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ORIGINAL RESEARCH

Association between disease-modifying antirheumatic drugs for rheumatoid arthritis and risk of incident dementia: a systematic review with meta-analysis

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ABSTRACT

Background Dysregulation of several inflammatory cytokines including tumour necrosis factor (TNF) in dementia patients has also been identified as a key factor in the pathogenesis of rheumatoid arthritis (RA). We aimed to investigate the association of disease-modifying antirheumatic drugs (DMARDs) therapy for RA with risk of incident dementia.

Methods Electronic database searches of PubMed, EMBASE and Cochrane Library were performed. Observational studies that assessed the association of dementia with DMARDs in RA were included. Pooled risk ratios (RRs) with 95% CIs were used as summary statistic. The certainty of evidence was judged by using the Grading of Recommendations Assessment, Development and Evaluation system.

Results Overall, 14 studies involving 940 442 patients with RA were included. Pooled RR for developing dementia was 0.76 (95% CI 0.72 to 0.80) in patients taking biological DMARDs overall versus those taking conventional synthetic DMARDs, with 24% for TNF inhibitors (RR 0.76, 95% CI 0.71 to 0.82), 24% for non-TNF biologics (RR 0.76, 95% CI 0.70 to 0.83), separately. There was a significant subgroup effect among different types of TNF inhibitors (RR 0.58 [95%CI 0.53 to 0.65], 0.65 [95% CI 0.59 to 0.72], 0.80 [95% CI 0.72 to 0.88] for etanercept, adalimumab, infliximab, respectively; p value between groups=0.002). However, compared with non-users of DMARDs or investigative treatment, no significant effect on dementia incidence was observed in those receiving conventional synthetic DMARDs overall (RR 0.84, 95% CI 0.59 to 1.20), methotrexate (RR 0.78, 95% CI 0.54 to 1.12), hydroxychloroquine (RR 0.95, 95% CI 0.63 to 1.44), except for sulfasalazine (RR 1.27, 95% CI 1.06 to 1.50).

Conclusions Biological DMARDs for RA are associated with decreased dementia risk, while protective effect is not observed in conventional synthetic DMARDs. Controlled clinical trials on TNF inhibitors are necessary to test their neuroprotective potentials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dementia is a prevalent neurodegenerative disorder without effective therapies, leading to a high economic and social burden. Existing epidemiological evidence also suggests an increased risk of incident dementia associated with rheumatoid arthritis (RA).

⇒ Chronic systemic inflammation is believed to be involved in the development of dementia. Dysregulation of several inflammatory cytokines including tumour necrosis factor (TNF) in dementia patients has also been identified as a key factor in the pathogenesis of RA.

⇒ Modulating systemic inflammation with disease-modifying antirheumatic drugs (DMARDs) is hypothesised to attenuate the development of dementia. But results of potential benefit from DMARDs on dementia risk are still highly controversial in clinical observations.

WHAT THIS STUDY ADDS

⇒ We found treatment with biological DMARDs was associated with approximately 30% reduction in dementia risk in patients with RA.

⇒ There was a significant subgroup difference on dementia risk reduction among different types of TNF inhibitors, with the highest benefit for etanercept, followed by adalimumab and infliximab.

⇒ No decreased risk of dementia incidence was observed in conventional syntheticDMARDs users.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings have clinical implications in choosing medications for RA patients at high risk for dementia in daily practice.

⇒ These findings may also provide important insights into the prevention and treatment of dementia. Controlled clinical trials on TNF inhibitors are necessary to test their neuroprotective potentials.

INTRODUCTION

Populations across the globe are ageing quickly, with this trend being particularly evident in developed countries.[1 2] In the ageing population, the number of individuals living with dementia is increasing, estimated to be up to 152 million by 2050.[2 3] Dementia is a prevalent neurodegenerative disorder,

leading to a high economic and social burden.[4] The global spending on dementia has been increased by 4.5% annually, rising to over 2 trillion dollars in 2019.[5] Despite of extensive research, there has been very little progress in developing effective therapies.

In general, chronic systemic inflammation is believed to be involved in the development of dementia, including Alzheimer's disease (AD) and vascular dementia (VD).[6–8] Dysregulation of several inflammatory cytokines including tumour necrosis factor (TNF), interleukin (IL)-6 in dementia patients has also been identified as a key factor in the pathogenesis of rheumatoid arthritis (RA).[9–11] Existing epidemiological evidence also suggests an increased risk of incident dementia associated with RA.[12 13] Under such conditions, modulating systemic inflammation is hypothesised to attenuate the development of dementia, and antirheumatic drugs are, therefore, considered as a potential strategy for dementia intervention in patients with RA. A meta-analysis in 1996 reviewing 17 epidemiological studies revealed that anti-inflammatory treatment with non-steroidal anti-inflammatory drugs and steroids might decrease the risk of AD.[14] Disease-modifying antirheumatic drugs (DMARDs) are the most principal therapeutic approaches for RA, which can effectively control inflammation with different modes of action. Currently, DMARDs can be classified into conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).[15] In an animal model, TNF inhibition was observed to ameliorate neuroinflammation, neuronal loss and cognitive impairment, exerting preclinical neuroprotective effects.[16 17] Clinically, a potential protective effect on dementia from DMARDs therapies has been reported to different degree in some observational studies, but results are still highly controversial.[18–24] Moreover, targeted therapies with bDMARDs or tsDMARDs confer more prominent anti-inflammatory effect than csDMARDs.[25 26] However, whether they can bring greater clinical benefits than csDMARDs on dementia risk has not yet been clarified. To gain a comprehensive overview of their associations and conclusively quantify the effects of different kinds of DMARDs on the risk of incident dementia in patients with RA, we performed a systematic review and meta-analysis of observational studies.

