outcome was assessed using a Begg's test,[23] Egger's test[24] and a funnel plot. Results were defined as statistically significant if $P < .05$. All statistical analyses were performed using STATA software ver. 12 (StataCorp, College Station, TX, USA).[25]

## 3. Results

### 3.1. Baseline characteristics and quality assessment

Of the 718 records retrieved, only 10 clinical trials[8–17] were included in our meta-analysis (Fig. 1). The 10 clinical trials consisted of 3 cohort studies, 2 cross-sectional studies, 1 case–control study, and 4 nest case–control studies. A total of 195,416 participants were included, of whom 4259 had CVEs. The mean age of study participants ranged from 41 to 70 years, the mean follow-up time ranged from 1 to 13 years, and the mean duration of disease ranged from 1 to 15 years. Details of the baseline characteristics of individual studies are reported in Table 1.

Each included study had an NOS score greater than 5 points, indicating that the included studies were of high-quality (100%). The score for each category is shown in Table 2.

### 3.2. Efficacy outcomes

Overall, the studies showed that MTX could prevent CVEs in patients with RA. The pooled effect size of RR was 0.798 (95% CI 0.726–0.876, $P < .001$; Fig. 2), indicating that MTX had a protective effect in this process. The heterogeneity among the 10 included studies was 27.9%; therefore, the fixed effect model was applied.

We performed subgroup analyses based on MTX exposure and adjusted factors in the original regression models of each study to observe the effects of MTX on CVEs. We also analyzed the heterogeneity in each subgroup. In addition, the effects of mixing HR and RR/OR and the effects of different clinical trial types on the results were also clarified through subgroup analyses. The results of the subgroup analyses are shown in Table 3.

MTX exposure statuses include "MTX ever-users" and " MTX current-users." "Ever" therapy indicated that the patients had received MTX therapy at any time up to and including the observation period. "Current" therapy indicated patients who had received MTX therapy within 6 months of the index event. MTX ever-users included 7 studies, of which the pooled RR was 0.807 (95% CI 0.720–0.904, $P = .003$, $I^2 = 50.1\%$). The MTX

