Ther Adv Chronic Dis
2020, Vol. 11: 1–12
DOI: 10.1177/2040622319899300

Risk of epilepsy in rheumatoid arthritis: a meta-analysis of population based studies and bioinformatics analysis

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Abstract

Background: An increasing number of studies support an association between rheumatoid arthritis (RA) and brain disorders. This study aims to determine the association between RA and epilepsy.

Methods: A comprehensive search of databases in both English and Chinese was performed. Data from the selected studies were extracted and analyzed independently by two authors. Genes associated with epilepsy and RA were also collected and analyzed.

Results: We included six nationwide population based studies ($n = 7{,}094{,}113$ cases in total) for the meta-analysis. The risk of epilepsy was increased in RA patients [risk ratio (RR) = 1.601; 95% confidence interval (CI): 1.089–2.354; $p = 0.017$; $n = 3{,}803{,}535$ cases] and children born to mothers with RA (RR = 1.475; 95% CI: 1.333–1.633; $p < 0.001$, $n = 3{,}290{,}578$ cases). Subgroup analysis and meta-regression showed the RR of epilepsy in RA was negatively correlated with age. Furthermore, we found that 433 identified genes in a coexpression network from the hippocampi of 129 epileptic patients were enriched in the RA and related Kyoto Encyclopedia of Genes and Genomes pathways, while 13 genes (mainly related to inflammatory cytokines and chemokines) were identified as potential key genes bridging the RA and epilepsy.

Conclusions: Our study, utilizing meta-analysis and bioinformatical data, highlights a close association between epilepsy and RA. Further studies are still warranted to expand these findings, especially for a population that is exposed to RA during fetal and childhood periods.

Keywords: bioinformatics, comorbidity, epilepsy, meta-analysis, rheumatoid arthritis

Received: 22 August 2019; revised manuscript accepted: 10 December 2019.

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Introduction

Epilepsy is a neurologic disorder, characterized by recurrent epileptic seizures, which affects about 0.5–1.0% of the population.[1] Despite developing a broad range of treatment approaches, such as antiepileptic drug (AED) therapy and surgery, about one-third of patients continue to have seizures.[2] Uncontrolled epileptic seizures may result in cognitive impairments and even sudden death.[3] Recently, increasing evidence has shown a close association between epilepsy and autoimmune diseases.[4] For example, one meta-analysis study found that the risk of epilepsy is increased in autoimmune diseases and *vice versa*.[5] Moreover, it is frequently reported that patients with autoimmune encephalopathy are resistant to AED therapy;[6] however, the relationship between specific autoimmune diseases and epilepsy remains unclear.

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases that affects about 1.0% of the population, especially women and the elderly.[7] RA is characterized by persistent synovitis, systemic inflammation, and autoantibodies. Tumor necrosis factor α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6) are key inflammatory cytokines implicated in RA. Their inhibitors are licensed for the treatment of RA

and may be beneficial for other related comorbidities.[8] IgM- and IgA-rheumatoid factors, as well as anticitrullinated protein autoantibodies, are representative pathogenic markers in RA, which have also been used to diagnose RA.[9] These systemic inflammatory cytokines and autoantibodies in RA may contribute to epileptogenesis and ictalgenesis.[10] For example, blocking TNFα-driven astrocyte purinergic signaling restores normal synaptic activity during epileptogenesis,[11] and recombinant IL-1 receptor antagonist, anakinra, may help to control febrile infection-related epilepsy syndrome.[12] Recently, we found the accumulation of the inflammatory cytokine, IL-1 beta (IL1B), was related to the diazepam resistant phenomenon of prolonged status epilepticus.[13] Thus, it is important to further clarify the association between RA and epilepsy. This may help in the development of future protective or individualized treatment options for epilepsy in RA.

Here we collected and conducted a comprehensive meta-analysis on nationwide, population based studies regarding the association between epilepsy and RA. We further collected and analyzed 443 previously identified epilepsy related genes from a coexpression network from hippocampi of 129 epileptic patients. Our meta-analysis highlights the risk of epilepsy in RA by providing both meta-analysis and bioinformatical evidence.

Materials and methods

Literature search

Two authors (H.Z. and S.L.) independently performed a systematic search of PubMed, Web of Science and Cochrane Library for English-language studies up to 14 October 2019 by using the terms: "seizure" or "epilepsy" and "arthritis". We also performed a systematic search of WanFang DATA (http://www.wanfangdata.com.cn/), VIP (http://www.cqvip.com/), and the Chinese National Knowledge Infrastructure (http://www.cnki.net/) for Chinese-language studies using the terms: "Dian-Xian" (meaning epilepsy) and "Guan-Jie-Yan" (meaning arthritis). Our study protocol was reviewed and registered in PROSPERO (ID: CRD42019121929) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14] Ethical approval is not required as the current study was based on published data.

