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Maria Inês Agonia Ferreira

Polimorfismos da Il-17, IL-21 e IL-22 na artrite reumatoide: uma revisão sistemática e meta-análise/

IL-17, IL-21 and IL-22 polymorphisms in rheumatoid arthritis: A systematic review and meta-analysis

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Doutor Bernardo Sousa Pinto

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FMUP

Eu, Maria Inês Agonia Ferreira, abaixo assinado, nº mecanográfico 201403735, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

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Faculdade de Medicina da Universidade do Porto, 29/12/2019

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UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

Maria Inês Agonia Ferreira

NÚMERO DE ESTUDANTE	E-MAIL
201403735	inesagoniaferreira@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Imunologia

TÍTULO DISSERTAÇÃO

IL-17, IL-21 and IL-22 polymorphisms in rheumatoid arthritis: A systematic review and meta-analysis.

ORIENTADOR

Bernardo Sousa Pinto

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 27/12/2019

Assinatura conforme cartão de identificação: Maria Inês Agonia Ferreira

Dedicatória

Agradeço ao meu orientador Doutor Bernardo Sousa Pinto, não só pelos conhecimentos transmitidos, mas principalmente pela disponibilidade e apoio dispensados para a concretização deste projeto.

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A todos os amigos, aos que a faculdade trouxe, e aos de sempre.

Um gigante obrigado.

ABSTRACT

Background: Rheumatoid Arthritis (RA) is an autoimmune systemic disease and in its pathogenesis participate several proinflammatory cytokines, including those produced by Th17 cells. We performed a systematic review aiming to assess the associations between polymorphisms in Th17 cytokines, namely IL-17A, IL-17F, IL-21 and IL-22, and susceptibility to RA.

Methods: We searched three electronic databases (MEDLINE, Scopus and Web of Science) for observational studies assessing the association between susceptibility to RA (or its clinical presentation) and polymorphisms of the cytokines IL-17A, IL-17F, IL-21 and IL-22. From the selected studies, we extracted information on the studied polymorphisms, assessed outcomes, and demographic characteristics of participants. We performed random effects meta-analyses assessing the associations between susceptibility to RA and different genotypes of the IL-17A rs2275913, IL-17F rs763780 and IL-17F rs2397084 polymorphisms. Primary studies' quality was assessed using the Q-Genie tool.

Results: Fifteen studies were included in this systematic review. Five IL-17A polymorphisms were reported to be associated with susceptibility to RA. For the IL-17A rs2275913 polymorphism, our meta-analysis showed the AA genotype to be significantly associated with lower susceptibility to RA (OR=0.76; 95%CI=0.61-0.93; *p*=0.01), while the opposite was observed for the GG genotype (OR=1.20; 95%CI=1.06-1.35; *p*=0.01). Concerning IL-17F rs763780 polymorphism, the TT genotype of was found to be significantly less frequent in RA patients (OR=0.49; 95%CI=0.31-0.77; *p*=0.002), while the opposite was observed for the CT genotype (OR=2.00; 95%CI=1.03-3.87; *p*=0.04). No significant associations were found regarding rs2397084 polymorphisms. For IL-21, rs6822844 and rs4505848 were described to have significant associations with susceptibility to RA. No studies were found assessing IL-22 polymorphisms in RA.

Conclusions: IL-17A rs2275913 and IL-17F rs763780 polymorphisms are significantly associated with susceptibility to RA and with different clinical characteristics of this disease.

HIGHLIGHTS:

- The IL-17A rs2275913 AA genotype associates with less risk of rheumatoid arthritis.
- The IL-17A rs2275913 GG genotype associates with susceptibility to rheumatoid arthritis.
- The 17F rs763780 TT genotype associates with less risk of rheumatoid arthritis.
- The 17F rs763780 CT genotype relates to more susceptibility to rheumatoid arthritis.
- The IL-17F rs2397084 polymorphism is not associated with the risk of the disease.

KEYWORDS: Interleukins; Interleukin-17; Interleukin-21; Th17 Cells; Polymorphism; Rheumatoid Arthritis

ABBREVIATIONS:

- **Th17:** T helper 17
- **Treg:** Regulatory T cells
- **RA:** Rheumatoid arthritis
- **IL:** Interleukin

- **IFN-γ:** Interferon gamma
- **OR:** Odds ratio
- **CI:** Confidence interval
- **NFAT:** Nuclear factor of activated T-cells
- **TNF-α:** Tumor necrosis factor alpha

1. INTRODUCTION

Chronic inflammatory diseases are believed to be mediated by dysfunctional innate and/or adaptive immune responses, involving the secretion of cytokines that damage tissues and lead to further inflammation [1]. In fact, in homeostatic conditions, there is a balance between $CD4^+$ T-cells secreting inflammatory cytokines (including T helper 1 and T helper 17 cells) and $FOXP3^+$ regulatory T-cells (Treg). On the other hand, in inflammatory autoimmune diseases, there is a relative increase in the activity of autoreactive pro-inflammatory $CD4^+$ T cells and loss of Treg function [2]. These diseases include, among others, rheumatoid arthritis (RA), an autoimmune systemic disease associated with destruction of affected joints [3], whose prevalence is estimated to be about 0.6% in European countries, 1.3% in American countries and 0.4% in the Western Pacific region [4].

Several cytokines play an important role in the pathogenesis of RA, initiating and maintaining the inflammatory response in the joints [3,5]. By producing effector cytokines – such as IL-17 and IL-22 –, T helper 17 (Th17) cells promote the development of autoimmune responses [6]. For example, Th17.1 cells, a subset of IL-17/IFN-γ-producing Th17 cells, were identified as pathogenic drivers in autoimmune conditions, including RA and multiple sclerosis [7]. Hence, IL-17 has been the focus of many relevant discoveries regarding not only RA, but also many other autoimmune diseases. In fact, IL-17A has been shown to promote germinal centre formation in murine autoimmune disease models, and immunoglobulin class switching in human B cells [8-9]. On the other hand, IL-21 is necessary for continuous IL-17 production [10-12] and regulates human Th17 cells in RA, enhancing their proliferation and suppressing FOXP3 expression [13]. In addition to IL-17 and IL-21, IL-22 is also produced by Th17 cells, regulating chronic inflammation, and stimulating synovial fibroblasts to induce cell proliferation and the production of inflammatory chemokines [1].

Genetic variation in Th17 cytokines can influence their transcriptional regulation and, therefore, promote disease susceptibility; for instance, polymorphisms in Th17 enhancers have been associated with RA, as well as with Crohn's disease, multiple sclerosis and juvenile idiopathic arthritis [6]. In the last decade, genome-wide association studies have identified more than 100 risk-associated loci for RA [14-15], nearly 20 of them encoding proteins directly involved in Th17 cell differentiation and function [16]. Other systematic reviews had already addressed the possible associations between IL-17 polymorphisms and susceptibility to RA [17-18]. However, they did not account for other cytokines produced by Th17 cells, there have been relevant primary studies published afterwards and, one of these systematic reviews mixed together studies assessing patients with RA and with other forms of arthritis (such as giant cell arthritis). Therefore, in this study, we aimed to systematically review the associations between IL-17, IL-21 and IL-22 polymorphisms and (i) susceptibility to RA, and (ii) clinical and inflammatory features of this disease.

2. MATERIAL AND METHODS

2.1. Selection criteria

In this systematic review, we searched for observational cohort or case-control studies performed in humans and which assessed the associations between IL-17A, IL-17F, IL-21 or IL-22 polymorphisms, and (i) susceptibility to RA or (ii) clinical manifestations/laboratorial presentations (e.g., altered levels of relevant biomarkers) within the context of RA. Studies without a comparison or control group were excluded, as they do not allow the assessment of the association between expression of polymorphisms and RA. We also excluded systematic reviews and studies performed in animals.

2.2. Search strategy

We performed a comprehensive search in Web of Science, Scopus and MEDLINE (using PubMed), using the following keywords and MeSH terms: rheumatoid arthritis, gene, polymorphisms, interleukin-17, IL-17, interleukin-21, IL-21, interleukin-22, and IL-22. The queries used are available in Table 1. The final search was performed in March 2019, and no language or date restrictions were applied. In addition, we searched the references of included studies and of relevant previously performed systematic reviews [17-18].

Databases	Queries
Web of Science	TS=((rheumathoid arthritis) AND (gene* OR polymorphi*) AND ((interleukin-17 OR IL-17) OR (interleukin-21 OR IL-21) OR (interleukin-22 OR IL-22)))
Scopus	(rheumathoid arthritis) AND (gene* OR polymorphi*) AND ((interleukin-17 OR IL-17) OR (interleukin-21 OR IL-21) OR (interleukin-22 OR IL-22))
MEDLINE (Pubmed)	("Arthritis, Rheumatoid" [Mesh] OR rheumatoid arthritis) AND ("Polymorphism, Genetic"[Mesh] OR gene* OR polymorphi*) AND (("Interleukin-17" [Mesh] OR IL-17 OR interleukin-17) OR (“Interleukin-21"[Mesh] OR IL-21 OR interleukin-21) OR ("Interleukin-22"[Mesh] OR IL-22 OR interleukin-22))

Table 1. List of queries used for searching online databases.

2.3. Study selection, data extraction and quality assessment

After eliminating duplicates, two authors independently participated in study selection. Studies were firstly selected after reading their titles and abstracts. Articles were excluded if they did not assess the association between IL-17, IL-21 and IL-22 and RA and if they did not meet eligibility criteria (e.g., studies performed in animals). Subsequently, the full texts of studies not excluded in the screening phase were independently read by at least two authors who selected those that met the predefined inclusion and exclusion criteria. Disagreements in the selection process were solved by consensus. We made efforts to contact researchers to obtain publications not accessible by other means.

Selected articles were analyzed and data was extracted by two independent researchers in regards to the study design, number of and demographic characteristics (age, gender, and nationality) of participants, number of participants with RA, adopted definition of RA, assessed polymorphisms, number of participants with those polymorphisms (in particular, the number of participants presenting with each genotype), other assessed clinical and laboratorial outcomes (i.e., RA clinical manifestations, or altered levels of relevant biomarkers) and number of participants with those outcomes. For primary studies published in languages other than English, we contacted the authors asking for relevant information.

The Q-Genie tool [19] was used for assessing the quality of the included genetic association primary studies. This tool was developed and subsequently validated to enable the quality assessment of genetic primary studies for systematic reviewing purposes. It includes 11 items comprising an evaluation of the research question, sample size, statistical analyses and methods, classification of the genetic variant and of the outcome, sources of bias, test of assumptions in the genetic studies, comparison between groups and acceptable interpretation of the results [19]. Quality assessment was performed by two independent researchers (any disagreement was solved by consensus) and summarized in a risk-of-bias graph and in a summary of bias graph.