MATERIALS AND METHODS

A systematic literature review and meta-analysis were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[27] We developed and followed a protocol for all steps of this systematic review and meta-analysis in the format of a PROSPERO registration (see online supplemental appendix S1,S2 for the study protocol and protocol deviations).

Literature search and inclusion criteria

We conducted a literature search of PubMed, EMBASE and the Cochrane Library databases without language restrictions from inception through 10 November 2022 for relevant studies that assessed the association of DMARDs treatment with incident dementia. The search strategy was designed by combining two search themes. The first theme is RA. The second theme, dementia, combined the terms dementia, Alzheimer disease, AD and Alzheimer*. The details of the search strategy are included in online supplemental appendix S3. In addition, we also handsearched reference lists of relevant studies and abstracts of the American College of Rheumatology and European League against Rheumatism (2017–2022) for potential additional studies.

Studies that fulfilled the following inclusion criteria were included: (1) case–control, prospective or retrospective cohort studies enrolling patients with RA without dementia at entry; (2) included at least one of DMARDs with a suitable control group of another DMARD treatment (eg, TNF inhibitors vs methotrexate), or non-use of the investigative treatment (methotrexate user vs methotrexate never-user); (3) reported risks estimates with 95% CI, including OR, risk ratio (RR) and HR. An exception is the report from Fardet *et al* evaluating the association between hydroxychloroquine/chloroquine usage and dementia risk.[21] In this study, RA or other connective tissue diseases were included with no separate data on RA, but we finally decided to include this study due to dominant proportion of RA (over 70%). Two reviewing authors (WX and YH) independently assessed the eligibility for inclusion according to the predesigned criteria and disagreements were resolved by a third experienced investigator (ZZ).

Data extraction and outcome assessments

Two investigators (WX and YH) independently extracted the following data according to predefined data collection form: first author, publication year, country, study design, data source, study period, sample size, demographics and clinical features (age, sex, body mass index, smoking, drinking, comorbidities, medication used, RA duration and RA disease activity), treatments under investigation, duration of follow-up, incidence of dementia (including AD and VD), risk estimates for dementia and adjustments. The corresponding author was contacted for additional information when necessary.

The primary outcome was the association of bDMARDs, tsDMARDs and csDMARDs with incidence of dementia overall or AD. The secondary outcome was the association between an individual DMARD (eg, TNF inhibitors, methotrexate) and incident dementia. The csDMARDs overall or specific csDMARD (eg, methotrexate) was used as a comparator when quantifying the effect of bDMARDs or tsDMARDs. Non-use of any DMARDs or investigative DMARDs was set as the comparator when quantifying the effect of specific type of csDMARDs.

Risk-of-bias and certainty-of-evidence assessment

Two reviewers (WX and YH) independently assessed the risk of bias of included studies using the Risk of Bias in

Nonrandomised Studies of Interventions (ROBINS-I) tool.[28] In brief, ROBINS-I consists of the following seven domains, and each domain is rated as low risk, moderate risk, serious risk, critical risk and no information. Any discrepancies were handled by a senior investigator (ZZ).

The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which divides all evidence into four levels: very low, low, moderate and high. The quality of the evidence from observational studies is initially categorised as 'low' and then were upgraded or downgraded based on predefined criteria. The certainty of evidence for each outcome was independently judged by two investigators (WX and YH), and any discrepancies were then resolved by a third reviewer (ZZ).

Data synthesis and analysis

Extracted data for meta-analysis were performed with Stata Statistical Software V.13.0. A two-sided p<0.05 was considered significant. Pooled RR with 95% CI was calculated as an effect measure for summarising their relationship. The heterogeneity across studies was quantified by I^2 statistic (0%–25% represents low heterogeneity, 25%–50% moderate heterogeneity, 50%–75% substantial heterogeneity and 75%–100% high heterogeneity). A random-effects model (DerSimonian and Laird method) was used for substantial or high heterogeneity and a fixed-effects (Mantel-Haenszel method) model for low or moderate heterogeneity. We used OR and HR as RR in our pooled analysis because the OR, HR and RR approximate one another when event rates are small.[29] When several models of adjustment were reported, the most adjusted estimates were used in the final analysis. When duplicate reports were identified, the one with the largest sample size or presented more detailed information was selected. To explore subgroup differences and potential sources of the heterogeneity, subgroup analyses were performed stratifying for median year of publication (before 2021 vs after 2021), study location (USA vs non-USA), study design (case–control vs cohort), method of ascertainment of RA, dementia, median sample size, mean age of population (>65 vs <65 years), quality of study (low, moderate or serious risk of bias), median follow-up period, type of effect measures (OR vs HR) and adjustments (adjusted vs unadjusted estimates). To further explore the influence of adjustments number, we roughly divided commonly known risk factors of dementia into four categories: age, lifestyle factors (diet, obesity, exercise, alcohol use, smoking, etc), specific comorbidities (hypertension, diabetes, depression, cardiovascular diseases, etc) and others (family history, education level, socioeconomic status, head trauma, air pollution, certain medications, etc). Included studies were classified into two classes according to the coverage of adjustments: studies with sufficient adjustments (≥3 above-mentioned risk factor categories) and studies with insufficient adjustments (<3 above-mentioned risk factor categories). Additional subgroup analysis was performed between studies with sufficient adjustments and insufficient adjustments. A difference between the estimates of these subgroups was considered significant for a p<0.10. Sensitivity analysis was conducted using the leave-one-out approach to evaluate the robustness of pooled results. Potential publication bias was assessed by visualisation of funnel plot with both Egger's test and Begg's test.