Study selection criteria

The inclusion criteria were: (a) only peer-reviewed, published studies were eligible to be included; (b) studies were required to be population based; (c) the studies included RA and epilepsy.

The exclusion criteria were: (a) studies without controls; (b) data were not available or were repeatedly published; (c) reviews, editorials, case reports, letters, and commentaries.

Data extraction

Two reviewers (H.Z. and S.L.) independently reviewed studies to extract potentially eligible studies and data. The number of patients with RA, the number of patients with epilepsy, and the total cases of each group were collected. Any disagreements were discussed and resolved by consensus with the corresponding author (Z.X.).

Methodological quality assessment

Two authors (H.Z. and S.L.) assessed study quality using the Newcastle Ottawa Scale (NOS).[15] Low quality studies yielded scores of 0–3, medium quality studies 4–6, and high quality studies 7–9. Any disagreements were discussed and resolved by consensus with the corresponding author (Z.X.).

Systems biological analysis

Genes associated with RA were collected from the following three databases as seen in our previous studies:[16,17] Online Mendelian Inheritance in Man (http://www.omim.org),[18] Genetic Association Database (http://geneticassociationdb.nih.gov/),[19] and Kyoto Encyclopedia of Genes and Genomes (KEGG; http://www.kegg.jp).[20] Gene coexpression network associated with epilepsy was utilized from a previous study, which was generated from hippocampi of 129 temporal lobe epilepsy (TLE) patients (Gene Expression Omnibus: GSE63808).[21]

The enriched pathways were analyzed using Cytoscape 3.2.1 with ClueGO plugin.[22,23] The ClueGO options were set as pathway with a p value cut off = 0.05, kappa score cut off = 0.4, number of genes cut off = 3, and percent of genes cut off = 4%. Enrich/depletion (two-sided) hypergeometric test, Bonferroni step down p value correction, and ClueGO grouping method were used.

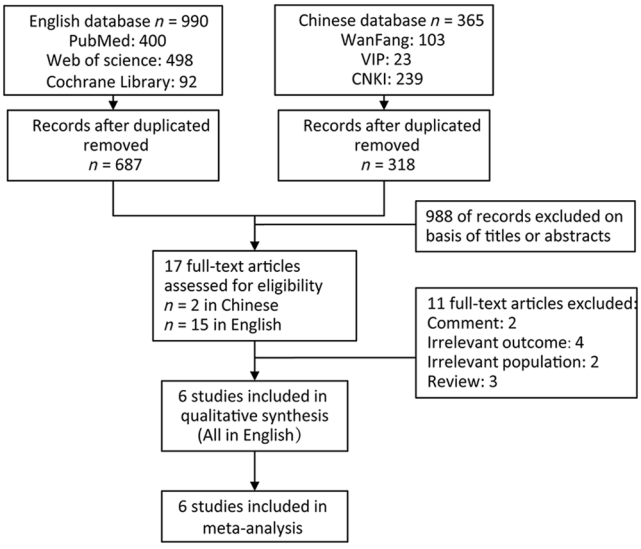

Figure 1. Flow diagram of the study selection process.

The protein–protein interaction (PPI) network was generated by the String plugin in Cytoscape 3.2.1. A PPI score of >0.4 was considered significant. The clusters of PPI networks were further analyzed by Molecular Complex Detection (MCODE) plugin in Cytoscape 3.2.1. The MCODE options were set as degree cutoff = 2, K-Core = 2, and Node Score Cutoff = 0.2.

Statistical analysis

Comprehensive meta-analysis was performed to calculate risk ratios (RRs) and their 95% confidence interval (CI) in R with the Metafor Package.[24] Meta-regression was also conducted in R with the Metafor Package[24] and by partly referring to a book.[25] Statistical heterogeneity was assessed by Cochran's Q statistic and the I^2 statistic. Similar to our previous studies,[17,26,27] the fixed effects model was used to pool studies when statistical heterogeneity was absent (the $I^2 < 50\%$ or Q-p value > 0.1); otherwise, the random effects model was employed. $p < 0.05$ was considered to indicate a statistically significant difference. Egger's test and Begg's funnel plot were performed for assessing publication bias when possible.