2.4. Quantitative synthesis

For each study, associations between the assessed outcomes and the frequency of IL-17, IL-21 or IL-22 polymorphisms were expressed using odds ratios (OR). Unadjusted OR were directly obtained from studies or, when not provided, calculated by classical methods.

We performed random effects meta-analyses weighted by the inverse of variance (using the method of DerSimonian and Laird [20]) to assess the associations between RA and each of the different genotypes of the (i) IL-17A rs2275913 polymorphism (AA, GG and AG genotypes), (ii) IL-17F rs763780 polymorphism (TT, CC and CT genotypes), and (iii) IL-17F rs2397084 polymorphism (TT, CC and CT genotypes). Pooled OR were calculated with the respective 95% confidence intervals (CI); whenever a cell had a zero count, a continuity correction of 0.5 was added. Heterogeneity was evaluated using I^2 and Cochran Q statistics – an I^2 >40% and a Cochran Q test p value <0.10 were considered to represent severe and significant heterogeneity, respectively. In the presence of significant/severe heterogeneity, leave-one-out sensitivity analyses (i.e., repeating the meta-analysis excluding each study at a time) and subgroup analyses (i.e., separate analyses) based on the study region and RA diagnostic criteria were performed. No other genetic variant was assessed by more than two studies, and therefore we were not able to perform meta-analysis for polymorphisms other than rs2275913, rs763780 and rs2397084. The possibility of publication bias was assessed using funnel plots. All statistical analyses and funnel plots were performed using Review Manager 5.3 software [21] (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

3. RESULTS

3.1. Search results

In our database search, we obtained 400 studies. After duplicate removal and selection by title and abstract screening, we obtained 34 studies. Eighteen studies were excluded after full text reading. One additional article was excluded, as it was written in Japanese [22] - in spite of our attempt to contact the authors, no response was received. No relevant additional studies were identified by analyzing the references of previous systematic reviews [17-18]. Thus, a total of 15 studies published between 2009 and 2018 were included in this systematic review (Figure 1) [3,5,23-35].

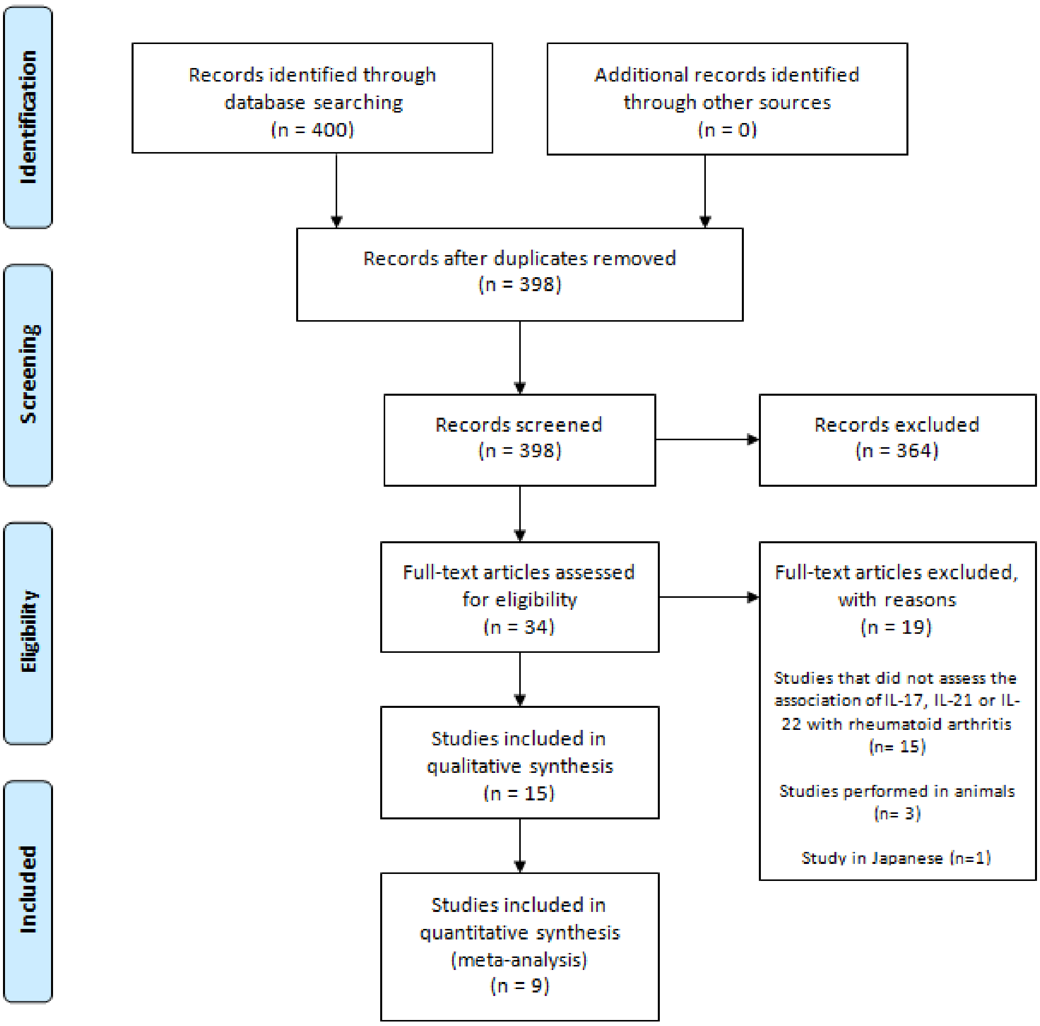


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the studies' selection process.

3.2. Description of studies

The included publications assessed a total of 11,121 individuals (range of 206-2,967 participants *per* study), of whom 5,602 had been diagnosed with RA (50.4%; range across studies: 42.3-67.5%) [3,5,23-35]. Rheumatoid arthritis was defined according to the 2010 American College of Rheumatology's criteria [36] in six of the included studies [3,23,26,32,33,35] or the American Rheumatism Association 1987 revised criteria for the classification of RA [37] in ten studies [5,24-25,27-31,33,34]. Therefore, in one study [33], the authors used both criteria [34,35] even though they did not provide details regarding how they applied them. The mean age of all assessed participants was 50.3 years old [3,5,23-35], and 71.4 % of them were females. Concerning the 5,602 patients diagnosed with RA, their mean age was 53.7 years old [3,5,23-35], and 79.0% of them were females. Included studies were performed in 16 different countries: Nine countries in Europe [3,23,25,26,28,30,31], three in Latin America [24,27,33,35], two in Africa [29,32,34], one in Asia [5] and one in Oceania [28]. From the 15 articles reviewed, 14 evaluated the susceptibility to RA (Table 3) [3,5,23-29,31-35], and 12 assessed other outcomes [3,23,25-30,32-35] (listed in Table 2).

The included publications assessed the frequency of polymorphisms in the genes coding for IL-17A, IL-17F and IL-21 (regarding IL-22, no studies assessing the association between its polymorphisms and RA were found). A total of 14 polymorphisms have been assessed by the included studies; of those, four have been assessed in more than one study, namely rs2275913 (11 studies) [3,5,23,26-29,32-35], rs763780 (8 studies) [3,23,25-27,29,33-34], rs2397084 (5 studies) [3,23,25,29,34] and rs6822844 (3 studies) [24,30,31] (Table 3). The remaining 10 polymorphisms were only assessed by one study each.

Outcome	IL	Polymorphism	Study	OR (95% CI)	p-value
Rheumatoid Factor	IL-17A	rs2275913 AG	Pawlik A et al. (2016)	NA	0.35
	IL-17A	rs2275913 AG	Silva I et al. (2017)	0.72 (0.34-1.49)	0.49
	IL-17A	rs2275913 GG	Nordang GB et al. (2009)	NA	NS
	IL-17A	rs2275913 GG	Dhaouadi T et al. (2018)	NA	0.84
	IL-17A	rs2275913	García de la Peña M et al. (2017)	NA	0.40
	IL-17F	rs763780 CT	Pawlik A et al. (2016)	NA	0.70
	IL-17F	rs763780 CT	Silva I et al. (2017)	0.46 (0.10-2.03)	0.50
	IL-17F	rs2397084 CT	Pawlik A et al. (2016)	NA	0.06
	IL-17F	rs11465553 CT	Pawlik A et al. (2016)	NA	1.00
	IL-21	rs6822844	Daha NA et al. (2009)	1.09 (0.80–1.48)	0.58
Anti-CCP	IL-17A	rs2275913 GG	Nordang GB et al. (2009)	NA	NS
	IL-17A	rs2275913 GG	Dhaouadi T et al. (2018)	NA	0.49
	IL-17A	rs2275913	García de la Peña M et al. (2017)	NA	0.70
CRP	IL-17A	rs2275913 AG	Silva I et al. (2017)	1.15 (0.49-2.65)	0.91
	IL-17F	rs763780 CT	Silva I et al. (2017)	2.35 (0.27-19.97)	0.70
	IL-17F	rs2397084 CT	Erkol Inal E et al. (2015)	NA	0.06
ESR	IL-17A	rs2275913 AG	Silva I et al. (2017)	1.22 (0.59-2.52)	0.72
	IL-17F	rs763780 TT	Louahchi S et al. (2016)	NA	0.02
	IL-17F	rs763780 CT	Silva I et al. (2017)	1.77 (0.41-7.60)	0.67
Creatinine	IL-17F	rs763780 CT	Paradowska-Gorycka A et al. (2010)	NA	0.02
Clinical Features [a]	IL-17A	rs2275913 AG	Carvalho CN et al. (2016)	NA	NA
Severity	IL-17A	rs2275913 AG	Carvalho CN et al. (2016)	NA	NA
	IL-17F	rs763780 CT	Marwa O et al. (2017)	2.83 (1.11-6.90)	0.02
	IL-17F	rs2397084 CT	Marwa O et al. (2017)	3.90 (1.84-8.20)	0.001
DAS-28-CRP	IL-17A	rs2275913 AG	Silva I et al. (2017)	2.33 (0.86-6.28)	0.14
	IL-17A	rs2275913	García de la Peña M et al. (2017)	NA	0.20
	IL-17F	rs763780 CT	Paradowska-Gorycka A et al. (2010)	NA	0.06
	IL-17F	rs763780 CT	Carvalho CN et al. (2016)	NA	NA
	IL-17F	rs763780 CT	Silva I et al. (2017)	0.511 (0.06-4.34)	0.86
HAQ	IL-17A	rs2275913	García de la Peña M et al. (2017)	NA	0.10
	IL-17F	rs763780 CT	Paradowska-Gorycka A et al. (2010)	NA	0.08
Progression	IL-17A	rs2275913 AG	Carvalho CN et al. (2016)	NA	NA
	IL-17A	rs2275913 AG	Bogunia-Kubit K et al. (2015)	NA	0.06
	IL-17A	rs2275913 GG	Nordang GB et al. (2009)	NA	NS