RESULTS

Study selection and characteristics

From a total of 4324 citations identified using initial search strategy, 14 studies were included in systematic reviews[18–24 30–36] and 12 of them further into meta-analysis.[18–22 24 30–32 34–36] The flow chart for study inclusion is presented in figure 1. A full list of excluded studies with specific reasons is provided in online supplemental appendix S4. Online supplemental table S1 summarises characteristics of the selected articles. The included studies were based on 12 datasets published between 2017 and 2022. Three studies were published in letter[21 22 30] and the rest studies were published as full texts. Of these, seven originated from the USA,[18 31–36] five from Europe[20–22 24 30] and two from China.[19 23] The majority of the included studies employed cohort design, except three adopted case–control studies.[18 19 24] The ascertainment of RA and dementia was dominantly based on international classification code. There were a total of 940 442 patients in the included studies. In the three case–control studies,[18 19 24] 1608 cases of dementia and 2981 matched controls were included. In the 11 cohort studies,[20–23 30–36] there were a total of 935 853 patients with mean follow-up of 0.5–13.8 years, reporting incidence of dementia from 0.18% to 11.6%. At baseline, patients exposed to different therapeutic regimens generally had comparable demographical characteristics. A tabular summary of characteristic including corresponding adjustments for each study is shown in table 1. Regarding risk of bias, there was a serious risk of bias overall in three studies,[21 24 30] moderate risk of bias overall in seven studies[18 19 22 23 31 34 35] and a low risk of bias overall in four studies[20 32 33 36] according to the ROBINS-I tool. Online supplemental table S2 provides detailed assessment of risk of bias for each domain of included studies.

bDMARDs or tsDMARDs treatment and dementia risk

The association between bDMARDs and dementia development in patients with RA was assessed in 10 articles.[18 19 22 30–36] Of these, half of them specifically focused on TNF inhibitors.[22 30–32 36] The csDMARDs overall or a specific csDMARD (eg, methotrexate) was used as the comparator across all studies, except the study by Desai *et al* using abatacept as the comparator.[33] In pooled analysis of 9 combinable studies based on 10 databases,[18 19 22 30–34 36] treatment with bDMARDs for RA was associated with a significant reduction in the risk of dementia as compared with csDMARDs (RR 0.76, 95% CI 0.72 to 0.80, I^2=14.4%)

