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ORIGINAL RESEARCH

Association between infection and the onset of giant cell arteritis and polymyalgia rheumatica: a systematic review and meta-analysis

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ABSTRACT

Objective We aimed to analyse the association between infections and the subsequent risk of giant cell arteritis (GCA) and/or polymyalgia rheumatica (PMR) by a systematic review and a meta-analysis of observational studies.

Methods Two databases (Medline and Embase) were systematically reviewed. Epidemiological studies studying the association between any prior infection and the onset of GCA/PMR were eligible. Risk of bias was assessed using the Newcastle-Ottawa quality assessment scale. Outcomes and pooled statistics were reported as OR and their 95% CI.

Results Eleven studies (10 case–control studies and one cohort study) were analysed, seven of them were included in the meta-analysis. Eight were at low risk of bias. A positive and significant association was found between prior overall infections and prior *Herpes Zoster* (HZ) infections with pooled OR (95% CI) of 1.27 (1.18 to 1.37) and 1.20 (1.08 to 1.21), respectively. When analysed separately, hospital-treated and community-treated infections, were still significantly associated with the risk of GCA, but only when infections occurring within the year prior to diagnosis were considered (pooled OR (95% CI) 1.92 (1.67 to 2.21); 1.67 (1.54 to 1.82), respectively). This association was no longer found when infections occurring within the year prior to diagnosis were excluded.

Conclusion Our study showed a positive association between the risk of GCA and prior overall infections (occurring in the year before), and prior HZ infections. Infections might be the reflect of an altered immunity of GCA patients or trigger the disease. However, reverse causation cannot be excluded.

PROSPERO REGISTRATION NUMBER

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WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ Giant cell arteritis (GCA) is the leading form of primary vasculitis of medium and large vessels, affecting adults over the age of 50 years. GCA is often associated, with polymyalgia rheumatica (PMR), suggesting a common pathophysiological mechanism.
⇒ Several elements suggest an infectious mechanism as an etiological or triggering factor, but studies have been conflicting.

WHAT THIS STUDY ADD

⇒ Through a systematic literature review and meta-analysis, we confirm the positive association between overall infections, and prior Herpes Zoster infections and the risk of GCA.
⇒ Regarding hospital-treated and community infections, the association was only found when infections occurring within the year before GCA onset were considered.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study adds to the understanding of GCA pathophysiology.
⇒ Infections might be the reflect of an altered immunity in GCA patients or be the disease trigger. However, reverse causation cannot be excluded.

INTRODUCTION

Giant cell arteritis (GCA) is the leading cause of primary vasculitis of medium and large vessels, affecting adults over the age of 50 years.[1–3] It is often associated with polymyalgia rheumatica (PMR), suggesting a common pathophysiological mechanism.

Despite the advances in the knowledge on their pathophysiology, the etiological mechanisms of these diseases are still uncertain. In addition with a predisposed genetic background (HLA DR4),[4] several elements suggest an infectious mechanism as an etiological or triggering factor.

Indeed, several epidemiological studies, in different geographical areas,[1 5 6] have observed epidemic peaks and seasonal variations in the incidence of GCA or PMR, suggesting a link with environmental factors. However, studies on the seasonality have shown conflicting results, and a meta-analysis of 22 studies did not confirm a seasonal onset.[7]

In addition, GCA pathogenesis involve vascular parietal inflammation in response to a hypothetic antigenic trigger, not yet identified.[8 9] This could lead to an activation of dendritic cells via their Toll Like Receptors[10] within the adventitia of the arteries and the triggering of a Th1 and Th17 lymphocyte adaptive immune response,[11] two classical pathways of anti-infectious response.

Therefore, for the last 25 years, many infectious agents have been suspected to trigger or cause GCA, foremost among them *Varicella Zoster Virus* (VZV).[12 13] However, data remained inconsistent,[14–16] as most studies have focused on the direct search for a pathogen on temporal artery biopsy sections, with no standardisation of the methods to confirm the presence of the pathogen (different PCR expansion targets, different expansion thresholds, etc.), which could explain the absence of an unequivocal response.

Finally, many epidemiological studies (mostly case–controls studies) have attempted to assess the association between infections and the risk of GCA or PMR, using different populations, and different definitions of the infections.