Results

Study selection

The study selection process is depicted in (Figure 1). A total of 687 unique articles in English and 318 in Chinese were identified. Three population based studies were excluded because they combined RA with other diseases, such as other types of arthritis[28–30] or other autoimmune diseases.[31] Ultimately, six population based studies (n = 7,094,113 cases in total) were included in the current meta-analysis.[32–37]

Study characteristics

Among the six included studies, four of them (n = 3,803,535 in total) were related to the comorbidity of epilepsy and RA[34–37] and the other two (n = 3,290,578 in total) focused on children born to mothers with RA.[32,33] Chang and colleagues[34] and Ong and colleagues[35] excluded a history of epilepsy before the diagnosis of RA. Téllez-Zenteno and colleagues[36] and Gaitatzis and colleagues[37] provided the prevalence of RA that preceded, cooccurred with, or followed the diagnosis of epilepsy. In addition, Téllez-Zenteno and colleagues[36] used data from two independent Canadian health surveys: the National Population Health Survey (n = 49,000 cases) and the Community Health Survey (n = 130,882 cases). In addition, Ong and colleagues[35] enrolled children (<18 years) and nonelderly adults (18–65 years), Gaitatzis and colleagues[37] enrolled nonelderly adults (16–64 years) and elder adults (>64 years), Chang and colleagues[34] enrolled nonelderly adults (20–64 years) and elder adults (>64 years), and Téllez-Zenteno and colleagues[36] enrolled all ages or age >12 years. All six studies

Table 1. Details of included studies.

Studies	Areas	Diagnosis of EP and RA	RA sample size (% females, Age)	Total sample size (% females, Age)	NOS score
Risk of epilepsy in RA patients					
Chang *et al.*[34]	Taiwan	ICD-9	32,005 (77.4%, >20)	64,010 (77.4%, >20)	7
Ong *et al.*[35]	US	ICD-9	22,890 (NA, <65)	2,518,034 (51.7%, <65)	9
Téllez-Zenteno *et al.*[36]	Canada	Self-report	6619 (NA, All)	49,026 (51%, All)	5
Téllez-Zenteno *et al.*[36]	Canada	Self-report	19,885 (NA, >12)	130,822 (54%, >12)	5
Gaitatzis *et al.*[37]	UK	ICD-9	4735 (NA, >16)	1,041,643 (51.1%, >16)	7
Risk of epilepsy in children that exposed maternal RA					
Jolving *et al.*[32]	Denmark	ICD-8 and ICD-10	2106 (49.3%, <25.9)	1,378,539 (48.7%, <25.9)	9
Rom *et al.*[33]	Denmark	ICD-8 and ICD-10	13,511 (49.0%, <34)	1,896,422 (48.7%, <34)	9

EP, epilepsy; ICD, International Classification of Diseases; NA, Not available; NOS, Newcastle-Ottawa Scale; RA, rheumatoid arthritis; UK, United Kingdom; US, United States.

are nationwide studies with a NOS score of five or more. The details of each study are represented in Table 1 and the NOS scores are in Supplementary Table 1.

Risk of epilepsy in RA patients

The prevalence of epilepsy in RA and non-RA were extracted or calculated from the four included studies.[34–37] Since statistical heterogeneity among studies was significant ($I^2 = 94.23\%$ and $p < 0.001$), the random effects model was used. Results showed that RA was associated with an increased risk of epilepsy (0.83% in RA *versus* 0.44% in non-RA; RR 1.601; 95% CI: 1.089–2.354, $p = 0.017$; based on $n = 3{,}803{,}535$; Figure 2).

Risk of epilepsy in children exposed to maternal RA

The prevalence of epilepsy in children exposed to maternal RA or unexposed was extracted from the other two studies.[32,33] Since statistical heterogeneity between studies was not significant ($I^2 = 0.0\%$ and $p > 0.1$), a fixed effects model was used. The risk of epilepsy was increased in children exposed to maternal RA compared with unexposed children (2.36% in exposure *versus* 1.50% in nonexposure; RR 1.475; 95% CI: 1.333–1.633, $p < 0.001$, based on $n = 3{,}290{,}578$) (Figure 2).

Subgroup analysis and meta-regression

Because of the high heterogeneity of the included studies regarding the risk of epilepsy in RA patients, further subgroup meta-analyses and meta-regression were performed. Subgroup analysis found the risk of epilepsy in RA patients decreased with age (Table 2). When age was >64 years, epilepsy in RA patients was not associated with RA. Meta-regression further showed that the RR of epilepsy in RA was negatively correlated with age [Figure 3 (a) and (b)]. Of note, 42.02% (including the 'all age or age >12' group) and 41.45% (excluding the 'all age or age >12' group) of heterogeneity could be explained by the age.