2-year Radiographic Progression	IL-17A	rs2275913 GG	Nordang GB et al. (2009)	NA	0.44
No responsiveness to anti-TNF therapy	IL-17A	rs2275913 AG	Bogunia-Kubit K et al. (2015)	NA	0.04
Age at diagnosis	IL-17A	rs2275913 AG	Erkol Inal E et al. (2015)	NA	NS
	IL-17A	rs2275913 AG	Pawlik A et al. (2016)	NA	0.56
	IL-17F	rs763780 CT	Pawlik A et al. (2016)	NA	0.69
	IL-17F	rs2397084 CT	Pawlik A et al. (2016)	NA	0.69
	IL-17F	rs11465553 CT	Pawlik A et al. (2016)	NA	0.63
Disease duration in people with RA	IL-17A	rs2275913	García de la Peña M et al. (2017)	NA	0.30
	IL-17F	rs2397084 TT	Louahchi S et al. (2016)	NA	0.003
	IL-17F	rs2397084 CT	Paradowska-Gorycka A et al. (2010) [b]	NA	0.07
	IL-17F	rs2397084 CT	Marwa O et al. (2017) [c]	19.4 (2.19-522)	NA
Erosive disease	IL-17A	rs2275913 AG	Pawlik A et al. (2016)	NA	0.64
	IL-17A	rs2275913 AG	Silva I et al. (2017)	1.72 (0.64-4.62)	0.40
	IL-17A	rs2275913 GG	Dhaouadi T et al. (2018)	NA	0.13
	IL-17F	rs763780 CT	Pawlik A et al. (2016)	NA	0.52
	IL-17F	rs763780 CT	Silva I et al. (2017)	NS	NS
	IL-17F	rs2397084 CT	Pawlik A et al. (2016)	NA	0.78
	IL-17F	rs11465553 CT	Pawlik A et al. (2016)	NA	0.69
Tender Joints	IL-17F	rs763780 CT	Paradowska-Gorycka A et al. (2010)	NA	0.03
Extra-articular manifestations	IL-17A	rs2275913 AG	Pawlik A et al. (2016)	NA	0.25
	IL-17F	rs763780 CT	Pawlik A et al. (2016)	NA	0.14
	IL-17F	rs2397084 CT	Pawlik A et al. (2016)	NA	0.69
	IL-17F	rs11465553 CT	Pawlik A et al. (2016)	NA	0.08

Anti-CCP: cyclic citrullinated peptide antibodies; CRP: C-Reactive Protein; DAS28-CRP: Disease Activity Score 28-C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; IL: Interleukin; NA: Not available; NS: No information other than non significant association (>0.05).

[a] RSFR – Resting Saliva Flow Rate; Schirmer test; Xerostomia; Xerophthalmia; Biopsy. [b]<1 year vs >1 year; [c] ≤2 years vs 3-5 years.

Table 2. Assessed associations between RA clinical and laboratorial characteristics and IL-17A, IL-17F and IL-21 polymorphisms.

Interleukin	Polymorphism (Location)	Study	Study Design	Geographic Area	Genotype	*p* value	OR (95% CI)	Population				
								RA cases		Controls		
								Total	With polymorphism – *n* (%)	Total	With polymorphism – *n* (%)	Total
IL-17A	rs2275913 (Position 52186235 in Chr 6)	Pawlik A et al. (2016)	CC	Poland	AA	0.33	0.80 (0.53-1.22)	422 [a]	51 (12.2)	337	50 (14.84)	759
					AG	NA	0.83 (0.62-1.11)		193 (46.3)		169 (50.2)	
					GG	0.17	1.28 (0.95-1.72)		173 (41.5)		118 (35.0)	
		Shen L et al. (2015)	CC	China	AA	0.04	0.77 (0.59-0.99)	615 [b]	114 (18.9)	839	194 (23.3)	1454
					AG	NA	1.08 (0.87-1.33)		292 (48.3)		383 (46.0)	
					GG	NA	1.09 (0.87-1.36)		198 (32.8)		255 (30.7)	
		Erkol Inal E et al. (2015)	CC	Turkey	AA	NS	NA	161 [a]	32 (19.9)	88	NA	249
					AG	NS	NA		61 (37.89)		NA	
					GG	NS	NA		68 (42.2)		NA	
		Bogunia-Kubit K et al. (2015)	CH	Poland	AA	NA	0.82 (0.38-1.77)	89 [a]	12 (13.6)	125	20 (16.0)	214
					AG	NA	0.85 (0.49-1.46)		44 (50.0)		67 (53.6)	
					GG	NA	1.29 (0.72-2.29)		32 (36.4)		38 (30.4)	
		Carvalho CN et al. (2016)	CC	Brazil	AA	0.53	0.47 (0.16-1.36)	131 [b]	7 (5.3)	75	8 (6.0)	206
					AG		1.68 (0.91-3.16)		50 (38.2)		20 (26.7)	
					GG		0.69 (0.38-1.24)		74 (56.5)		49 (65.3)	
		Nordang GB et al. (2009) [c]	CC	Norway; New Zealand	GG	0.02	1.19 (1.02-1.37)	950; 580 [b]	396 (42.2); NA	933; 504	335 (36.4); NA	1883; 1084
		Louahchi S et al. (2016)	CC	Algeria	NA	NS	NA	343 [b]	NA	323	NA	666
		Silva I et al. (2017)	CC	Brazil	GG	0.03	3.18 (1.13-9.95)	127 [a,b]	81 (63.8)	134	75 (56.0)	261
		Marwa O et al. (2017)	CC	Tunisia	AG	0.66	0.87 (0.51-1.47)	108 [b]	34 (31.5)	202	70 (64.8)	310
		Dhaouadi T et al. (2018)	CC	Tunisia	AG	0.92	1.12 (0.60-2.10)	115 [a]	86 (74.8)	91	66 (72.5)	206
		García de la Peña M et al. (2017)	CC	Mexico	NA	<0.01	5.6 (1.5-20.9)	76 [a]	12 (15)	94	3 (3)	170
	rs3819024 (Position 52185988 in Chr 6)	Shen L et al. (2015)	CC	China	AA	NA	1.08 (0.86-1.36)	615 [b,d]	176 (29.3)	839 [d]	227 (27.3)	1454
					AG	NA	1.08 (0.88-1.33)		304 (50.6)		399 (48.1)	
					GG	0.05	0.77 (0.60-1.00)		121 (20.1)		204 (24.6)	
	rs3819025 (Position 52186476 in Chr 6)				AA	0.58	1.19 (0.64-2.23)		19 (3.1)		22 (2.7)	
					AG	0.03	1.29 (1.02-1.63)		181 (29.4)		209 (25.2)	
					GG	NA	0.76 (0.61-0.95)		404 (66.9)		600 (72.3)	
	rs4711998 (Position 52185555 in Chr 6)				AA	NA	0.98 (0.79-1.21)		328 (51.7)		452 (53.2)	
					AG	NA	0.97 (0.78-1.20)		243 (40.9)		338 (40.9)	
					GG	0.27	1.27 (0.83-1.94)		44 (7.4)		49 (5.9)	
	rs8193036 (Position 52185695 in Chr 6)				AA	NA	1.13 (0.78-1.64)		55 (9.6)		67 (8.3)	
					AG	0.01	1.36 (1.10-1.68)		234 (40.8)		281 (34.6)	
					GG	NA	0.69 (0.56-0.85)		284 (49.6)		464 (57.1)	
	rs8193037 (Position 52186311 in Chr 6)				AA	0.67	1.19 (0.55-2.58)		12 (2.0)		14 (1.7)	
					AG	NA	0.88 (0.67-1.14)		116 (19.2)		176 (21.2)	
					GG	NA	1.04 (0.81-1.33)		475 (78.8)		642 (77.2)	
IL-17F	rs763780 (Position 52236941 in Chr 6)	Bogunia-Kubit K et al. (2015)	CH	Poland	TT	NA	0.25 (0.11-0.53)	89 [a]	64 (71.9)	125	114 (91.2)	214
					CT	NA	2.27 (1.00-5.17)		16 (18.0)		11 (8.8)	
					CC	NA	-		9 (10.1)		0	
		Paradowska-Gorycka A et al. (2010)	CC	Poland	TT	0.87	0.64 (0.27-1.46)	220 [b]	195 (88.6)	106	98 (92.5)	326
					CT	0.50	1.50 (0.65-3.46)		24 (10.9)		8 (7.5)	
					CC	0.71	-		1 (0.5)		0	
		Carvalho CN et al. (2016)	CC	Brazil	TT	0.24	0.58 (0.21-1.61)	131 [b]	87 (87.0)	75	69 (92.0)	206
					CT		2.67 (0.71-10.05)		10 (10.0)		3 (4.0)	
					CC		0.74 (0.15-3.79)		3 (3.0)		3 (4.0)	