Despite all this literature, a meta-analysis summarising infections as a risk factor for GCA/PMR has never been conducted. Here, we analysed the association between infections and the onset of GCA/PMR by conducting a systematic review and a meta-analysis of observational studies.

MATERIAL AND METHODS

Search strategy

Two authors (LP and YN) independently performed a systematic review of two electronic databases (Medline and Embase) since their inception to 31 December 2022, without language restriction.

The medical subject headings and text words used for our search strategy are presented in online supplemental appendix 1.

Conference abstracts from selected Rheumatology meetings (EULAR and the American College of Rheumatology (ACR) from 2021 to 2022) were also searched and manually reviewed for inclusion. When studies' full texts were unavailable, the authors were also contacted. Discrepancies were solved by discussing with a third author (RS).

Study selection

Inclusion criteria were as follows: (1) the design is a case–control study, cohort study or cross-sectional study evaluating the association between infections and GCA/PMR; (2) the study is published in full-text form, except for congress abstracts; (3) diagnosis of GCA is made by clinicians' ascertainment, by positive temporal artery biopsy, by ACR 1990 criteria[17] and/or by ICD-10 code; diagnosis of PMR is made by clinician's ascertainment, by ACR/EULAR 2012 criteria[18] and/or by diagnosis codes; (4) infection is defined by a clinical event and/or serology at diagnosis of GCA/PMR and/or the use of anti-infectious medication and (5) specific data are provided, including OR or HR with their 95% CI, or sufficient data are available to calculate them.

Studies were excluded if: (1) sample size <20 cases; (2) the study is a case report or a case series, a histological series, a study on ecological correlation or a review; (3) the evaluated trigger is a vaccine; (4) the infection follows diagnosis of GCA/PMR or the temporality is uncertain and (5) no OR and/or HR are provided, or data are insufficient to calculate them.

Data extraction and management

A standardised form was designed for extraction data. Two authors (LP and YN) independently extracted data using the form to identify eligible studies. Information was collected as follows: title, author, year of publication, country, study design, case definition, definition of exposure, number of cases, number of controls, matching and adjustment criteria, OR/HR and their 95% CI for each exposure. When information was missing, we tried to contact the authors of original reports.

Quality assessment

The risk of bias among the selected studies was independently evaluated by two authors (LP and YN) according to the Newcastle–Ottawa quality assessment scale (NOS),[19] a rating system on nine stars attributed according to 'Selection', 'Comparability', 'Exposure' or 'Outcome' items. High-quality studies were defined with six stars or more. Quality of records limited to conference abstracts was not assessed because of the paucity of available information.

Statistical analysis

Studies assessing the same outcome were eligible for the quantitative analysis. Pooled statistics were calculated as ORs with 95% CIs. Heterogeneity was assessed looking at CI overlap between studies. If CIs for the results of individual studies have poor overlap, it generally indicates the presence of statistical heterogeneity. More formally, heterogeneity was assessed using Cochran's Q statistic, and Higgins and Thompsons' I^2. A I^2 between 30% and 60% was interpreted as moderate heterogeneity and I^2>60% as substantial heterogeneity. In case of apparent heterogeneity, random-effects models were used and fixed-model otherwise to obtain adequate CIs. A two-sided p-value<0.05 was considered statistically significant. All analyses were conducted using RevMan V.5.3.

Research ethics approval statement

The review protocol followed the declaration of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] and was submitted to PROSPERO.

Patient and public involvement

Patients and/or the public were not involved in the study.