In addition, as shown in the inset of Figure 3 (b), the mean percentage of patients with epilepsy in the

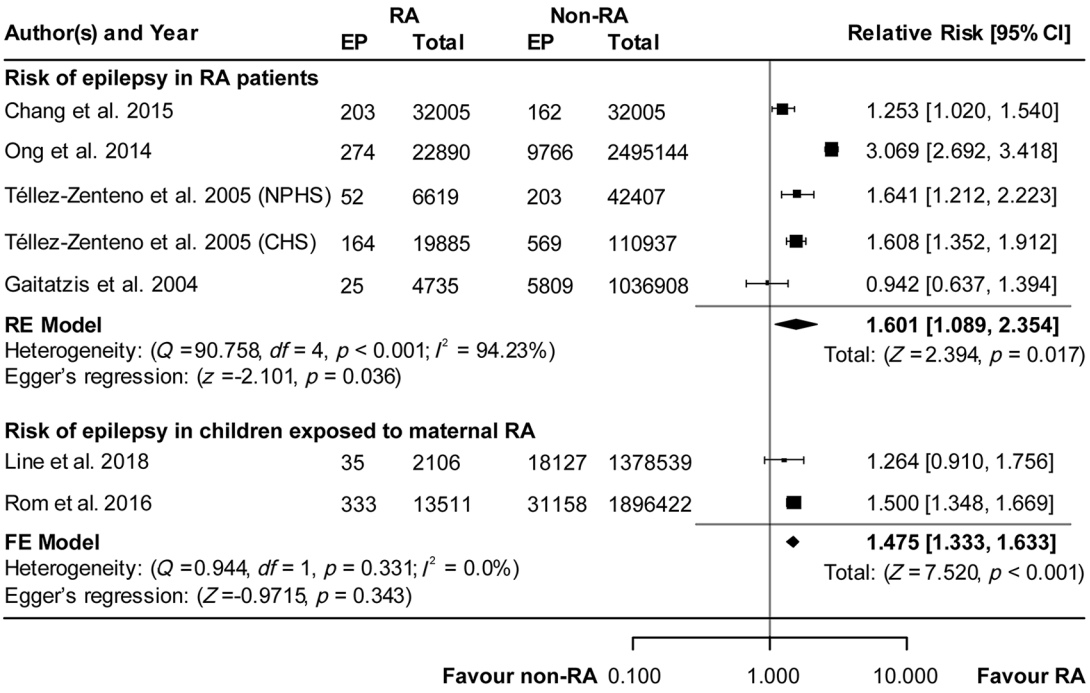

Figure 2. Forest plots of studies estimating the relative risk of epilepsy in patients with RA and children exposed to maternal RA.
95% CI, 95% confidence interval; CHS, Community Health Survey; EP, epilepsy; FE, fixed effects model; NPHS, National Population Health Study; RA, rheumatoid arthritis; RE, random effects model (restricted maximum-likelihood estimator).

total elderly population was higher than that in the total nonelderly (young) adult population (0.85% for total elderly population *versus* 0.45% for total nonelderly population), which is similar in non-RA population (0.85% for non-RA elderly population *versus* 0.42% for non-RA nonelderly population). On the contrary, the mean percentage of patients with epilepsy in the elderly RA population was comparable with that in the nonelderly adult RA population (0.81% for elderly RA population *versus* 0.74% for nonelderly RA population).

Genes association between epilepsy and RA

To further interpret the relationship between RA and epilepsy, we collected 433 genes in a coexpression network of hippocampi of 129 TLE patients from a previous study.[21] We found 433 genes were mainly enriched in an RA related ClueGO group of KEGG pathways, which contains 38.46% of all KEGG pathways [Figure 4 (a) and (b)]. The details of each enriched ClueGO group were shown in Figure 4 (c).

To further analyze the relationship between RA and epilepsy, we compared these 433 epilepsy-associated genes with 672 RA associated genes from previous studies[16,17] and found that 36 genes were associated with both RA and epilepsy [Figure 5 (a)]. The PPI network of the 36 cogenes is shown in Figure 5 (b). We further identified 13 genes by MCODE clustering of the PPI network of the 36 cogenes, which mainly contained inflammatory cytokines such as IL-1 alpha (IL1A), IL1B, and tumor necrosis factor (TNF), as well as chemokines such as C-C motif chemokine ligand 2 (CCL2), C-C motif chemokine ligand 3 (CCL3), and C-C motif chemokine ligand 5 [CCL5; Figure 5 (c)].