		Pawlik A et al. (2016)	CC	Poland	TT	0.33	0.62 (0.35-1.10)	422 [a]	385 (91.2)	337	318 (94.4)	759
					CT	NA	1.60 (0.89-2.88)		35 (8.3)		18 (5.3)	
					CC	1.00	1.60 (0.14-17.77)		2 (0.5)		1 (0.3)	
		Erkol Inal E et al. (2015)	CC	Turkey	TT	NS	NA	161 [a]	132 (82.0)	88	NA	249
					CT	NS	NA		6 (3.7)		NA	
					CC	NS	NA		23 (14.3)		NA	
		Louahchi S et al. (2016)	CC	Algeria	NA	NS	NA	343 [b]	NA	323	NA	666
		Marwa O et al. (2017)	CC	Tunisia	CT	<0.01	6.40 (3.26-12.67)	108 [b]	40 (37.0)	202	17 (8.4)	310
		Silva I et al. (2017)	CC	Brazil	CT	0.40	0.66 (0.24-1.71)	127 [a,b]	8 (6.3)	134	13 (9.7)	261
					CC	0.99	-		0		1 (0.8)	
	rs2397084 (Position 52237046 in Chr 6)	Paradowska-Gorycka A et al. (2010)	CC	Poland	TT	0.95	1.14 (0.64-2.04)	220 [b]	179 (81.4)	106	84 (79.2)	326
					CT	0.63	0.80 (0.44-1.43)		38 (17.3)		22 (20.8)	
					CC	0.56	-		3 (1.4)		0	
		Pawlik A et al. (2016)	CC	Poland	TT	0.13	1.02 (0.72-1.46)	422 [a]	337 (79.9)	337	268 (79.3)	759
					CT	NA	1.09 (0.75-1.57)		83 (20.7)		62 (18.4)	
					CC	0.09	0.23 (0.05-1.09)		2 (0.5)		7 (2.1)	
		Erkol Inal E et al. (2015)	CC	Turkey	CT	NS	NA	161 [a]	NA	88	NA	249
		Louahchi S et al. (2016)	CC	Algeria	NA	NS	NA	343 [b]	NA	323	NA	666
		Marwa O et al. (2017)	CC	Tunisia	CT	<0.01	5.80 (3.32-10.50)	108 [b]	51 (47.2)	202	27 (13.4)	310
	rs11465553 (Position 52236960 in Chr 6)	Pawlik A et al. (2016)	CC	Poland	TT	NA	NA	422 [a]	0	337	0	759
					CT	NA	1.01 (0.63-1.63)		43 (10.2)		34 (10.4)	
					CC	0.96	0.99 (0.62-1.59)		379 (89.8)		303 (89.6)	
IL-21	rs6822844 (Position 122588266 in Chr 4)	Maiti AK et al. (2010)	CC; MA	Colombia	NA	0.02	0.61 (0.40–0.92)	354 [b]	NA	368	NA	722
		Daha N et al. (2009)	CC; MA	Netherlands	NA	0.05	0.84 (0.70-1.00)	877 [b]	NA	866	NA	1743
		Teixeira VH et al. (2009)	CC	Europe (Italy, France, Spain, Belgium, The Netherlands, Portugal)	TT	0.64	0.72 (0.61-0.86)	434 [b]	8 (1.8)	434	11 (2.5)	868
					GG	0.32	1.18 (0.87-1.60)		327 (75.3)		313 (72.1)	
					TG	0.43	0.87 (0.64-1.19)		99 (22.8)		110 (25.4)	
	rs4505848 (Position 122211337 in Chr 4)				AA	0.28	0.85 (0.65-1.11)	433 [b]	182 (42.0)	433	199 (46.0)	866
					AG	0.04	1.32 (1.01-1.72)		213 (49.2)		183 (42.3)	
					GG	0.18	0.72 (0.46-1.12)		38 (8.8)		51 (11.8)	
	rs11732095 (Position 122427190 in Chr 4)				AA	0.23	1.23 (0.9-1.68)	434 [b]	340 (78.3)	434	324 (74.7)	868
					AG	0.28	0.83 (0.6-1.15)		87 (20.0)		101 (23.3)	
					GG	0.80	0.77 (0.28-2.09)		7 (1.6)		9 (2.1)	
	rs4492018 (Position 122593373 in Chr 4)				AA	0.49	0.79 (0.46-1.36)	434 [b]	25 (5.8)	434	31 (7.1)	868
					AG	0.89	1.03 (0.78-1.35)		174 (40.1)		171 (39.4)	
					GG	0.89	1.03 (0.79-1.35)		235 (54.2)		232 (53.5)	
	rs1398553 (Position 122626913 in Chr 4)				AA	0.30	0.77 (0.49-1.21)	434 [b]	35 (8.1)	434	45 (10.4)	868
					AG	0.20	1.20 (0.92-1.57)		195 (44.9)		175 (40.3)	
					GG	0.54	0.91 (0.7-1.19)		204 (47.0)		214 (49.3)	

Abbreviations: CC - case control study; CH - cohort study; Chr - chromosome; IL - interleukin; MA - meta-analysis study; NA - Not available; NS - No information other than non significant association (>0.05); RA - rheumatoid arthritis. [a] Diagnosis of RA according to the 2010 American College of Rheumatology's criteria [36]; [b] Diagnosis of RA according to the 1987 American Rheumatism Association revised criteria [37]. [c] No significant heterogeneity was observed between the Norwegian and New Zealand cohorts (Breslow–Day test, p: 0.20). [d] The genotyping was successful in: 604 cases and 832 controls for rs2275913 GA; 601 cases and 830 controls for rs3819024 AG; 604 cases and 831 controls for rs3819025 GA; 594 cases and 827 controls for rs4711998 AG; 573 cases and 812 controls for rs8193036 CT; and 603 cases and 832 controls for rs8193037 GA.

Table 3. Characteristics of included studies and associations between IL-17A, IL-17F and IL-21 polymorphisms and susceptibility to rheumatoid arthritis (RA).

3.3. Association between IL-17A polymorphisms and RA susceptibility

Eleven studies evaluated IL-17A polymorphisms, namely rs2275913, rs3819024, rs3819025, rs4711998, rs8193036 and rs8193037 [3,5,23,26-29,32-35]. These were mainly case-control studies, except for the study performed by Bogunia-Kubik, which consisted of a cohort study [26]. These studies assessed patients from 10 different countries; 72.2% of participants were female, and mean patients' age was 50.3 years (Table 3).

All these publications assessed the association between rs2275913 polymorphisms and susceptibility to RA [3,5,23,26-29,32-35]. Five studies did not find a significant association between the rs2275913 AA genotype and susceptibility to RA [3,23,27-29], while one study found that genotype to be significantly associated with lower risk of RA [5]. Our meta-analysis showed the AA genotype to be significantly associated with lower susceptibility to RA (OR=0.76; 95%CI=0.61-0.93; p=0.01) with no significant heterogeneity detected (Q Cochran p value=0.84; I^2=0%) (Figure 2A). Regarding the rs2275913 AG genotype, no study found significant associations between its expression and susceptibility to RA. Accordingly, our meta-analysis showed that the AG genotype was not significantly associated with susceptibility to RA (OR=1.00; 95%CI=0.85-1.17; p=0.99; Q Cochran p value=0.35; I^2=10%) (Figure 2B). On the other hand, rs2275913 GG genotype was found to have a significant association with increased susceptibility to RA according to two studies [28,33]. Our meta-analysis also showed the GG genotype to be significantly associated with susceptibility to RA (OR=1.20; 95%CI=1.06-1.35; p=0.01) with no substantial heterogeneity detected (Q Cochran p value=0.39; I^2=4%) (figure 2C). Of note, one study found rs2275913 AG polymorphism to be significantly associated with no responsiveness to anti-TNF therapy [26].

The remaining IL-17A polymorphisms (rs3819024, rs3819025, rs4711998, rs8193036 and rs8193037) were only assessed in one study [5], which found that the susceptibility to RA was significantly decreased in individuals with the GG genotype of rs3819024. That study also reported an increased risk of RA in patients with the AG genotype or with the A allele of the rs3819025 polymorphism, as well as with the AG genotype or A allele of the rs8193036 polymorphism. However, the G and A alleles did not reach the level of statistical significance in three other studies [32-34]. Moreover, Shen [5] found a decreased risk of RA in patients with the GG genotype of rs3819025 polymorphism and with the GG genotype of the rs8193036 polymorphism (Table 3).

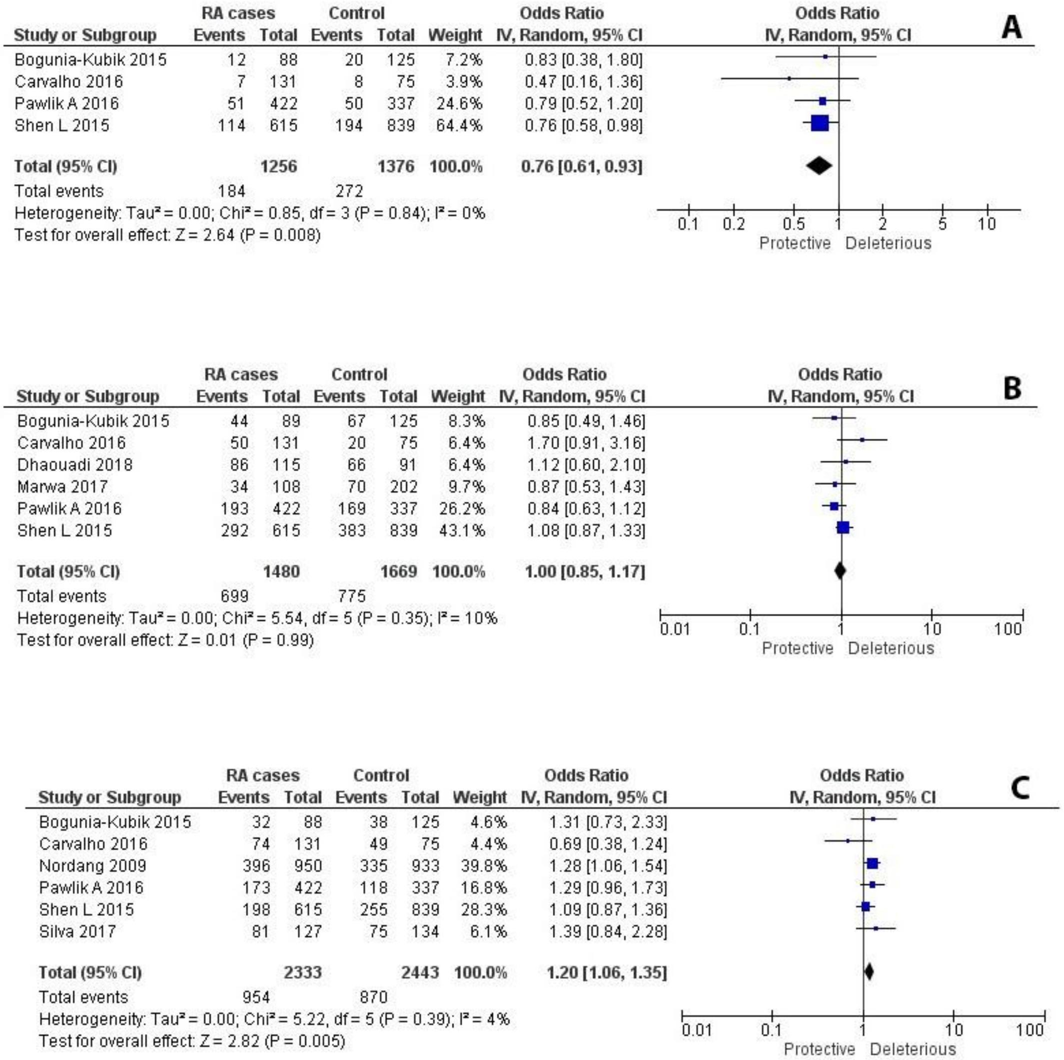


Figure 2: Forest plots assessing the association between the AA genotype (A), the AG genotype (B) and the GG genotype (C) of the IL-17A rs2275913 polymorphism with susceptibility to rheumatoid arthritis (RA). Forest plots were obtained by means of random-effects meta-analyses weighted by the inverse of variance. For each forest plot, the meta-analytical pooled odds ratio (OR) and the respective confidence interval is represented by a diamond, indicating whether the corresponding genotype is more common among patients without RA

("protective") or with RA ("deleterious"). Statistically significant associations occur when diamonds do not cross the OR=1 vertical line.