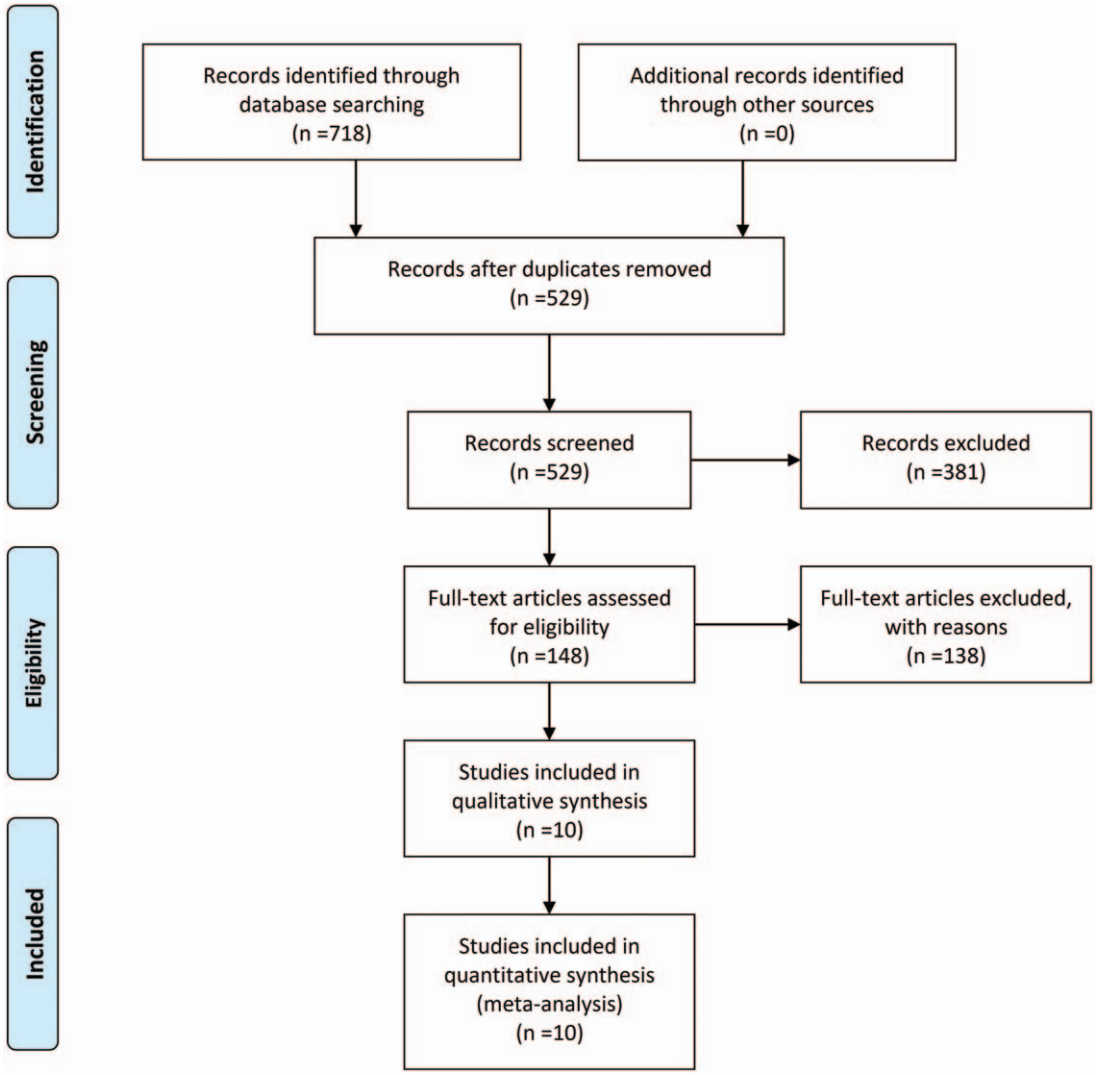


**Figure 1.** Screening of original articles.

current-users group included 3 studies, of which the pooled RR was 0.780 (95% CI 0.662–0.919, $P < .001$, $I^2 = 0.0\%$). In either exposure status, MTX could prevent the occurrence of CVEs in patients with RA.

A total of 3 studies reported the effect of MTX monotherapy and their pooled RR value was 0.855 (95% CI 0.726–1.007, $P = .06$, $I^2 = 0\,0\%$). A total of 7 studies that reported mixed effects of MTX had a pooled RR of 0.771 (95% CI 0.688–0.865,

**Table 1**

**Baseline characteristics of the individual studies.**

| Study | Year | Design | Patients | Outcome | Events | Exposure status | Follow-up (yr) | Mean age (yr) | Duration of disease (yr) | Adjusted factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Choi[8] | 2002 | Cohort | 1240 | CVD mortality | 84 | Ever | 6 | 57 | 9.4 | 1,2,3,4 |
| Bernatsky[9] | 2005 | Nested case–control | 41,885 | CHF hospitalization | 520 | Current | 1 | 65 | NR | 1,3,4 |
| Prodanowich[10] | 2005 | Cohort | 6707 | CVD events | 2017 | Ever | NR | 64.4 | NR | 1,3,4 |
| van Halm[11] | 2006 | Case control | 613 | AMI hospitalization | 72 | Ever | 9.2 | 63 | 8 | 1,2,4 |
| Suissa[12] | 2006 | Nested case–control | 10,7908 | CVD events | 558 | Current | 1.2 | 65 | NR | 1,3,4 |
| Wolfe[13] | 2008 | Nested case–control | 16,748 | Ischemic stroke | 223 | Ever | 3 | 41 | NR | 2,3 |
| Nadareishvili[14] | 2008 | Nested case–control | 4351 | MI | 59 | Ever | 3.9 | 70 | 15.9 | 2,4 |
| Ajeganova[15] | 2013 | Cohort | 741 | MI | 177 | Current | 13 | 55 | <1 | 1,2,3,4 |
| Jin[16] | 2017 | Cross-sectional | 13,210 | CVD events | 293 | Ever | NR | 52.9 | 4 | 1,2,4 |
| Li[17] | 2017 | Cross-sectional | 2013 | CVD events | 256 | Ever | NR | 55.5 | 6 | 1,2,3,4 |

Adjusted factors consisted of 1, 2, 3, and 4, which were demographic information, disease severity, cardiovascular risk factors, and anti-rheumatic drugs, respectively.
AMI = acute myocardial infarction, CHF = chronic heart failure, CVD = cardiovascular disease, MI = myocardial infarction, NR = not reported.