Discussion

In the present study, we found that: (a) RA patients had a higher risk of epilepsy than the non-RA population; (b) the relative risk of epilepsy was increased in children exposed to maternal RA relative to unexposed children; (c) the relative risk of epilepsy in RA was negatively correlated with age; (d) when age was >64 years, epilepsy in RA patients was not associated with RA; (e) genes in the hippocampal coexpression network associated with epilepsy were enriched for RA related KEGG pathways; (f) 13 genes that mainly related to inflammatory cytokines and chemokines were overlapping in RA and epilepsy.

Table 2. The subgroup meta-analysis (age).

Subgroup	Study (age)	RR (95% CI)	*p* value
<18	Ong *et al.*[34] (<18)	2.995 (1.350, 6.646)	
	Subtotal (fixed effects model)	**2.995 (1.350, 6.646)**	**0.007**
16–65	Chang *et al.*[34] (20–64)	1.500 (1.127, 1.997)	
	Ong *et al.*[35] (18–65)	3.010 (2.688, 3.424)	
	Gaitatzis *et al.*[37] (16–64)	1.023 (0.617, 1.696)	
	Subtotal (random effects model)	**1.728 (0.923, 3.237)**	**0.087**
All ages or >12	Téllez-Zenteno *et al.*[36] (NPHS, all age)	1.641 (1.212, 2.223)	
	Téllez-Zenteno *et al.*[36] (CHS, >12)	1.608 (1.352, 1.912)	
	Subtotal (fixed effects model)	**1.608 (1.352, 1.878)**	**<0.001**
>64	Chang *et al.*[34] (>64)	1.024 (0.759, 1.381)	
	Gaitatzis *et al.*[37] (>64)	0.831 (0.447, 1.545)	
	Subtotal (fixed effects model)	**0.984 (0.752, 1.289)**	**0.909**

95% CI, 95% confidence interval; CHS, Community Health Survey; NPHS, National Population Health Study; RR, risk ratio.

Thus, our results highlight a strong association between RA and epilepsy.

Several previous meta-analysis studies have found an association between autoimmune diseases and epilepsy;[5,38] however, the relationship between specific autoimmune diseases and epilepsy is still not well understood. Here we included five high quality studies with NOS > 7[32–35,37] and one medium quality study with NOS = 5.[36] NOS score had no significant correlation to the RR of epilepsy in RA patients. The quality of these studies gives our meta-analysis reliability. Among these studies, two[34,35] (which excluded a history of epilepsy before the diagnosis of RA) indicate that RA might be an etiological factor in epilepsy. Inversely, two other included studies (which did not exclude a history of epilepsy before the diagnosis of RA studies) demonstrated comorbidity of epilepsy and RA.[36,37] One supported the bidirectional association between epilepsy and RA,[36] while the other study indicated a slightly increased risk of developing RA in epilepsy but not *vice versa*.[37] In our meta-analysis, based on these four studies, we showed that RA patients had a higher risk of developing epilepsy than non-RA patients.

Given the high level of heterogeneity, we conducted a subgroup meta-analysis. Subgroup meta-analysis showed that the RR of epilepsy decreased with age in RA patients. Furthermore, meta-regression showed a negative correlation between age and relative risk of epilepsy in this population. These results suggest early exposure of RA may be a risk factor of epilepsy. Of note, (a) only one study provided data regarding epilepsy in children with RA;[35] (b) only 42.02% (including the 'all age or age >12' group) and 41.45% (excluding the 'all age or age >12' group) of heterogeneity could be explained by the age, and the heterogeneity was still high in the nonelderly adult subgroup (though the heterogeneity in children, all age, or elderly group became absent), suggesting other confounding factors may still exist in this subgroup. Further studies on the risk of epilepsy in RA patients, particularly in children, are warranted.

We also reviewed the two other high-quality and nonheterogeneous studies on the prevalence of epilepsy in children born to mothers with RA.[32,33] We found that the risk of epilepsy was increased in children exposed to maternal RA. This result is