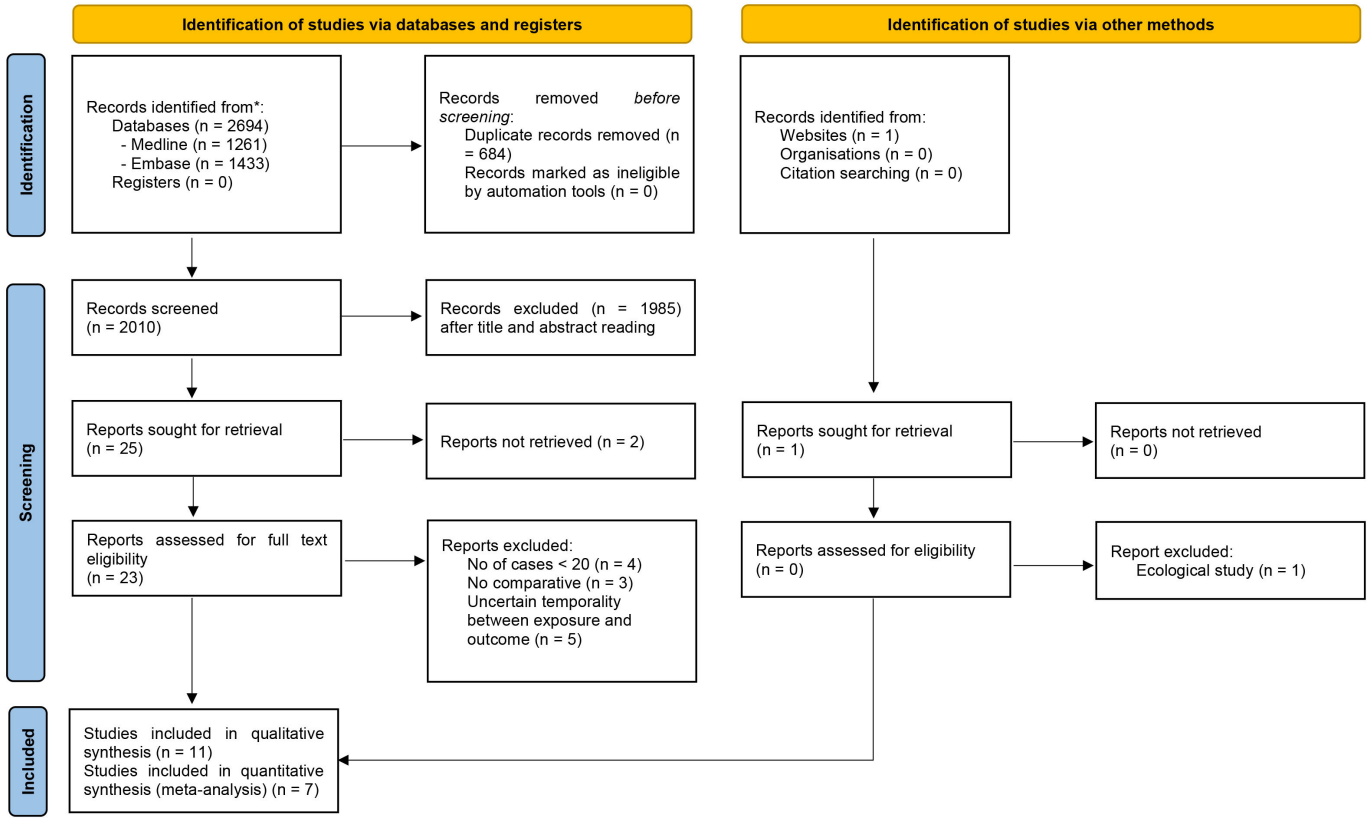

Figure 1 Flow chart.

RESULTS

Results of literature search

Our search equation identified 2695 reports, drawn from two databases and other sources (Medline 1261, EMBASE 1433, EULAR conference abstract 1). After excluding 684 duplicates, 1985 reports were excluded based on the title and abstract,

and two full-texts were not retrieved, leaving 23 reports that were assessed for eligibility by reviewing the full-text. Eleven of them met the inclusion criteria,[4 21–30] of which seven[24–30] were included in the meta-analysis. Nine of these studies were published in English, and two in French. Details on the screening, number of articles identified, included, excluded is described in the study PRISMA flow chart (figure 1).

Characteristics and quality assessment of the included study

Of these 11 studies, 10 were case–control studies and one was a cohort study. Six only assessed the risk of GCA, two only the risk of PMR and three evaluated both, resulting in a total of 14 114 patients with GCA and 5592 with PMR compared with 16 787 345 controls. Most controls came from the study by England *et al*,[25] which used a health insurance database. Control groups were at least age and sex-matched in eight studies. Case definition was heterogeneous: GCA was defined by International Classification of Diseases (ICD) code only (n=3), by ICD code associated with use of glucocorticoids (n=1), ACR 1990 criteria (n=1), positive temporal arterial biopsy (n=3) or expert review (n=1). PMR was defined by clinicians' ascertainment (n=3), by ICD code (n=1) or according to ACR/EULAR 2012 (n=1).