**Table 2**

**Quality assessment for individual studies.**

| | Selection | | | | Comparability | Exposure or outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| Study | (1) | (2) | (3) | (4) | (1) | (1) | (2) | (3) | Score |
| Ajeganova | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7 |
| Bernatsky | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 6 |
| Choi | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |
| Jin | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 5 |
| Li | 1 | 1 | 0 | 1 | 2 | 0 | 1 | 0 | 6 |
| van Halm | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 5 |
| Suissa | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 6 |
| Wolfe | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 6 |
| Nadareishvili | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 7 |
| Prodanowich | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 5 |

$P < .001$, $I^2 = 40.5\%$), suggesting that the preventive effect of MTX on CVEs in RA patients could be impacted by treatment with other drugs.

There were 8 studies that adjusted for demographic information, such as age and sex, and their combined RR value was 0.780 (95% CI 0.706–0.862, $P < .001$, $I^2 = 31.6\%$). There were 2 studies with unadjusted demographic information and the combined RR value was 0.957 (95% CI 0.722–1.269, $P = .759$, $I^2 = 0.0\%$). These findings suggested that the preventive effect of MTX on CVEs in RA patients was affected by demographic information.

There were 7 studies that adjusted for disease severity and their combined RR was 0.762 (95% CI 0.654–0.888, $P = .001$, $I^2 = 49.4\%$). There were 3 studies that did not adjust for disease severity and they had a combined RR value of 0.820 (95% CI 0.728–0.924, $P = .001$, $I^2 = 0.0\%$). The preventive effect of MTX