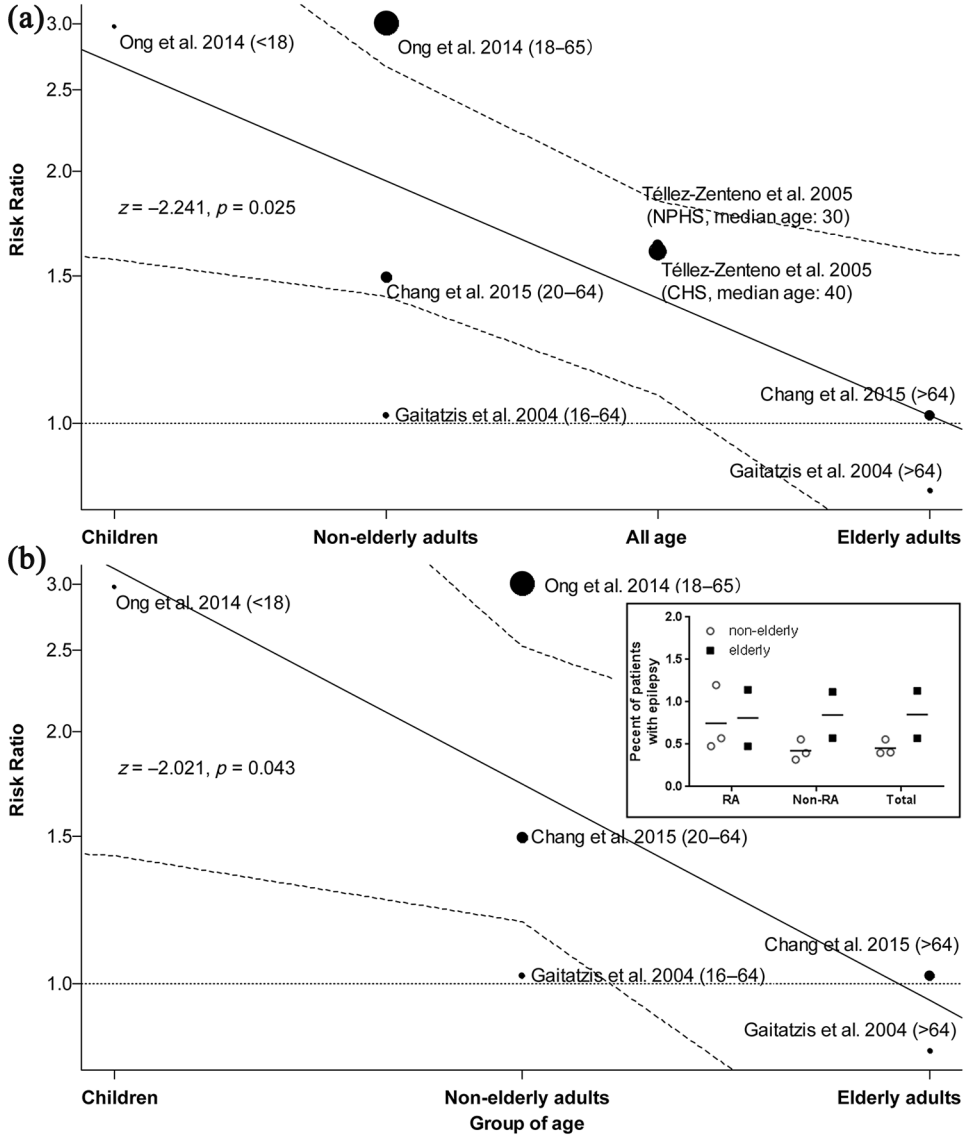

Figure 3. Meta-regression between risk ratio of epilepsy and groups of age in RA. (a) Set 'all age or age >12' as a group between nonelderly adults and elderly adults. (b) Excluded the 'all age or age >12' group; The inset showed the percent of patients with epilepsy in RA, non-RA and total populations (the solid lines in the inset of (b) represent the mean percentage of patients with epilepsy). The numbers under the *x* axis in the main plots of (a) and (b) mean the categorical variable of each group that used for meta-regression. Here *z* denotes *z* value and *p* denotes *p* value for the meta-regression. The radius of the points in the main plots of (a) and (b) is drawn proportional to the inverse of the standard errors. The solid line in the main plots of (a) and (b) is a trendline showing the RR of the individual studies plotted against the age, and the dotted line means the corresponding 95% confidence interval bounds.
CHS, Community Health Survey; NPHS, National Population Health Study; RA, rheumatoid arthritis.

consistent with our subgroup analysis and meta-regression finding and suggests early exposure of RA (maternal) during the fetal period is also a risk factor of epileptogenesis. Of note, one of these studies additionally demonstrated that paternal RA was not associated with epilepsy in offspring,[33] which highlights fetal-maternal interactions in pregnancy may be involved. Taken together, our results strongly indicate early exposure of RA may be a risk factor in the development of epilepsy. Nonetheless, additional studies on the risk of epilepsy in children born to mothers with RA are warranted, taking into account the influences of RA drugs and genetic factors.