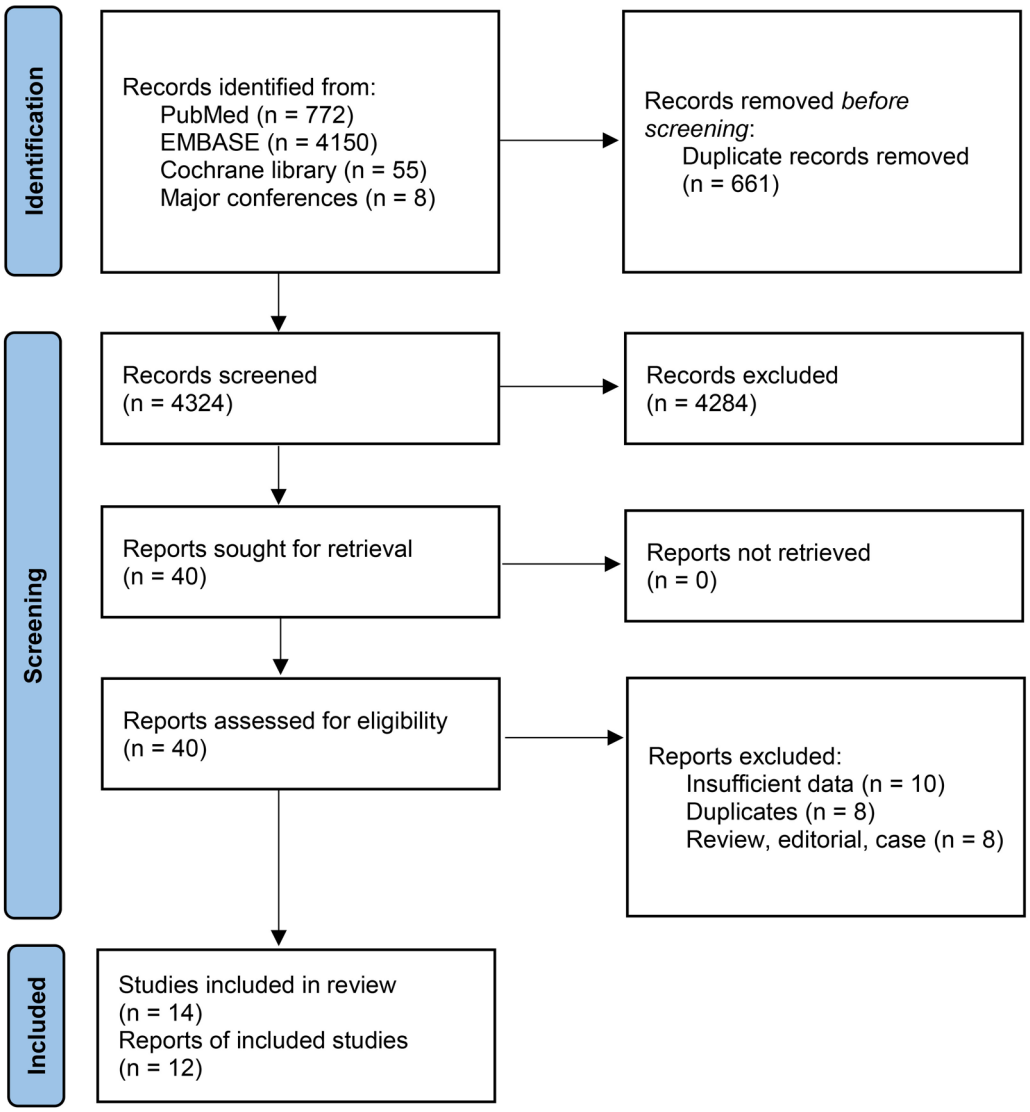

Figure 1 Search and selection of observational studies for systematic review and meta-analysis.

(figure 2, online supplemental figure S1). Separate analysis on TNF inhibitors alone in seven studies yielded a pooled RR of 0.76 (95% CI 0.71 to 0.82, I^2=34.2%) in comparison with csDMARDs[18 19 22 30–32 36] (figure 2, online supplemental figure S2). Sensitivity analysis using leave-one-out method suggested that pooled estimates were robust and not influenced excessively (online supplemental figure S3). No evident publication bias was found through visualisation of funnel plot, as well as the results from Egger and Begg tests regarding bDMARDs (figure 2, online supplemental figure S4). According to the GRADE system, the overall quality of evidence was low (online supplemental table S3).

To test the presence of subgroup differences for the association of bDMARDs with dementia, we performed subgroups analyses according to several characteristics of studies. Overall, no significant differences between subgroups were detected for publication year, study region, study design, the ascertainment method of RA and dementia, sample size, follow-up time, quality of study and effect estimate types (table 2, online supplemental figure S5–16). Switching to AD as the outcome, we found a 34% reduction risk with TNF inhibitors as compared with csDMARDs based on three studies with four databases (RR 0.66, 95% CI 0.54 to 0.80, I^2=42.8%)[18 31 32] (online supplemental figure S17). Moreover, risks of dementia associated with etanercept, adalimumab, infliximab exposure were simultaneously evaluated in three studies.[18 31 36] Pooled results indicated significant differences among TNF inhibitors (p value between groups=0.002), with RR of 0.58 for etanercept (95% CI 0.53 to 0.65, I^2=0%), 0.65 for adalimumab (95% CI 0.59 to 0.72, I^2=0%), and 0.80 for infliximab (95% CI 0.72 to 0.88, I^2=0%) compared with csDMARDs (figure 2, online supplemental figures S18–20).

Regarding non-TNF targeted DMARDs, there were only two studies reporting their associations with dementia comparing to csDMARDs and showing pooled RR of 0.76 (95% CI 0.70 to 0.83, I^2=0%)[18 35] (figure 2, online supplemental figure S21). In another report conducted by Desai *et al*, abatacept was used as a comparator.[33] Patients with RA treated with tocilizumab, or TNF inhibitors showed