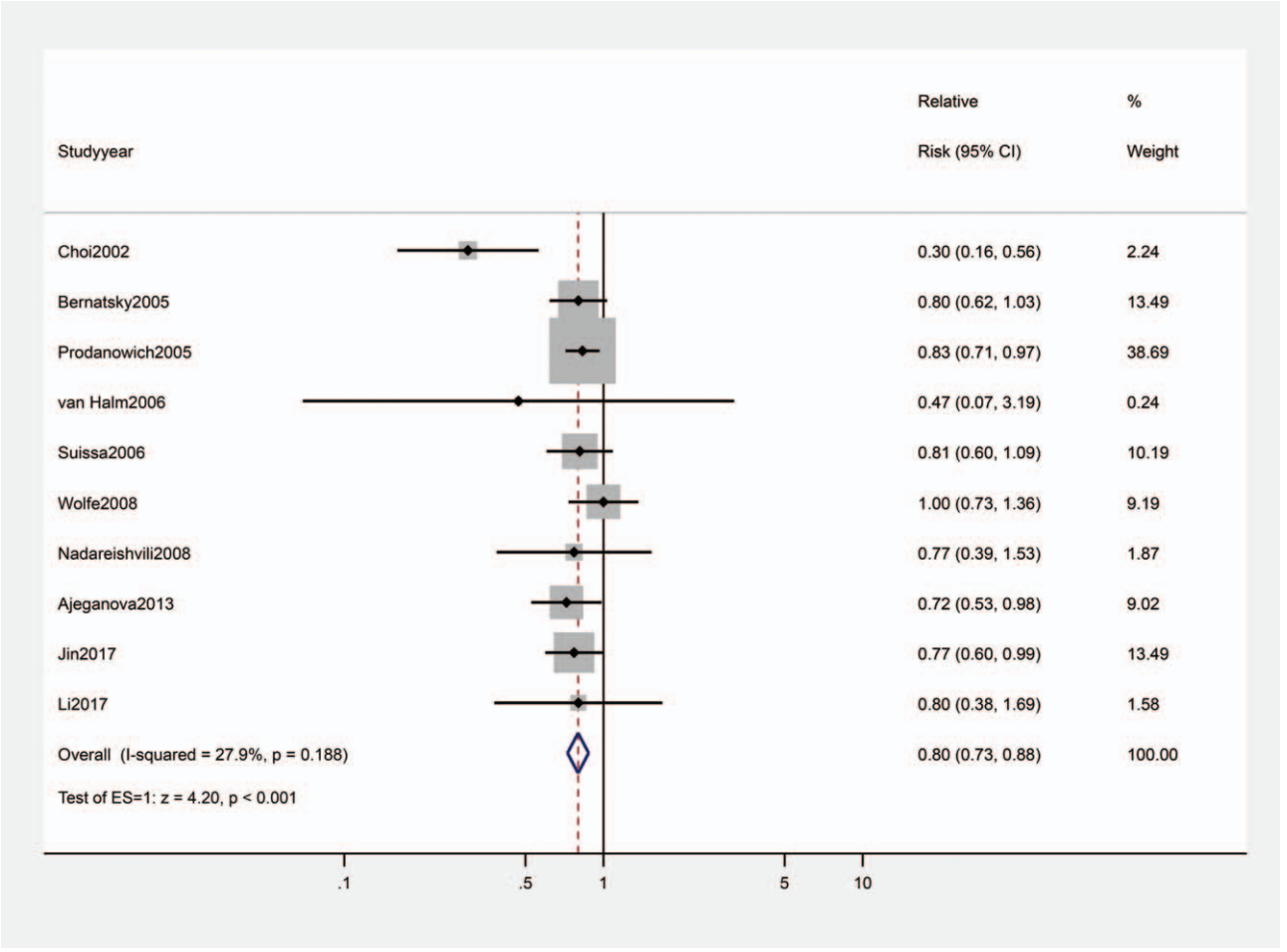


**Figure 2.** Forest plot of the effects of MTX on CVEs in RA patients. Each row represents the RR and 95% CI of the study, and the size of the markers represented weights. CVE = cardiovascular events, MTX = methotrexate, RA = rheumatoid arthritis, RR = relative risk.

**Table 3**

**Multiple variables were analyzed for the subgroup analysis.**

| Variable | | Number of studies | RR (95% CI) | *P* | $I^2$ |
|---|---|---|---|---|---|
| Relative risk | RR/OR | 8 | 0.826 (0.748–0.913) | <.001 | 0.0 |
| | HR | 2 | 0.605 (0.457–0.800) | <.001 | 83.4 |
| MTX exposure status | Cohort | 3 | 0.773 (0.677–0.883) | .003 | 79.6 |
| | Cross-sectional | 2 | 0.773 (0.607–0.984) | .003 | 0.0 |
| | Case–control | 1 | 0.470 (0.069–3.193) | .003 | NA |
| | Nest case–control | 4 | 0.850 (0.725–0.997) | .003 | 0.0 |
| Exposure | | | | | |
| MTX exposure status | Ever | 7 | 0.807 (0.720–0.904) | .003 | 50.1 |
| | Current | 3 | 0.780 (0.662–0.919) | .001 | 0.0 |
| MTX monotherapy | Yes | 3 | 0.855 (0.726–1.007) | .06 | 0.0 |
| | No | 7 | 0.771 (0.688–0.865) | <.001 | 40.5 |
| Adjusted factors | | | | | |
| Demographic factors | Yes | 8 | 0.780 (0.706–0.862) | <.001 | 31.6 |
| | No | 2 | 0.957 (0.722–1.269) | .759 | 0.0 |
| Disease severity | Yes | 7 | 0.762 (0.654–0.888) | .001 | 49.4 |
| | No | 3 | 0.820 (0.728–0.924) | .001 | 0.0 |
| Cardiovascular risk factors | Yes | 8 | 0.780 (0.706–0.862) | .003 | 31.6 |
| | No | 2 | 0.764 (0.603–0.969) | .026 | 0.0 |
| Medication factors | Yes | 9 | 0.780 (0.707–0.861) | <.001 | 21.8 |
| | No | 1 | 1.000 (0.700–1.300) | .837 | - |

The grouping factors were divided into 2 categories: MTX exposure and adjusted factors. The combined RR and 95% CI are shown in the table.
NA = not applied, RR = relative risk.

on CVEs in RA patients was not affected by the severity of the disease.