Among all screened infections, four types were included in the meta-analysis: overall infections, hospitalised infections only, community-treated infections only and VZV infections. Infections' definitions were also heterogeneous, assessed by serology at diagnosis of GCA/PMR in three studies, ICD code in four, review of medical records in two and declarative data in two.

All studies but one (Jaramillo *et al*, as it was a conference abstract) were evaluated by the NOS score, results showed that 8/10 had a score ≥6, indicating a low risk of bias (detailed in tables 1 and 2).

The main characteristics of the four studies included in qualitative synthesis only are shown in table 1, the main characteristics of the seven studies included in quantitative synthesis are shown in table 2.

Meta-analysis

The original data of the four selected types of infections, from the seven studies included in the meta-analysis were pooled using random-effects model or fixed-effects model, according to results of the heterogeneity test. The results are summarised in table 3 and figures 2 and 3.

Overall infections

Three studies[27 28 30] reported an association between GCA and overall infection, consisting in any infection happening before the index date of GCA. Rhee *et al*[27] and Stamatis *et al*[30] excluded infections occurring 6

Table 1 Studies included in qualitative synthesis only (n=4)

Author, year of publication	Country	Study design	GCA and/or PMR; diagnosis criteria; no. of cases	No. of controls; matching criteria	Infection(s) and assessment method	Correlation with GCA/PMR	NOS score
Barrier *et al*, 1982[4]	France	Case–control study	GCA; clinical and histological; 94	110; sex, age, place of residence	Urinary tract infection (declarative) Bronchopulmonary infection (declarative) Cutaneous infection (declarative) Genital infection (declarative)	Positive association No association No association No association	7
Duhaut *et al*, 1999[21]	France	Case–control study	GCA; ACR 1990; 229 PMR only; clinical; 76	203; sex, age	HSV 1,2 (Serology) Measles virus (Serology) RSV (Serology) Parainfluenza virus 1,2,3 (Serology) Epstein Barr virus (Serology)	No association No association No association Positive association No association	7
Elling *et al*, 1980[22]	Denmark	Case–control study	GCA; histological; 17 PMR only: clinical; 26	684; none	Hepatitis B—(Serology)	No association or very weak	4
Nuti *et al*, 2005[23]	Italy	Case–control study	PMR; clinical; 51	51; sex, age	Borrelia—(Serology) Parvovirus B19—(Serology) Herpes Zoster—(Serology) HSV—(Serology) Hepatitis B—Serology	No association No association No association No association No association	8

ACR, American College of Rheumatology; GCA, giant cell arteritis; HSV, Herpes Simplex Virus; NOS, Newcastle-Ottawa scale; PMR, polymyalgia rheumatica; RSV, respiratory syncytial virus.

months and 30 days before the index date, respectively, and defined the infection by ICD code. Russo *et al*[28] included 'probable' and 'definite infections' within the 4 months prior the index date after reviewing medical records (table 3). There was no significant heterogeneity (I^2 = 46%; p=0.15). Using a fixed-effect model, we found a statistically significant and positive association between GCA and overall infection, with a pooled OR of 1.27 (95% CI 1.18 to 1.37) (Z=6.46, p<0.00001).

Hospital-treated infections

Giant cell arteritis

Two studies[24 30] reported an association between GCA and hospital-treated infections. ICD codes from Brault *et al*[24] defined two exclusive periods of exposure: (1) hospital-treated infections occurring only during the year before the date of GCA diagnosis (index date) and (2) infections occurring only more than 1 year before the index date of GCA. Using ICD code, Stamatis *et al*[30] considered every hospitalised treated infection before the index date.

Using exposure ≤1 year before the index date from Brault *et al*,[24] there was no significant heterogeneity (I^2 = 43%, p=0.19). Using a fixed-effect model, we found a statistically significant and positive association between GCA and hospitalised treated infections, with a pooled OR of 1.92 (95% CI 1.67 to 2.21) (Z=9.05, p<0.00001).

Using exposure occurring >1 year before the index date from Brault *et al*,[24] there was significant heterogeneity (I^2 = 89%, p=0.002). Using a random-effect model, we did not find statistically significant association between GCA and hospitalised treated infections, with a pooled OR of 1.38 (95% CI 0.94 to 2.02) (Z=1.65, p=0.10). When using a fixed-effect model, results became statistically significant with a pooled OR of 1.22 (95% CI 1.12 to 1.34) (online supplemental figure S1B).