Table 1 Summary of characteristic of included studies

Author, ref	Year	Country	Data source	Study period	Study design	RA diagnosis	Outcome	Dementia diagnosis	Sample size	Follow-up, years	Dementia incidence	Adjustments
Chou[18]	2016	USA	Claims data	2000–2007	Case–control	ICD-9	AD	ICD-9	1548	/	AD: 100% Non-AD: 0%	Age, sex, exposure assessment, MTX treatment, comorbidities
Chou[19]	2017	China	NHIRD	2000–2011	Case–control	ICD-9	Dementia	ICD-9	1914	/	Dementia: 100% Non- Dementia: 0%	None
Judge[20]	2017	UK	CPRD	1995–2011	Retrospective cohort	Read code	Dementia	Read code	5814	Up to 15	DMARD 1.5%, no DMARD 3%	Age, sex, BMI, drinking, smoking, calendar year, region, comorbidities, RA duration, severe RA, RA symptoms, medication use.
Fardet[21]	2018	UK	THIN	1996–2016	Retrospective cohort	ICD	Dementia	ICD	47 353	4.2–4.5	NR	Age, sex, underlying condition, GC, NSAIDs, IS therapies and vitamin D prescriptions, hypertension, hypercholesterolaemia, smoking, BMI.
McGuinness[22]	2018	UK	BSRBR-RA	2002–2007	Retrospective cohort	ICD-9	Dementia	ICD-9	17 248	6.4–7.3	TNFi 0.18%, csDMARD 0.59%	Age, gender, HAQ and NSAID
Huang[23]	2020	China	LHID 2000	2000–2005	Retrospective cohort	ICD-9	Dementia	ICD-9	20 707	NR	all 1.2%, DMARD 0.7%, no DMARD 2.3%.	Age, gender and comorbidities
Newby[24]	2020	Europe	EMIF	1995–2016	Case–control	ICD/ICPC/READ	Dementia	ICD/ICPC/READ	1127	/	Dementia: 100% Non- Dementia: 0%	Age, sex, BMI, stroke and AMI
Zafeiridi[30]	2020	UK	BHSCT	2000–2017	Retrospective cohort	NR	Dementia	Dementia medication prescription	21 370	NR	NR	NR
Zhou[31]	2020	USA	EHR in 360 hospitals	NR	Retrospective cohort	SNOMED-CT	Dementia	SNOMED-CT	514 440	NR	All 9.2%	Age, gender, race, BMI, drinking, insurance status, medication
Kern[32]	2021	USA	MDCR and Optum	2000–2019	Retrospective cohort	ICD-9/10	Dementia	ICD-9/10	22 100	2.2–2.9	Optum TNFi 1.39% MTX 1.39% MDCR TNFi 3.44% MTX 4.0%	Age, gender, index time, comorbidities, prescription drugs, all procedures received, RA severity including the number of RA-specific visits, GC, DMARDs, opioid use and joint surgeries.
Desai[33]	2022	USA	CMS	2007–2017	Retrospective cohort	ICD-9/10	Dementia	ICD-9/10 and at least 1 prescription claim for a symptomatic treatment	45 138	0.5–0.7	Tofacitinib 0.68% Tocilizumab 0.69% TNFi 0.94% Abatacept 0.90–1.07%	Age, sex, race, receipt of low-income subsidy, risk factors for dementia, including comorbidities, lifestyle factors (smoking, etc); measures of healthcare services use, a frailty indicator; RA-related treatments.
Kodishala[34]	2022	USA	REP	1980–2014	Retrospective cohort	1987 ACR criteria	Dementia	ICD-9/10	886	8.5	All 11.6%	Age, sex, calendar year, smoking, obesity, hypertension, diabetes mellitus, hyperlipidaemia, CVD.

Continued

Table 1 Continued

Author, ref	Year	Country	Data source	Study period	Study design	RA diagnosis	Outcome	Dementia diagnosis	Sample size	Follow-up, years	Dementia incidence	Adjustments
Sattui[35]	2022	USA	CMS	2006–2017	Retrospective cohort	ICD-9/10	Dementia	ICD-9/10 or a prescription of a dementia specific medication	233 271	3.1	csDMARD 1.41% b/tsDMARD 1.86%	Age, sex, race, CVD, CVD risk factors, medications, comorbidities, any hospitalisations, physician visits number
Zheng[36]	2022	USA	VHA-EHR	2000–2020	Retrospective cohort	ICD-9/10	Dementia	ICD-9/10	7526	13.8	Non-TNFi 5% TNFi 6%	Age, sex, race, marital status, year, region, rurality, known risk factors for dementia.

AMI, acute myocardial infarction; BHSCT, the Belfast Health and Social Care Trust; BMI, body mass index; BSRBR-RA, British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; CMS, Centre for Medicare & Medicare Services; CPRD, Clinical Practice Research Datalink; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CVD, cardiovascular diseases; EHR, electronic health record; EMIF, European Medical Information Framework; GC, glucocorticoids; HAQ, Health Assessment Questionnaire; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; IS, immunosuppressive; LHID, Longitudinal Health Insurance Database; MDCR, MarketScan Medicare Supplemental Database; MTX, methotrexate; NHIRD, National Health Insurance Research Database; NR, non-reported; NSAID, non-steroid anti-inflammatory drugs; SNOMED-CT, systematized nomenclature of medicine-clinical terms; THIN, The Health Improvement Network; TNFi, tumour necrosis factor inhibitors; VHA, Veterans Health Administration.

overall similar risk of incident dementia to those with abatacept treatment, but a potential decreased risk of dementia with TNF inhibitors versus abatacept subgroup analysis in patients with cardiovascular diseases. Dementia risk in tsDMARDs-exposed patients was shown as HR of 0.69 (95% CI 0.53 to 0.90) and 0.90 (95% CI 0.55 to 1.51) compared with those receiving csDMARDs or abatacept treatment, respectively.[33 35] In addition, the study from Huang *et al* showed a decreased dementia risk associated with bDMARDs or csDMARDs usage as compared with no DMARDs use (adjusted HR 0.68, 95% CI 0.49 to 0.94).[23]