A total of 8 studies adjusted for cardiovascular risk factors and had a combined RR value of 0.780 (95% CI 0.706–0.862, $P=.003$, $I^2=31.6\%$). Two studies did not adjust for cardiovascular risk factors and had a combined RR of 0.764 (95% CI 0.603–0.969, $P=.026$, $I^2=0.0\%$). This subgroup analysis suggested that the preventive effect of MTX on CVEs in RA patients was not affected by traditional cardiovascular risk factors.

### 3.3. Sensitivity analysis, meta regression, and publication bias

A sensitivity analysis was performed by excluding each study one by one. We found that the pooled RR and 95% CI did not

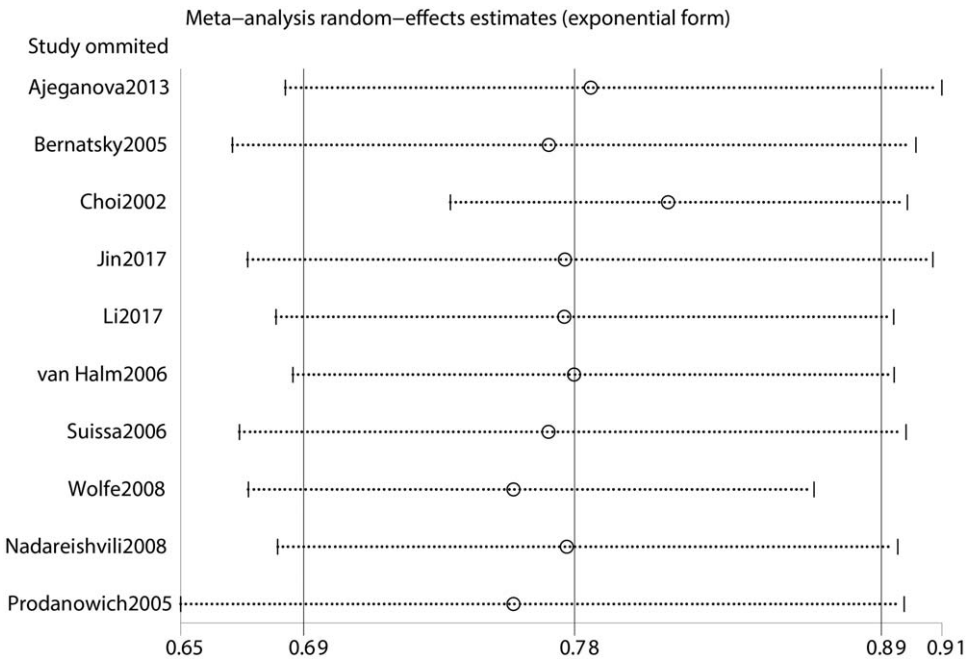


**Figure 3.** Sensitivity analysis. To observe the effect of a single study on the stability of the results, each row represents the results of the meta-analysis of the remaining studies after excluding each study. The circle represents the mean of RR and the dashed line represents the 95% CI. RR = relative risk.