3.4. Association between IL-17F polymorphisms and RA susceptibility

Eight studies evaluated IL-17F polymorphisms, namely rs763780, rs2397084, and rs11465553 [3,23,25-27,29,33-34]. These were mainly case-control studies, except for Bogunia-Kubik cohort study [26]; 74.3% of patients were female, and mean patients' age was 51.7 years (Table 3).

All 8 publications assessed the association between susceptibility to RA and rs763780 polymorphisms – Bogunia-Kubik [26] reported a decreased risk of RA in patients with the TT genotype, and an overall protective effect associated with the T allele. On the other hand, Marwa [34] found that patients carrying at least one copy of the C allele were 6.4 times more susceptible to develop RA. The remaining studies found no significant associations between rs763780 polymorphisms and RA susceptibility [3,23,25,27,29], although there were reports on those polymorphisms being significantly associated with tender joints, disease duration and higher creatinine levels and lower sedimentation rate [25,29,34] (Table 2).

Our meta-analysis showed that the TT genotype was significantly less common in patients with RA (OR=0.49; 95%CI=0.31-0.77; p=0.002), with no severe heterogeneity detected (Q Cochran p value=0.24; I^2=28%) (Figure 3A). On the other hand, the CT genotype was found to be significantly associated with susceptibility to RA (OR=2.00; 95%CI=1.03-3.87; p=0.04), but with substantial heterogeneity detected (Q Cochran p value=0.001; I^2=75%) (figure 3B). In the context of a leave-one-out sensitivity analysis, we observed that heterogeneity became non-severe (Q Cochran p value=0.26; I^2=24%) and that the association became non-significant (OR=1.51; 95%CI=0.98-2.32; p=0.06) after removing the Marwa study [34]. On the other hand, all subgroup analyses yielded severe heterogeneity, except when only European studies were assessed (OR=1.57; 95%CI=0.97-2.54; *p*=0.07; Q Cochran *p* value=0.90; I^2=0%). Finally, the CC genotype was not significantly associated with susceptibility to RA (OR=1.60; 95%CI=0.42-6.16; *p*=0.49; Q Cochran *p* value=0.22; I^2=30%) (Figure 3C).

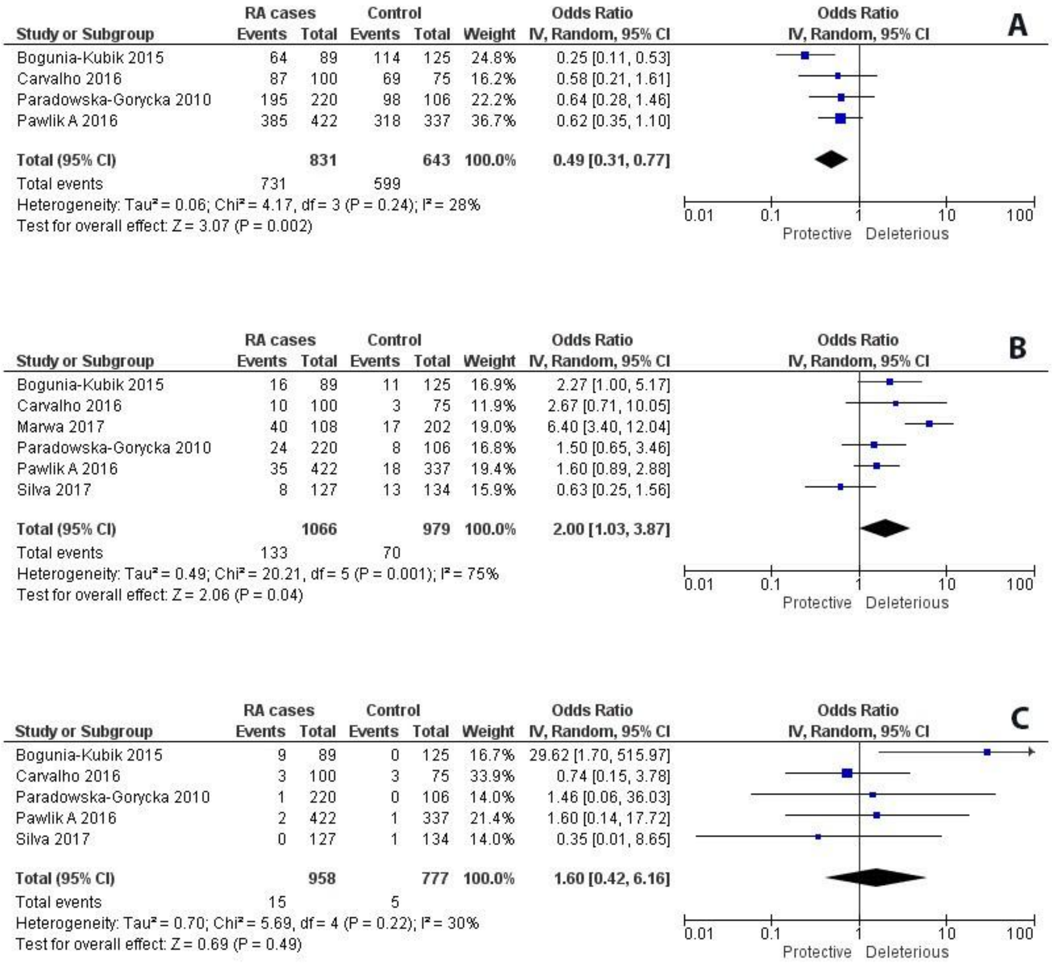


Figure 3: Forest plots assessing the association between the TT genotype (A), the CT genotype (B) and the CC genotype (C) of the IL-17F rs763780 polymorphism with susceptibility to rheumatoid arthritis (RA). Forest plots were obtained by means of random-effects meta-analyses weighted by the inverse of variance. For each forest plot, the meta-analytical pooled odds ratio (OR) and the respective confidence interval is represented by a diamond, indicating whether the corresponding genotype is more common among patients without RA ("protective") or with RA ("deleterious"). Statistically significant associations occur when diamonds do not cross the OR=1 vertical line.

Five publications [3,23,25,29,34] assessed the rs2397084 polymorphism and only one study [34] found significant associations between expression of this polymorphism and increased susceptibility to RA or disease severity. Accordingly, our meta-analyses found no significant association between RA and expression of the TT genotype (OR=1.05; 95%CI=0.78-1.43; p=0.74; Q Cochran p value=0.74; I^2=0%), the CC genotype (OR=0.65; 95%CI=0.05-8.76; p=0.33; Q Cochran p value=0.11; I^2=60%) or the CT genotype (OR=1.70; 95%CI=0.56-5.20; p=0.35; Q Cochran p value<0.01; I^2=93%). Regarding the latter analysis, no severe heterogeneity was found after removing the Marwa study (leaving only the two Polish studies) – OR=1.00; 95%CI=0.73-1.36; p=0.98; Q Cochran p value=0.38; I^2=0%. Finally, rs11465553 polymorphisms were only assessed in one study [3], which found no association between CC and TT genotypes, or T allele and susceptibility to RA.

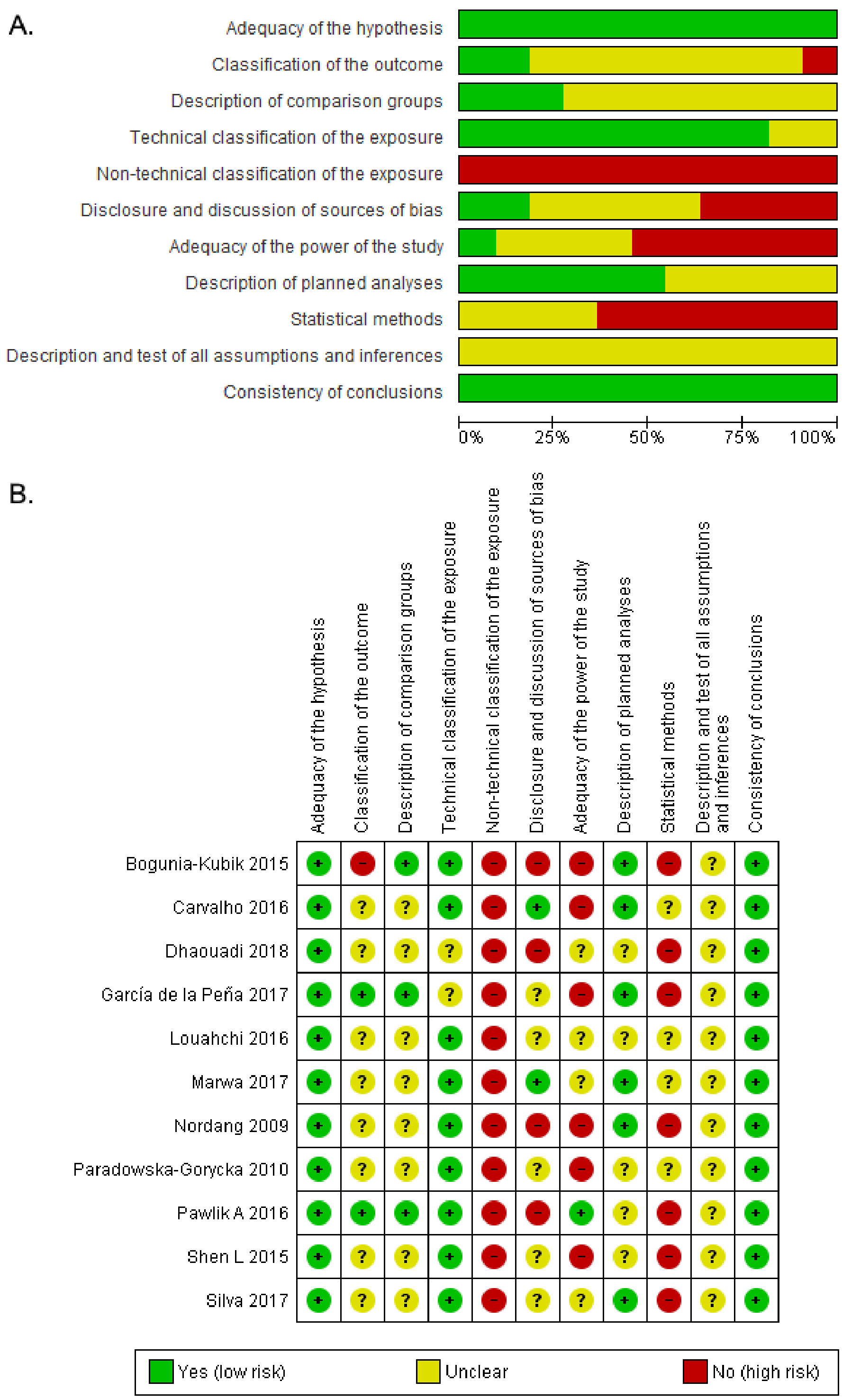
3.5. Association between the IL-21 polymorphisms and RA susceptibility

Three studies evaluated IL-21 polymorphisms [24,30-31], namely rs6822844, rs4505848, rs11732095, rs4492018 and rs1398553. These were all case-control studies, evaluating patients from Colombia and European countries (Table 1). No information was provided concerning patients' age or gender distribution.