csDMARDs treatment and dementia risk

Overall, the risk of dementia associated with csDMARDs was reported in seven studies,[18–21 24 31 34] frequently on methotrexate,[19 20 24 31 34] hydroxychloroquine[19 21 34] and sulfasalazine.[18 19 24] As compared with those without DMARDs or investigative DMARDs, there was no significant difference in dementia risk in patient with RA receiving csDMARDs overall (RR 0.84, 95% CI 0.59 to 1.20, I^2=94.6%), methotrexate (RR 0.78, 95% CI 0.54 to 1.12, I^2=91.3%) or hydroxychloroquine (RR 0.95, 95% CI 0.63 to 1.44, I^2=81.3%) (figure 2, online supplemental figures S22–24). Exposure to sulfasalazine was found to be linked to a 27% increase in dementia risk as compared with non-use of sulfasalazine (RR 1.27, 95% CI 1.06 to 1.50, I^2=42.6%), but the results were dominantly affected by study from Chou *et al* (figure 2, online supplemental figure S25).[19] The combined RRs were consistent without apparent fluctuation according to the results of sensitivity analysis for the association between csDMARDs overall and dementia risk (online supplemental figure S26). Based on the GRADE system, the overall quality of evidence was very low (online supplemental table S3).

Regarding the association of csDMARDs with dementia, subgroup analyses were also performed according to the study characteristics to explore potential sources of the high heterogeneity. As depicted in table 3, no significant differences between subgroups were detected for publication year, study region, study design, the ascertainment method of RA and dementia, sample size, follow-up time and quality of study (online supplemental figure S27–38). In addition, the impact of different csDMARDs exposure period on the risk of incident dementia is summarised and provided in online supplemental table S4. Of these, Newby *et al* reported a time-dependent protective effect of methotrexate on dementia incidence before dementia diagnosis,[24] however, neither confirmed by other reports, nor of other csDMARDs.[19 20 23 24]

DISCUSSION

Overall findings

To our knowledge, the present study for the first time assessed dementia risk associated with DMARDs therapy in patients with RA. Overall, treatment with targeted DMARDs was associated with approximately 30% reduction in dementia risk, while no decreased risk of dementia

Invetigative treatment	No. study	Comparator	Risk ratio (95% CI)	I^2	Egger	Begg
Biological DMARDs	9	csDMARDs	0.76 (0.72, 0.80)	14.4%	0.754	0.371
TNF inhibitors	7	csDMARDs	0.76 (0.71, 0.82)	34.2%	0.552	0.902
Etanercept	3	csDMARDs	0.58 (0.53, 0.65)	0.0%	0.461	1.000
Adalimumab	3	csDMARDs	0.65 (0.59, 0.72)	0.0%	0.797	1.000
Infliximab	3	csDMARDs	0.80 (0.72, 0.88)	0.0%	0.402	1.000
non-TNFi biologics	2	csDMARDs	0.76 (0.70, 0.83)	0.0%	/	/
Conventional synthetic DMARDs	7	no investgative csDMARDs	0.84 (0.59, 1.20)	94.6%	0.181	0.764
Methotrexate	5	no methotrexate	0.78 (0.54, 1.12)	91.3%	0.213	0.806
Hydroxychloroquine	3	no hydroxychloroquine	0.95 (0.63, 1.44)	81.3%	0.913	1.000
Sulfasalazine	3	no sulfasalazine	1.27 (1.06, 1.50)	42.6%	0.441	1.000

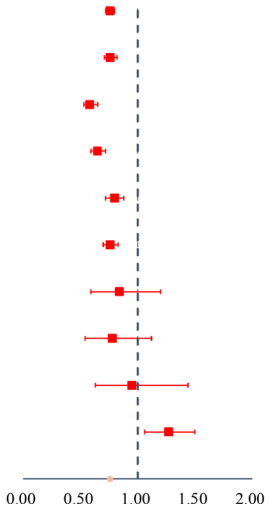

Figure 2 Meta-analysis of dementia risk associated with DMARDs in patients with rheumatoid arthritis. csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs.

incidence was observed in csDMARDs users. The results not only have clinical implications in determining treatment in patients with RA at high dementia risk but also indicate targeted DMARDs may hold some promise for prevention of dementia.