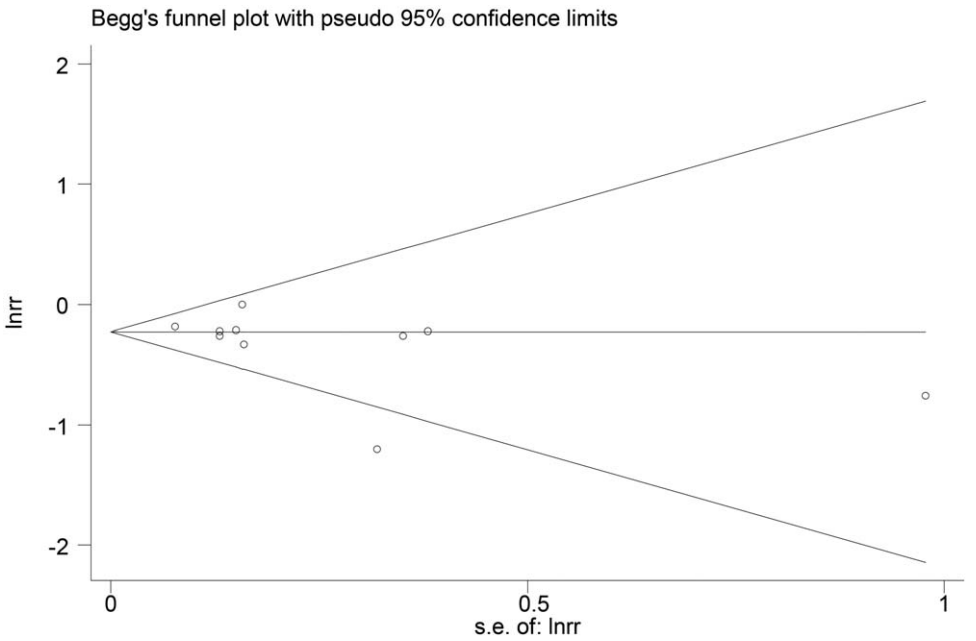


**Figure 4.** Funnel plot. Each point represents a clinical study and the upper and lower oblique lines represent 95% CI.

significantly shift with the exclusions of studies, indicating that the conclusions made by this meta-analysis were stable (Fig. 3).

A meta regression analysis was performed using the total number of participants (i.e., 195,416 participants) as the variable and obtained a *P* value of .783. This suggested that heterogeneity was not related to the total number of participants. When using the quality score as the variable, the *P* value was .153. These data indicated that heterogeneity was not related to the quality score.

The Begg's test had a *P* value of .209 and the Egger test had a *P* value of .416. The funnel plot was bilaterally symmetric, confirming that there was no publication bias (Fig. 4).

## 4. Discussion

The results of our meta-analysis showed that MTX could indeed prevent CVEs in RA patients (RR: 0.798, 95% CI 0.726–0.876, $P < .001$). The heterogeneity between the included studies was low ($I^2 = 27.9\%$) and we found that excluding some studies did not affect the final conclusion.

After further analyses of heterogeneity, we determined 2 main sources of heterogeneity: MTX exposure status and adjusted factors. Specifically, the MTX ever-users group included patients who were currently taking MTX and patients who had stopped using MTX and switched to other drugs. In addition, the MTX current-users group included patients who took MTX and other drugs. These 2 variables caused heterogeneity in the results because of combined effects due to other drug treatments. The adjusted factors (demographic information, disease severity, cardiovascular risk factors, and medications) varied among the included studies (Table 1). However, the adjusted factors in the table were simplified. For example, disease severity could be assessed by various indicators, specifically, some studies used indicators such as RF and CRP, while other studies used the DAS score. This difference in the adjusted factors in the included studies was also an important source of heterogeneity.

According to the results of previous studies on RA patients, MTX could prevent CVEs in RA patients. However, in the CIRT study,[7] we failed to migrate this conclusion from RA patients to CHD patients. This may be because the CIRT study included a population with a lower inflammation level. The CIRT study did not set the criteria for hs-CRP, resulting in a median hs-CRP level of only 1.6 mg/L. This level was lower than the currently defined residual inflammatory risk in CHD (2 mg/L), indicating that the study population was a low-risk group with limited anti-inflammatory benefits expected. In addition, Ajeganova reported that the median hs-CRP level of RA patients was 19 mg/L (interquartile range was 6–46 mg/L), which was much higher than 1.6 mg/L.[15] Therefore, no matter whether the level of hs-CRP in the CIRT study was compared with patients with RA or CHD, the CIRT study population had a low risk of inflammation, increasing the possibility of negative results. This could be remedied by redesigning the RCT trial with a restriction on the inflammation level and a stratified analysis of the CIRT study should be considered based on the inflammation level.

Another reason that the conclusions do not transfer from RA patients to CHD patients is because the population included in the CIRT had CHD history. The patients included in the CIRT study had a history of myocardial infarction or multiple coronary artery diseases and either type 2 diabetes or metabolic syndrome. However, the studies included in our meta-analysis excluded patients with a history of CVEs when patients entered the cohort. Compared to this series of observational studies, the intervention time point of the CIRT study for CHD was delayed. A new RCT study should be conducted in CHD patients without previous CVEs.