Polymyalgia rheumatica

Two studies[24 26] reported an association between PMR and hospital-treated infections. Jaramillo *et al*[26] defined the infection by reviewing medical records, and only selected infections occurring within the year before the index date of PMR, and Brault *et al* defined infection by ICD code, as previously described.[24] There was no significant heterogeneity (I^2 = 0%, p=0.68). Using a fixed-effect model, we found a statistically significant and positive association between PMR and hospitalised treated infections, with a pooled OR of 1.41 (95% CI 1.25 to 1.59) (Z=5.63, p<0.00001).

Table 2 Studies included in quantitative synthesis (n=7)

Author, year of publication	Country	Study design	GCA and/or PMR; diagnose criteria; no. of cases	No. of controls; matching criteria	Infection (assessment method)	NOS score
Brault *et al*, 2018[24]	Denmark	Case–control study	GCA; ICD-10 codes; 2125 PMR only; ICD-10 codes; 5100	72 250; sex, age, place of residence, time spent in the region	Hospitalised treated infection (codes) Community-treated infection (anti-infective use) HZ infection, community or hospitalised (codes and antiviral use)	6
England *et al*, 2017[25]	USA	Retrospective cohort study on databases	GCA; ICD-9 codes; 5942	16 680 403; NA	HZ infection, complicated or not (codes)	9
Jaramillo *et al*, 2019[26]	Argentina	Case–control study	PMR; ACR/Eular 2012; 169	169; sex, age	Community infections (review of medical records) Hospitalised infections (review of medical records)	NC
Rhee *et al*, 2017[27]	UK	Nested case–control study	GCA; > 50 y and codes and prescription for GC; 4559	22 795; sex, age, general practice	HZ infection (code) Overall infection (code) Respiratory tract infection (code) Urinary tract infection (code)	9
Russo *et al*, 1995[28]	USA	Case–control study	GCA; positive temporal artery biopsy;100	100; sex, age	Overall infection (review of medical records)	5
Sammel *et al*, 2020[29]	Australia	Case–control study	GCA; expert review; 20	38; none	HZ infection (declarative)	6
Stamatis *et al*, 2021[30]	Sweden	Case–control study	GCA; Codes for histological proof; 1005	1050; sex, age, area of residence	Overall infection (ICD-10 Code) HZ infection (ICD-10 Code) Acute upper respiratory tract (ICD-10 Code) Other acute infection in lower respiratory tract (ICD-10 Code) Urinary tract infections (ICD-10 Code)	8

ACR, American College of Rheumatology; Eular, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; HZ, Herpes Zoster; ICD, International classification disease; NC, non-calculable; NOS, Newcastle-Ottawa scale; PMR, polymyalgia rheumatica.

Community-treated infections

Giant cell arteritis

Two studies[24 30] reported an association between GCA and community-treated infections. Periods of exposure and methods of assessment are the same as described for hospital-treated infection.

Considering the community-treated infections ≤1 year before the index date from Brault *et al*,[24] there was no significant heterogeneity (I^2 = 30%, p=0.23). Using a fixed-effect model, we found a statistically significant and positive association between GCA and hospitalised treated infections, with a pooled OR of 1.67 (95% CI 1.54 to 1.82) (Z=12.02, p<0.00001).

Using the community-treated infections occurring >1 year before the index date from Brault *et al*,[24] there was significant heterogeneity (I^2 = 95%, p<0.00001). Using a random-effect model, we did not find statistically significant association between GCA and hospitalised treated infections, with a pooled OR of 1.41 (95% CI 0.85 to 2.32) (Z=1.33, p=0.18). When using a fixed-effect model, results became statistically significant with a pooled OR of 1.35 (95% CI 1.21 to 1.50) (online supplemental figure S1A).

Polymyalgia rheumatica

Two studies[24 26] reported an association between PMR and community-treated infections. Again, periods of exposure and methods of assessment are the same as described for hospital-treated infections. There was no significant heterogeneity (I^2 = 0%, p=0.81). Using a fixed-effect model, we found a statistically significant and positive association between PMR and hospitalised treated infections, with a pooled OR of 1.35 (95% CI 1.27 to 1.44) (Z=9.68, p<0.00001).