The rs6822844 polymorphism was assessed by those three studies - one [24] reported a strong association with RA and another one [30] reported no association (however, none of these studies specified the tested genotype). The third study [31] demonstrated that the TT genotype of this polymorphism associated with decreased susceptibility to RA. Finally, concerning rs6822844 T and G alleles, one study [30] found them to be associated with increased susceptibility to RA in Dutch patients. The remaining IL-21 polymorphisms (rs4505848, rs11732095, rs4492018 and rs1398553) were only assessed by one study [31].

3.6. Studies Quality Assessment

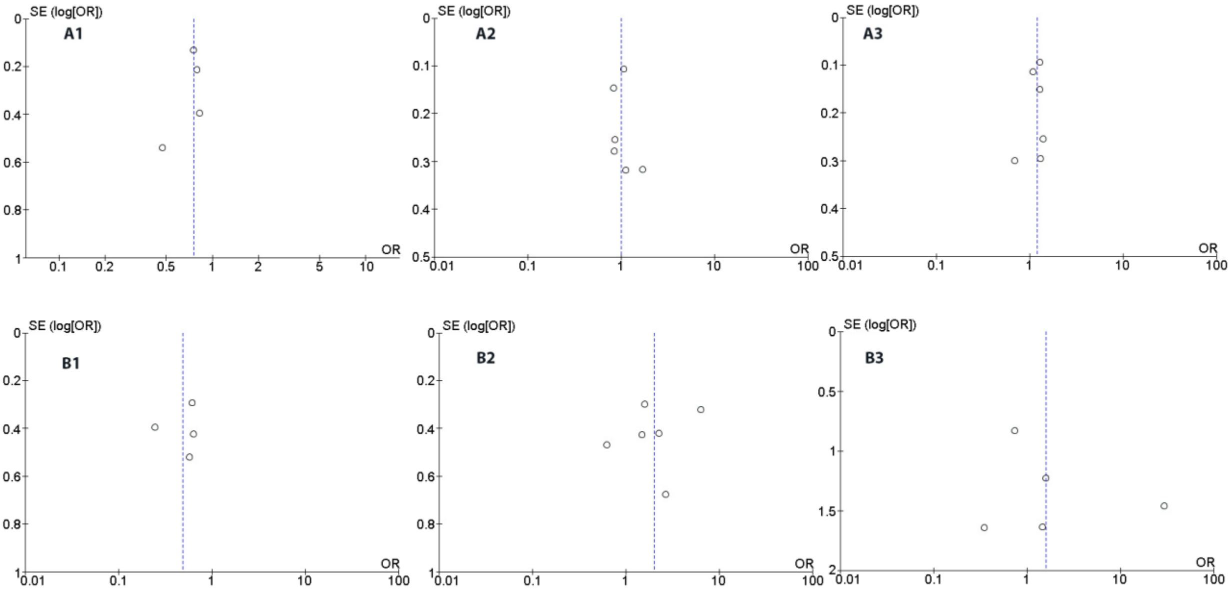
The Q-Genie tool generates a quality score for each study with corresponding ratings of ‘low’, ‘moderate’, or ‘high’ quality [19]. Applying these criteria to the 15 studies, we found that four of them were of high quality [3,27,31,34], while the other 11 were of moderate quality [5,23-26,28-30,32,33,35]. Of the moderate quality publications [5,23-26,28-30,32,33,35], the majority had a biased non-technical classification of the genetic variant, poor statistical methods and inadequate disclosure of potential sources of bias. Regarding high-quality studies [3,27,31,34], they were mostly adequately powered, had a very good technical classification of the genetic variant, and the analysis plan was appropriate and sufficiently described for all assumptions and inferences. All studies had an adequate hypothesis and rationale and the conclusions drawn by the authors were supported by the results and by appropriate methods (Supplementary Figure 1).



Supplementary figure 1: A - Risk of bias graph for the studies included in the meta-analyses: review authors' judgements about each risk of bias item presented as percentages across all included studies; **B:** Risk of bias summary for the studies included in the meta-analyses - review authors' judgements about each risk of bias item for each included study.

3.7. Publication bias

The funnel plots for the studies included in the meta-analyses are presented in Supplementary figure 2. The funnel plots do not show asymmetries suggestive of publication bias but the number of included studies is insufficient to allow for a clear interpretation of these plots.



Supplementary figure 2: Funnel plots for primary studies (circles) included in the meta-analyses assessing the associations between variants of the IL-17A rs2275913 and IL-17F rs763780 polymorphisms and susceptibility to rheumatoid arthritis. Presented plots concern assessments of the AA genotype (A1), the AG genotype (A2) and the GG genotype (A3) of the IL-17A rs2275913 polymorphism, and of the TT genotype (B1), the CT genotype (B2) and the CC genotype (B3) of the IL-17F rs763780 polymorphism; meta-analytical results are represented by dashed lines. For each funnel plot, a symmetrical triangular disposition of circles indicates absence of publication bias, while an asymmetrical disposition suggests the possibility of publication bias.

4. DISCUSSION

Recently, many interleukins have been described to participate in the pathogenesis of RA. Although it was originally thought that IL-17 was only produced by Th17 cells, it is now known that IL-17 is also produced by several other cell types [38]. Conversely, Th17 cells also produce the pro-inflammatory cytokines IL-21 and IL-22, resulting in a complex network of inflammatory agents involved in the pathogenesis of RA.

We found the rs2275913 IL-17A polymorphism to be associated with the frequency of RA. This polymorphism is located at position 197 and promotes an increased production of IL-17 [38]. Espinoza et al [40] showed that the IL17A rs2275913 A allele correlates to more efficient IL-17 production and higher affinity for the nuclear factor of activated T cells (NFAT) – this polymorphism is positioned close to two binding motifs for NFAT, which is a vital controller of the IL-17 promoter. Therefore, it is plausible that rs2275913 variations affect the transcriptional regulation of IL-17A, with the A allele promoting an increased production of IL-17 [17]. Our meta-analysis, however, showed that the AA genotype was significantly less frequent in RA patients (i.e., had a possibly protective effect), while the opposite was observed for the GG genotype. While this is surprising on account of the putative transcriptional role of rs2275913 A allele, the evidence from previous clinical studies is less clear – a recent meta-analysis [17] suggested that individuals carrying the rs2275913 A allele or GA genotype have an increased risk of inflammatory diseases, although this polymorphism was not observed to be associated with the risk of each disease individually. On the other hand, Zhang et al [41] concluded that, in ulcerative colitis, patients with the IL17A rs2275913 A allele tended to suffer milder lesions. All this considered, it is important to note that IL-17A production may also be affected by post-translational mechanisms/negative feedback loops and that, within the pathogenesis of RA, IL-17A acts as a component of a more complex cytokine network involving other proinflammatory cytokines (including TNF-α and IL-6) and chemokines [42]. Therefore, further research is required to understand the pathophysiological role of IL-17A and its clinical association with the described findings.

Concerning IL-17F, this cytokine contributes to neutrophil recruitment and activation through stimulation of cytokine and chemokine production. Several studies evaluated the effect of rs763780 on RA susceptibility, which has also been shown to be associated with other inflammatory diseases [43-45]. The mutated variant of this polymorphism is responsible for a His-to-Arg substitution at amino acid 161, which can change the conformation or molecular expression of IL-17F [46]. In fact, *in vitro* experiments demonstrated that, unlike wild-type IL-17F (TT genotype), this mutated variant lacked the ability to activate the mitogen-activated protein kinase pathway, with the CC genotype associating with lower cytokine production and chemokine production in bronchial epithelial cells. Our meta-analysis showed that the TT genotype was significantly more frequent in healthy individuals than in RA patients, while the opposite was observed for the CT genotype. Previous meta-analyses also found [17] that carriers of the rs763780 C allele, CT or CC genotypes had higher risks of developing RA than subjects with the T allele or TT genotype. Accordingly, Zhang et al [41] found the IL17F rs763780 CT variant to be associated with an increased risk for development of Crohn disease, as well as with clinical features of ulcerative colitis and Crohn disease. It is worth mentioning that, in our meta-analysis, we found substantial heterogeneity for the association between the CT genotype and RA susceptibility - heterogeneity was possibly related with the population characteristics of the Marwa study [34] (as it ceased to be significant following a sensitivity analysis removing this study), whose percentage of males in the control group was almost the double of the one found in the RA patients group. Population characteristics might also explain other inconsistencies – while our meta-analysis included primary studies performed in Europe, Northern Africa and Latin

America, the study of Kawaguchi et al [46] - which showed that patients carrying the CC genotype have decreased IL-17F expression in the bronchial cells - was performed in Japanese subjects, in whom there is a low frequency of the C variant in the general population.

Still concerning IL-17F polymorphisms, no association was found between any of the rs2397084 variants and RA susceptibility. Of note, a previous study [47] also found no significant differences between frequency of paediatric-onset systemic lupus erythematosus and expression of rs2397084, except when IL-17F rs2397084TT associated with IL-17A rs2275913GG and IL-17F rs763780CT. This is interesting because the TT genotype gains significance when associated with the same genotypes that we found significantly associated with the risk of RA.

Interleukin-21 is another cytokine involved in the Th17 cascade, and the rs6822844 polymorphism has been associated with several inflammatory diseases. We found contradictory results regarding the association between rs6822844 expression and increased susceptibility to RA – significant associations were observed for two studies, but not for a third one. However, this latter study [31] was performed in a small number of individuals, and used a family based-approach which can complicate the replication of the putative effect of the 4q27 locus in RA. Of note, the rs6822844 polymorphism is located within a noncoding region upstream of IL-21 and downstream of IL-22, which seems to encode a micro-RNA precursor. The substitution of the G allele by the T allele abolishes that micro-RNA producing ability, possibly affecting its function. While it is difficult to interpret polymorphisms in noncoding regions [2], more studies are required to characterize the relevant molecular pathways and phenotypic consequences of this IL-21 polymorphism [24].