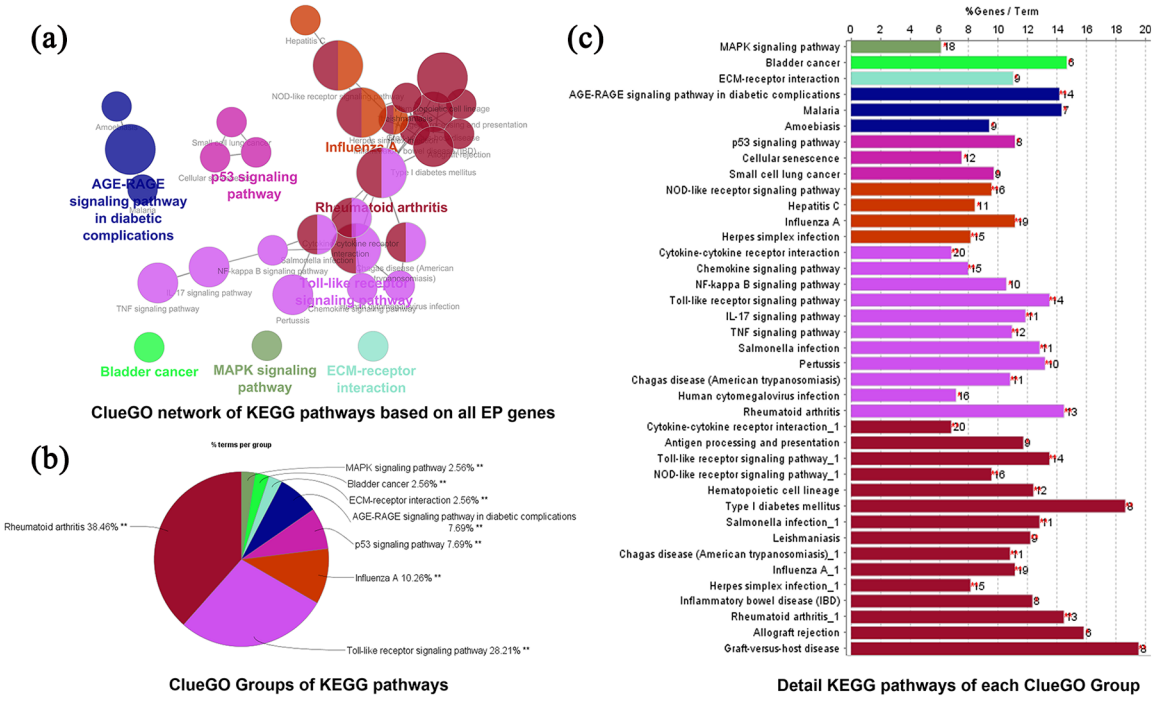

Figure 4. Genes in a coexpression network associated with epilepsy were enriched in RA. (a) Group of terms (pathways) shown as a network that generated by the ClueGO plugin in Cytoscape. One color means one ClueGO group, which is a functionally grouped annotation network that reflects the relationships between the terms (pathways) based on the similarity of their associated genes. The size of the nodes reflects the statistical significance of the terms. The degree of connectivity between terms (edges) is calculated using kappa statistics. (b) Percentage of terms per ClueGO group ($^{**}p < 0.01$ for group cluster test). (c) Percentage of gene per term ($^{*}p < 0.05$; $^{**}p < 0.01$ for each single pathway test). A term can be included in several groups.
EP, epilepsy; KEGG, Kyoto Encyclopedia of Genes and Genomes.

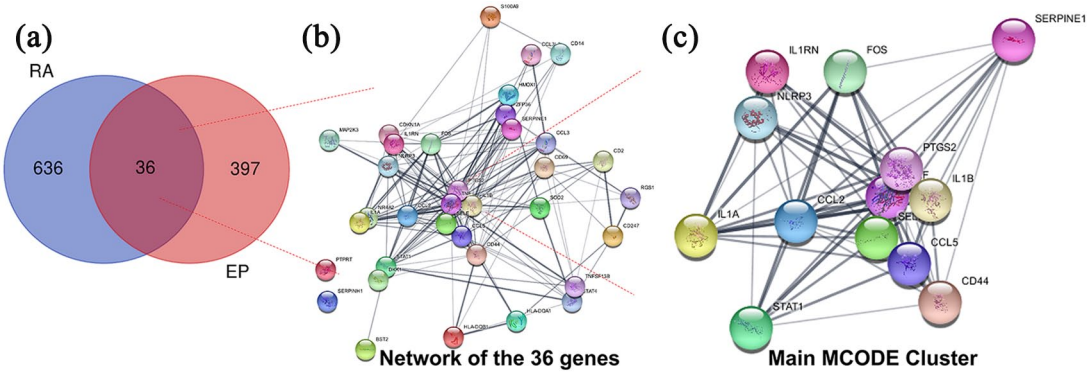

Figure 5. Potential genes associated with both epilepsy and RA: (a) Venn diagram of genes associated with epilepsy and RA; (b) PPI network of the 36 genes associated with both epilepsy and RA; (c) the main MCODE cluster of the PPI network of these 36 genes.
EP, epilepsy; MCODE, Molecular Complex Detection; PPI, protein–protein interaction; RA, rheumatoid arthritis.