Findings and putative mechanisms of TNF inhibitors

Systemic autoimmune-mediated inflammatory diseases such as RA, ankylosing spondylitis heighten the risk of dementia.[9–13 37] Chronic hyperactivation of immune response with excessive proinflammatory cytokines (eg, TNF and IL-6) in many organs or systems, especially in the brain, accounts for the increased risk of dementia in patients with RA. For instance, the increased level of TNF-α produced by microglia not only elicits a neuroinflammatory response associated with AD but also contributes to amyloid-(Aβ) plaques and tau protein hyperphosphorylation known to accumulate in the brains of patients with AD.[38] These proinflammatory cytokines are also elevated in the cerebrospinal fluid of dementia patients and correlated directly with disease progression.[39] Therefore, DMARDs treatment has been hypothesised to attenuate the risk of dementia in patients with RA via reducing inflammation. Moreover, experimental data in animal models of dementia have supported the therapeutic potential of intrathecal or intracerebroventricular administration of anti-TNF agents to improve cognitive function by decreasing TNF-α level and subsequent Aβ deposits.[16 17 40] Because TNF inhibitors cannot permeate cross the blood–brain barrier, the effect of subcutaneously administered anti-TNF therapies in RA is unclear. In previous observational studies, the preventive effects of subcutaneous anti-TNF therapies against dementia were possibly indicated, however, with a great controversy on the relationship. The present study with most comprehensive appraisal of the evidence to date showed treatment with TNF inhibitors was linked to a decrease in risk of dementia in patients with RA. There are a couple of implications of these findings in guiding clinical practice. On one hand, these may help rheumatologists to make more individualised decisions in daily practice. If the situation allows, TNF inhibitors, instead of csDMARDs may be preferred for patients with RA complicated by dementia or at high risk for dementia development according to our findings. On the other hand, the results provide comprehensive clinical evidence for the prevention and therapy of dementia. In consideration of our results, anti-TNF strategy may be worthy of further evaluations in future clinical trials for primary prevention in specific high-risk of dementia population (for instance, aged patients with RA). Interestingly, despite of overall improvement in dementia risk after anti-TNF treatment, there was significant difference among different kinds of TNF inhibitors. Our study showed etanercept conferred strongest clinical benefit in decreasing dementia risk, followed by adalimumab and infliximab. In fact, these findings were somewhat consistent with the data in animal models. In streptozotocin-induced dementia model in rats, both etanercept and infliximab significantly improved the performance scores on Morris's water maze and passive avoidance tests compared with those not treated with anti-TNF.[41] However, etanercept exposed group presented more improvement than those receiving infliximab. These suggest that other regulatory mechanisms for neuroprotection related to TNF blockades may exist, in addition to control of systemic inflammation. These findings need to be verified and the underlying mechanisms also needs to be investigated in future studies.

In patients diagnosed with dementia, the potential therapeutic effects of TNF inhibition have been preliminarily investigated. Previous open-label study and case reports showed the possible effects of perispinal administration of

Table 2 Subgroup analysis for association between bDMARDs and dementia risk according to study characteristics

	No study	Pooled estimate (95% CI)	I^2	$P_{between\ group}$
All*	10	0.76 (0.72 to 0.80)	14.4%	/
Publication year				
Before 2021	6	0.67 (0.58 to 0.78)	0%	0.234
After 2021	4	0.77 (0.73 to 0.82)	36.6%	
Country				
Non-USA	3	0.71 (0.51 to 1.01)	0%	0.899
USA	7	0.76 (0.72 to 0.80)	41.4%	
Study design				
Case–control	2	0.63 (0.44 to 0.90)	0%	0.421
Cohort	8	0.76 (0.72 to 0.80)	17.4%	
RA diagnosis				
ICD	7	0.77 (0.73 to 0.81)	20.9%	0.840
Thers	3	0.70 (0.59 to 0.82)	0%	
Dementia diagnosis				
ICD	8	0.77 (0.73 to 0.81)	19.0%	0.533
Thers	2	0.68 (0.58 to 0.81)	0%	
Sample size*				
<10 000	5	0.69 (0.58 to 0.82)	39.4%	0.652
>10 000	5	0.77 (0.73 to 0.81)	0%	
Mean age				
<65	4	0.68 (0.59 to 0.80)	0%	0.401
>65	6	0.77 (0.73 to 0.81)	39.2%	
Follow-up, years				
<4	3	0.78 (0.74 to 0.83)	8.5%	0.792
>4	3	0.67 (0.55 to 0.81)	0.5%	
Not reported	4	0.67 (0.58 to 0.78)	0%	
ROBINS-I				
Low risk	3	0.69 (0.58 to 0.83)	46.5%	0.678
Moderate or serious risk	7	0.77 (0.73 to 0.81)	0%	
Effect estimate				
OR	3	0.67 (0.58 to 0.78)	0%	0.239
Hazard risk	7	0.77 (0.73 to 0.82)	7.8%	
Adjusted estimate				
No	2	0.73 (0.49 to 1.10)	0%	0.996
Yes	8	0.76 (0.72 to 0.80)	32.5%	
Sufficient adjustments				
No	4	0.65 (0.48 to 0.89)	0%	0.475
Yes	6	0.76 (0.73 to 0.80)	39.7%	

*Kern *et al*[32] study reported two separate risk estimates based on two different databases and was therefore regarded as two studies in subgroup analyse.
bDMARDs, biological disease-modifying anti-rheumatic drugs; ICD, International Classification of Diseases; RA, rheumatoid arthritis; ROBINS-I, Risk of Bias in Nonrandomised Studies of Interventions.

etanercept to improve the cognitive function in patients with AD.[42–44] In a randomised controlled trial of 41 patients with AD, subcutaneous etanercept 50 mg once weekly showed a trend toward improvements in the Mini-Mental State Exam score (p=0.07) and neuropsychiatric inventory (p=0.02).[45] In another study, 15 patients with AD were randomised to receive etanercept 25 mg twice a week (n=8) or adalimumab twice a month (n=7)

Table 3 Subgroup analysis association between csDMARDs and dementia risk according to study characteristics