This study has several limitations. In fact, some of the included studies assessed a small sample size [26-27,32,35], while the possibility of substantial population stratification may explain the lack of association observed in some studies [24]. In addition, our search mainly comprised international online databases, while many studies with negative results might end up being published in non-indexed journals. In order to try to circumvent this issue, we searched more than one electronic bibliographic database and did not apply exclusion criteria based on the publication language. Besides, the included studies did not all adopt the same RA definition, and assessed different populations. Despite this, some strengths can be pointed out, as most articles included in this systematic review shared a similar methodology; in fact, our meta-analyses found no significant or substantial heterogeneity for most outcomes. Additionally, most assessed primary studies had a moderate quality according to the Q-genie tool.

In conclusion, several studies have been pursued in order to assess putative associations between predisposition and/or clinical/inflammatory features of RA and IL-17A, IL-17F or IL-21 polymorphisms, although often with contradictory results. Our meta-analyses revealed that the rs2275913 IL-17A polymorphism was associated with susceptibility to RA, with the AA genotype exerting an apparent protective effect, while the GG genotype had the opposite effect. Regarding the rs763780 IL-17F polymorphism, the TT genotype was found to be significantly more frequent in healthy individuals than in RA patients, while the opposite was observed for the CT genotype. This polymorphism was also associated with some clinical characteristics of the disease. Concerning the IL-17F rs2397084 polymorphism, no significant associations were found. Finally, regarding IL-21 polymorphisms, only rs6822844 was found to be significantly associated with a higher susceptibility to RA. Knowledge on these polymorphisms may provide new insights on the pathogenesis of RA, particularly concerning the role of cytokines of the Th17 axis. The latter might even be thought as a possible future therapeutic target of RA. Nevertheless, further studies on some polymorphisms are required in order to more accurately assess their associations with the development and outcomes of this systemic autoimmune disease.

5. ACKNOWLEDGEMENTS:

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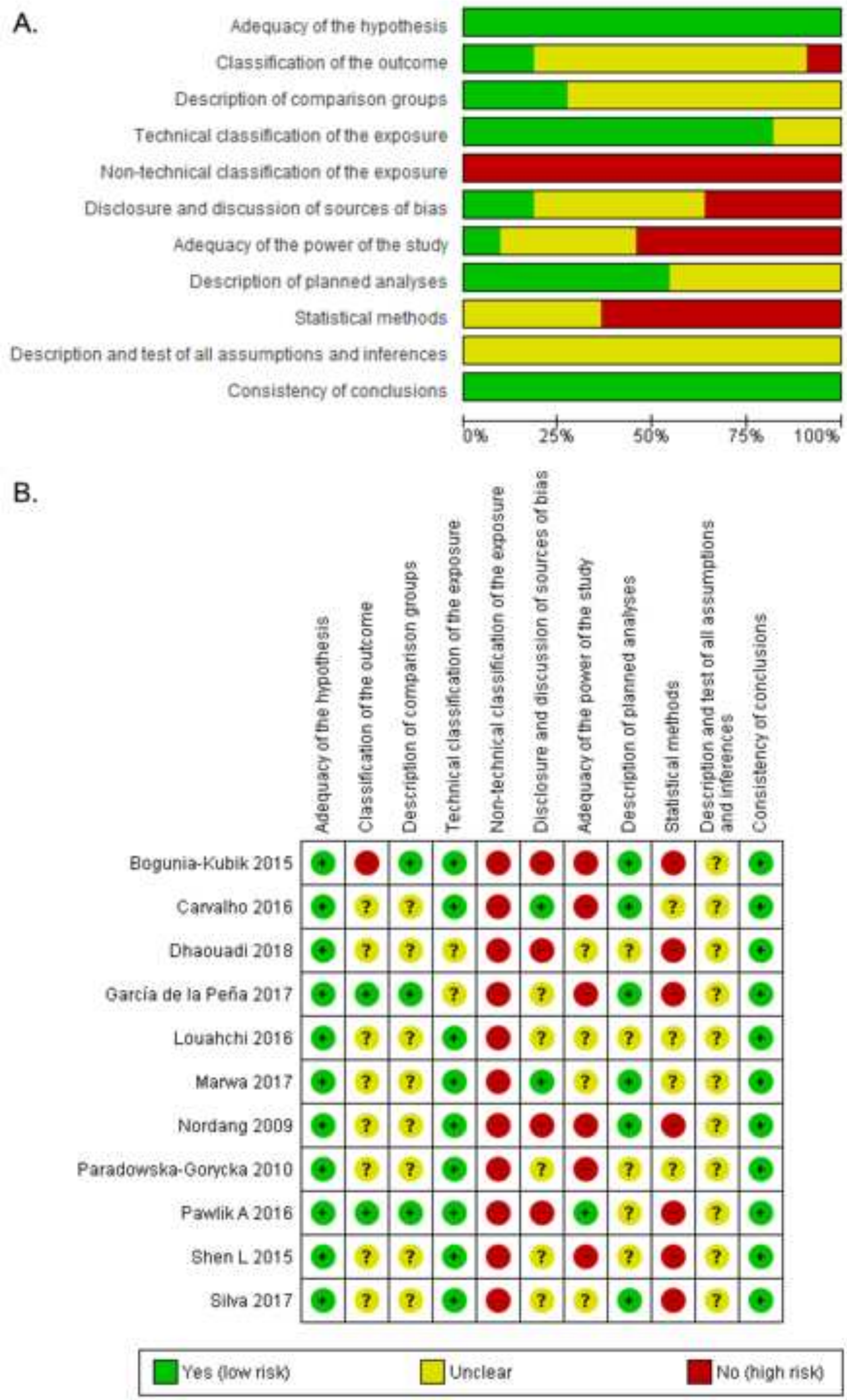

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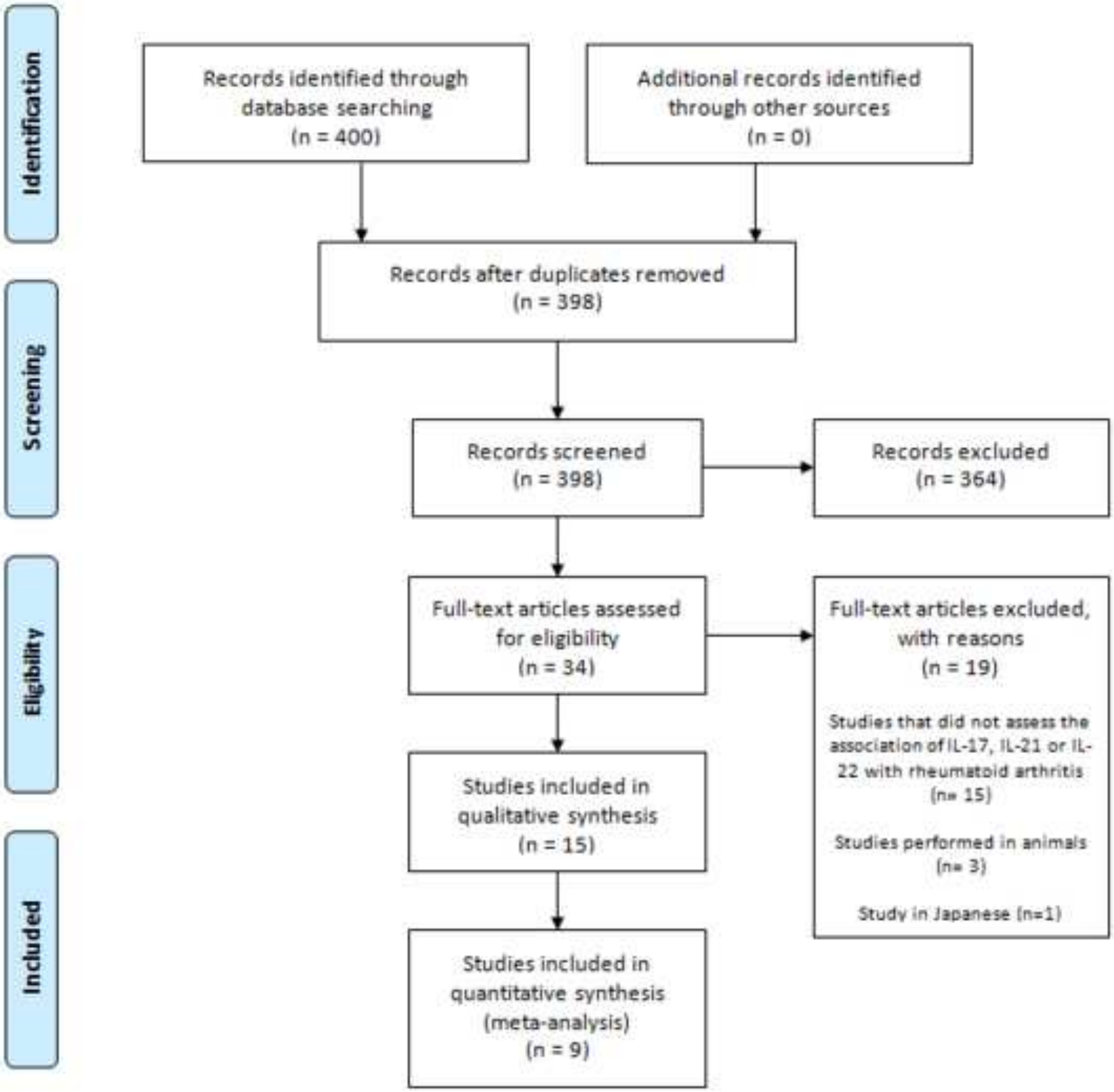