The mechanisms underlying both RA and epilepsy are complex. Increasing evidence suggests inflammatory processes contribute to epileptogenesis.[39,40] Here we found genes in the hippocampal coexpression network associated with epilepsy were mainly enriched in RA and its related KEGG pathways, which contains 38.46% of all enriched terms, such as cytokine–cytokine receptor interaction, antigen processing and presentation, toll-like receptor signaling pathway, and NOD-like receptor signaling

pathway. Moreover, the potential key genes are mainly related to inflammatory cytokines (such as IL1A, IL1B, and TNF) and chemokines (such as CCL2, CCL3, and CCL5), which may result in a dysfunction of neural circuits and hyperexcitability when they access the brain.[41] Thus, our results may provide insight and targets for further studies to understand and prevent epilepsy in RA.

On the other hand, when it comes to the age related risk of epilepsy in RA, the development of the blood–brain barrier (BBB) may be involved, especially in children exposed to maternal RA.[42] The BBB is a gateway for inflammatory cytokines accessing the brain, which may be dysfunctional in RA.[43,44] BBB dysfunction has also been considered a potential biomarker for epileptogenesis.[45] Another explanation for the age-associated risk of epilepsy in RA patients may be the developing brain.[46] For example, proper synaptic pruning may be lost or altered when microglia are activated by an improper balance of cytokines.[47] In addition, the development and maintenance of the central nervous system surveillance pathways used by the peripheral immune system, such as the meningeal lymphatic system,[48] might also be involved.

For adults, the occurrence of epilepsy peaks in the elderly. Consistent with this, we also found the mean percentage of patients with epilepsy in the total (or non-RA) elderly population was about twice as many as that in the total (or non-RA) nonelderly (young) adult population. However, the mean percentage of epilepsy in elderly RA patients was comparable with that of the nonelderly adult RA patients as well as the non-RA elderly population (0.81% for elderly RA population, 0.74% for nonelderly adult RA population, and 0.85% for non-RA elderly population). Immune system aging, which was considered as an accelerator for other age-related pathologies, occurs prematurely in patients with RA.[49,50] Thus, these results suggest that the increased risk of epilepsy in RA may be related to the accelerated aging of the brain in adult RA, which might be also an explanation of the phenomenon that epilepsy in RA patients was not associated with RA when their age was >64 years. It has been reported that BBB permeability was increased because of both aging[51] and RA,[52] suggesting increased BBB dysfunction might be an important factor in the higher risk of epilepsy in the nonelderly adult RA patients than that of the elderly RA patients. Taken together, our results also provide some additional potential clues to further studying the age-related association between RA and epilepsy in adults from the angle of neuroinflammation.

Although we included nationwide and high quality studies, several limitations in our meta-analysis should be noted as follows: (a) a limited number of studies were included and heterogeneity is high among studies; (b) two studies on children born to mothers with RA were conducted in the same country; (c) the trial design varied among studies, such as the selection of control groups, thus possibly interfering with the validity of our findings.

Conclusion

Our meta-analysis highlights an association between epilepsy and RA indicates an age dependent risk of epilepsy in RA and provides related bioinformatical evidence. Further studies are still warranted to confirm these findings, especially for a population that was exposed to RA during the fetal and childhood period.

Acknowledgements

Z.X. would like to thank all members of Filiano Lab, Kurtzberg Lab and Marcus Center for Cellular Cures (MC3) at Duke University.

H.Z. and Z.X. designed the study. H.Z. and S.L. performed the systematic search. H.Z. and S.L. reviewed studies to extract potentially eligible studies and the data. M.X. and R.C. helped to check the extracted data for analysis. H.Z. and Z.X. analyzed the data and wrote the manuscript in consultation with H.L., C.W., and A.J.F.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by Medical Science and Technology Project of Zhejiang Province (grant number 2019329880) and National Natural Science Foundation of China (grant number 81673623). Partly supported by the National Key Research and Development Program of China (grant number 2018YFC1705501), the Project of the national education steering committee for postgraduate students majoring in traditional Chinese medicine (20190723-FJ-B23), and the Foundation of

Zhejiang Chinese Medical University (grant numbers ZYX2018002 and Q2019Y02).

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Consent statement and ethical approval

Consent statement and ethical approval are not required as the current study was based on published data.

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Supplementary material

Supplemental material for this article is available online.

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