Moreover, the CIRT study evaluated the effect of MTX monotherapy as a randomized controlled trial, thus the intervention effects of the MTX group were compared with the placebo group. However, most studies included in our meta-analysis reported the mixed effects of MTX, indicating that

patients would not be excluded if they took other anti-rheumatic drugs in addition to MTX. We note that none of the studies that reported the effect of MTX monotherapy found that MTX had an effect on CVEs in RA patients.[9,12,13] This suggested that even when the level of inflammation was high in patients, MTX monotherapy might not prevent CVEs, as the preventive effect might actually come from other drugs or the interaction of multiple drugs. Considering that it was difficult for observational studies to balance various confounding factors, future randomized control studies should be designed to report monotherapy effects.

In RA patients, this meta-analysis reinforced MTX as the preferred drug from the perspective of preventing CVEs. However, there is not sufficient evidence for or against the use of MTX in patients with CHD to prevent CVEs. According to the results of the CIRT study, MTX was ineffective at preventing CVEs in the unselected CHD population. However, the effect of MTX in CHD patients with high residual inflammatory risks or with no previous history of CVEs requires further research.

Although from the results of the CIRT study, MTX cannot prevent the occurrence of CVEs in CHD patients, it still has the potential to interfere with CVEs through anti-inflammatory pathways. In addition to MTX, other DMARDs have also been shown to have cardiovascular protection effects.[26] In our study, MTX combined with other drugs could further reduce the incidence of CVEs compared to the MTX monotherapy (0.855 vs 0.771). This suggested that the combination of anti-inflammatory drugs might be more effective to treat CHD, but the side effects of this strategy need to be more carefully evaluated.

This meta-analysis included a large number of participants (>190,000 individuals), of which 4259 had CVEs. The analysis of the large sample size contributed to the accuracy of the conclusions. Another advantage of this meta-analysis is the addition of Chinese patients.[16,17] The addition of RA patients from China made the conclusions applicable to a wider range of population. Moreover, this meta-analysis summarized the sources of heterogeneity. We attributed the sources of heterogeneity to the MTX exposure status and model adjustment factors, providing a reference for future research. The final advantage of this study was the possibility of using MTX in CHD patients, with a further discussion of future research directions.

This meta-analysis did have limitations. Specifically, all of the studies included were observational studies, which could not balance irrelevant factor differences between groups and could cause potential bias. And different research types had little influence on the conclusions. Each study remedied possible biases by incorporating these factors into regression models. In addition, the adjustment factors in the various studies were not completely consistent. Besides, our study did not distinguish between HR, RR and OR, which may lead to the omission of the time factor, although the conclusions are similar in the HR group and the OR/RR group. Finally, the monotherapy effect of MTX cannot be confirmed. Only 3 studies explicitly reported the monotherapy of MTX and the other studies presented mixed effects of MTX and other drugs. The subgroup analysis suggested that MTX monotherapy might have a protective effect (RR = 0.855, 95% CI 0.726–1.007), but this was not statistically significant ($P = .06$). The mixed effect results suggested an overestimation of the protective effect of MTX (RR = 0.771, 95% CI 0.688–0.865, $P < .001$).

## 5. Conclusions

In RA patients, MTX could prevent CVEs. Sufficient evidence is lacking related to the use of MTX for the treatment of patients with CHD. Therefore, future studies should be conducted to determine whether MTX can be used to treat patients with CHD.

## Author contributions

**Conceptualization:** Danyan Xu.
**Data curation:** Kai-jun Sun, Lei-ling Liu.
**Formal analysis:** Kai-jun Sun, Lei-ling Liu.
**Methodology:** Kai-jun Sun, Danyan Xu.
**Project administration:** Danyan Xu.
**Software:** Kai-jun Sun, Lei-ling Liu.
**Writing – original draft:** Kai-jun Sun.
**Writing – review & editing:** Jia-hui Hu, Yan-ying Chen, Danyan Xu.

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