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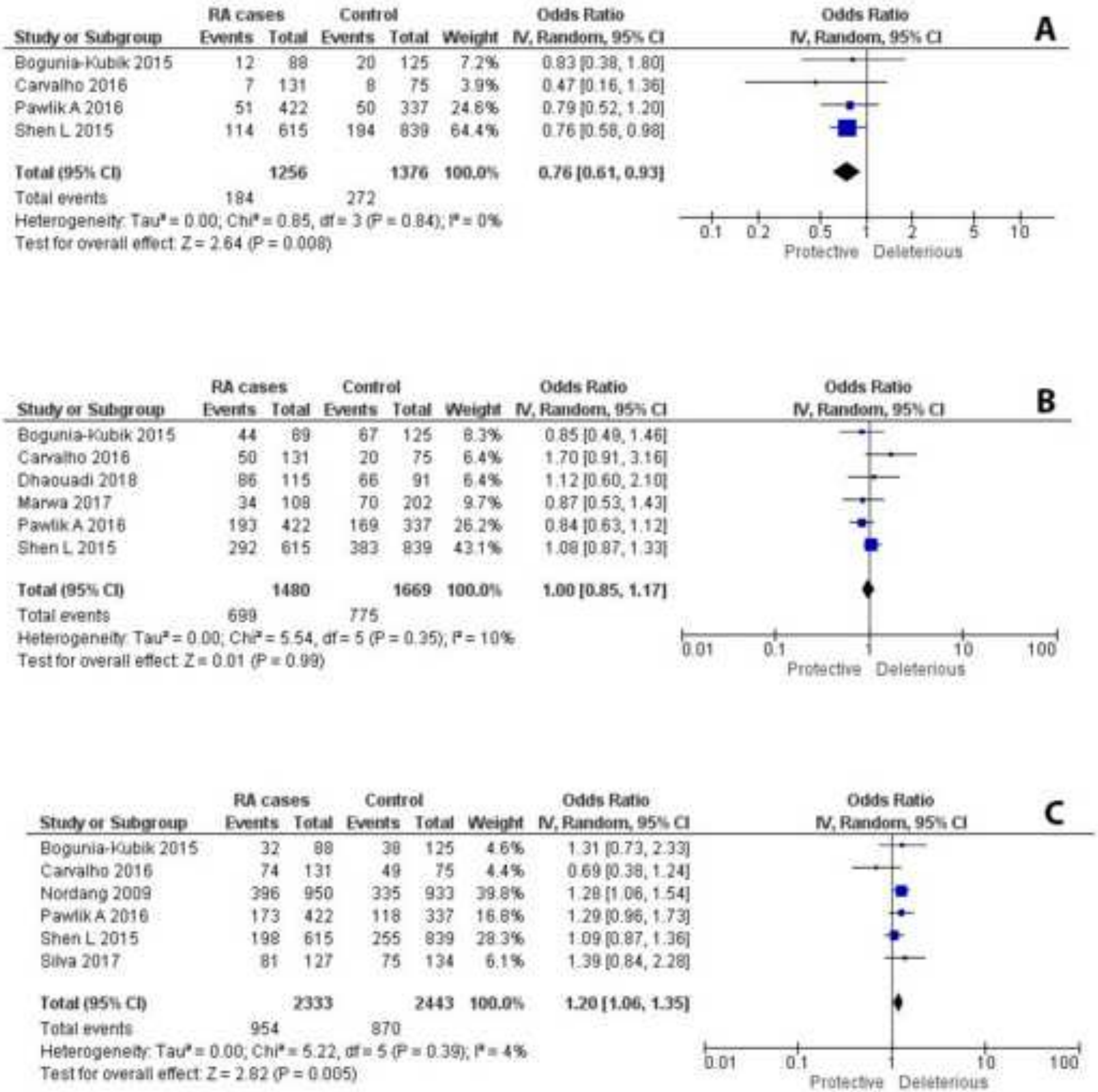

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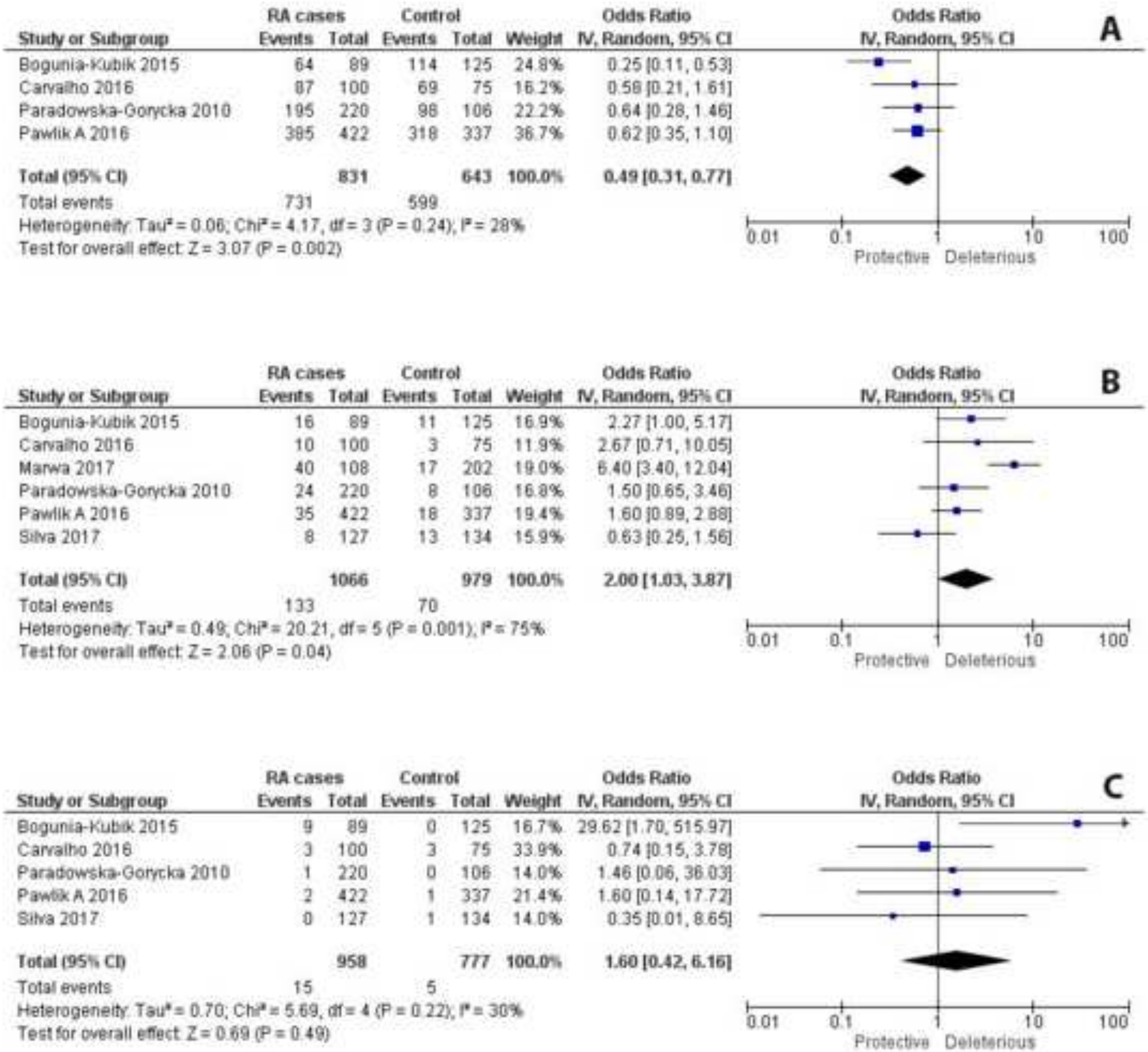

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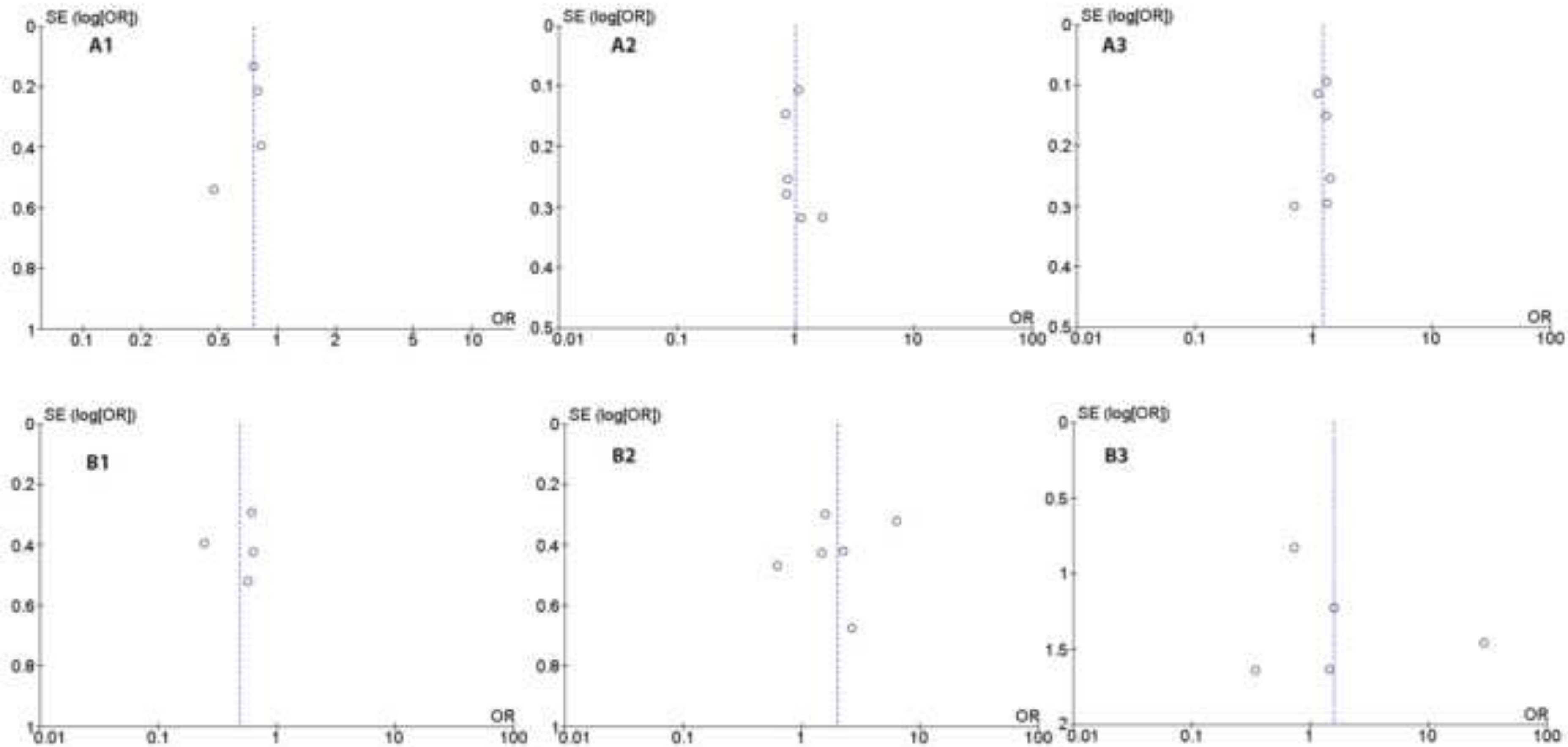

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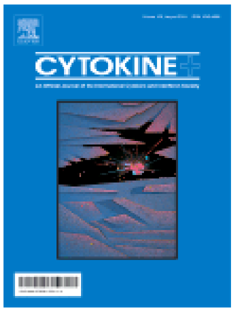
TABLE OF CONTENTS



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