	No study	Pooled estimate (95% CI)	I^2	$P_{between\ group}$
All	7	0.84 (0.59 to 1.20)	94.6%	/
Publication year				
Before 2020	4	0.95 (0.57 to 1.59)	90.9%	0.383
After 2020	3	0.69 (0.53 to 0.90)	73.3%	
Country				
Non-USA	2	1.12 (0.53 to 2.36)	95.1%	0.170
USA	5	0.70 (0.56 to 0.88)	71.0%	
Study design				
Case-control	3	1.10 (0.59 to 2.04)	90.3%	0.134
Cohort	4	0.69 (0.54 to 0.86)	75.7%	
RA diagnosis				
ICD	4	1.01 (0.64 to 1.58)	89.8%	0.172
Thers	3	0.62 (0.51 to 0.76)	42.6%	
Dementia diagnosis				
ICD	7	0.99 (0.68 to 1.44)	86.6%	0.103
Thers	2	0.58 (0.56 to 0.60)	0%	
Sample size				
<5000	4	1.05 (0.65 to 1.71)	86.3%	0.108
>5000	3	0.65 (0.52 to 0.82)	77.8%	
Mean age				
<65	3	0.65 (0.52 to 0.82)	77.8%	0.108
>65	4	1.05 (0.65 to 1.71)	86.3%	
Follow-up, years				
>4	2	0.83 (0.68 to 1.01)	0%	0.952
Not reported	5	0.84 (0.51 to 1.37)	96.0%	
ROBINS-I				
Low or moderate risk	5	0.87 (0.50 to 1.51)	96.0%	0.793
Serious risk	2	0.79 (0.67 to 0.93)	0%	
Effect estimate				
OR	4	0.91 (0.50 to 1.66)	97.0%	0.607
Hazard risk	3	0.76 (0.62 to 0.94)	23.4%	
Adjusted estimate				
No	1	1.63 (1.33 to 2.00)	90.3%	/
Yes	6	0.71 (0.58 to 0.86)	75.7%	
Sufficient adjustments				
No	3	1.10 (0.59 to 2.04)	90.3%	0.134
Yes	4	0.69 (0.54 to 0.86)	75.7%	

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ICD, International Classification of Diseases; RA, rheumatoid arthritis; ROBINS-I, Risk of Bias in Nonrandomised Studies of Interventions.

subcutaneously. After therapy, cognitive function defined by Mini-Mental State Exam score was ameliorated in 11 (73.3%) patients with significant improvement of score (24.47±4.55 vs 26.33±3.06; p=0.006).[46] These suggest the therapeutic potentials of TNF inhibition in slowing down the cognitive decline in patients with AD. Future well-designed studies with large-volume are needed to clarify the final effect.

Findings of other DMARDs

A potential neuroprotective effect of other bDMARDs and tsDMARDs was indicated in limited clinical studies,

with similar magnitude of dementia risk reduction to TNF inhibitors. In a most recent cohort study of different types of targeted DMARDs,[33] no difference in the risk of dementia was detected in patients treated with tofacitinib, tocilizumab or TNF inhibitors as compared with those treated with abatacept. Future large-scale studies are still needed to further investigate the association. Regarding csDMARDs, no significant effect on dementia risk was observed with methotrexate, hydroxychloroquine or csDMARDs overall. One possible explanation is their relatively weak anti-inflammatory capacity as compared with targeted DMARDs.[25 26] In a double-blind, parallel-group, multicentre trial of 168 patients with early AD, hydroxychloroquine exposure for 18 months showed similar cognitive changes to placebo.[47] Expectation to inflammation inhibition with csDMARDs does not appear to be optimistic to dementia, either for prevention or for treatment purpose. Nevertheless, a retrospective matched case–control study comparing the incidence of dementia among patients with variable exposure periods of methotrexate showed that significant reduction in dementia occurrence was only observed in those exposed to methotrexate for over 1500 days, however, not for those exposed <432 days or 432–1500 days, in comparison with the methotrexate nonusers.[24] From this point of view, longitudinal studies with prolonged observation may be worth trying for further clarification. In terms of sulfasalazine, increased risk of dementia was reported in our studies. Admittedly, the results must be interpreted with caution due to few reports included for the association, and moreover, this result was mainly affected by Chou *et al*'s study.[19]

Study limitations

This study has several limitations. First, as all meta-analyses, the present study inherited the limitations of each included observational study, including selection bias, recall bias and confounding bias. A causal link between DMARDs use and dementia can be determined based on observational data. Second, most of the included studies were from the USA and European countries. This may limit the generalisation of the findings to the patients in other ethnicities and geographical regions. Further prospective cohort studies are warranted to prove these findings in other ethnic groups and regions in the future. Third, due to lack of original data, the association between DMARDs and dementia cannot be investigated in different population groups (eg, populations of different ages, different period of DMARDs use). This subgroup relationship merits further investigation and discussion. Fourth, most of included studies were based on nationwide electronic database, where information on drug usage duration, dosage or patient adherence is limited. Therefore, the impact of drug exposure duration on association between DMARDs and dementia could not be analysed. Last, statistical power is intrinsically limited based on few studies identified, especially for non-TNF targeted DMARDs and individual csDMARD. Future studies are needed.

CONCLUSION

The present study provides comprehensive evidence on the beneficial effects of bDMARDs, however, not csDMARDs, on dementia development in patients with RA. These findings have clinical implications in choosing DMARDs for patients with RA at high risk for dementia and may also provide important insights into the prevention and treatment of dementia. Controlled clinical trials on TNF inhibitors are necessary to test their neuroprotective potentials.

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