Herpes Zoster infections

Five studies[24 25 27 29 30] reported an association between GCA and HZ infections, one of them[24] considered patients with GCA and PMR simultaneously.

ICD code for any HZ infection from Brault *et al*,[24] Rhee *et al*[27] and Stamatis *et al*[30] excluded infections occurring 1 year, 6 months and 30 days before the index date, respectively. Sammel *et al*[29] considered a declarative

Table 3 Original data from studies included in the meta-analysis (n=7) according to selected infections

Infection	Studies included	Definition of exposure and timing	GCA/PMR	OR/HR (95% CI)
Overall	Russo *et al*, 1995[28]	Probable and definite infections*, within 4 months prior to index date	GCA	2.90 (1.25 to 6.73)
	Rhee *et al*, 2017[27]	Codes (Read), all infections excluding 6 months prior index date	GCA	1.26 (1.16 to 1.37)†
	Stamatis *et al*, 2021[30]	Codes (ICD-9), all infections since 1998, excluding 30 days prior index date	GCA	1.27 (1.09 to 1.48)
Hospital-treated	Stamatis *et al*, 2021[30] Brault *et al*, 2018[24]	Codes (ICD-9), all infections since 1998 before the index date	GCA	1.70 (1.35 to 2.14)
		Codes (ICD-10), all hospitalised infections excluding 1 year prior index date	GCA	1.15 (1.04 to 1.27)‡
		Codes (ICD-10), only hospitalised infections 1 year prior index date	GCA	2.07 (1.73 to 2.48)‡
		Codes (ICD-10), only hospitalised infections 1 year prior index date	PMR	1.41 (1.25 to 1.59)‡
	Jaramillo *et al*, 2019[26]	Review of medical records for 1 year before index date	PMR	2.02 (0.37 to 11.2)
Community-treated	Stamatis *et al*, 2021[30]	Codes (ICD-9), all infections since 1998 before the index date	GCA	1.82 (1.54 to 2.14)
		Codes (ICD-10), all community-treated excluding 1 year prior index date	GCA	1.09 (0.95 to 1.25)‡
	Brault *et al*, 2018[24]	Codes (ICD-10), only community-treated 1 year prior index date	GCA	1.62 (1.47 to 1.79)‡
		Codes (ICD-10), only community-treated infections 1 year prior index date	PMR	1.35 (1.27 to 1.44)‡
	Jaramillo *et al*, 2019[26]	Review of medical records for 1 year before index date	PMR	1.46 (0.76 to 2.79)
HZ infection	Brault *et al*, 2018[24]	Codes (ICD-10), all HZ infections excluding 1 year prior index date	GCA/PMR	1.04 (0.74 to 1.46)‡
	England *et al*, 2017[25]	Codes (ICD-9), uncomplicated§ HZ infections before index date	GCA	1.44 (1.14 to 1.82)¶
	Rhee *et al*, 2017[27]	Codes (Read), all HZ infections excluding 6 months prior index date	GCA	1.17 (1.04 to 1.32)†
	Sammel *et al*, 2020[29]	Retrospective declarative assessment of HZ infection during lifetime prior index date	GCA	0.43 (0.11 to 1.78)
	Stamatis *et al*, 2021[30]	Codes (ICD-9), all HZ infections since 1998, excluding 30 days prior index date	GCA	1.18 (0.44 to 3.16)

*Definite infections: occurrence up to 2 months before the onset of symptoms related to GCA and with confirmatory, objective evidence of infection; pobable infections: by clinical diagnosis based on physical examination, included questionable or equivocal evidence on diagnostic tests or infections that were confirmed by diagnostic tests but which occurred 2–4 months before the onset of symptoms.
†Adjusted for Charlson Comorbidity Index, alcohol use, smoking history, prior use of immunosuppressive therapies and prior use of oral glucocorticoids.
‡Adjusted for diabetes, chronic alcoholism-related diseases, disorders involving the immune system, immunosuppressive treatment including corticosteroids, chronic kidney insufficiency, malnutrition and neoplasia.
§Without HZ meningitis, other nervous system, ophthalmic or other complications.
¶Adjusted for sex, race, corticosteroid use during the 12 months prior to the index date, number of visits during the 12 months prior to the index date.
GCA, giant cell arteritis; HZ, Herpes Zoster; ICD, International Classification Disease; PMR, polymyalgia rheumatica.

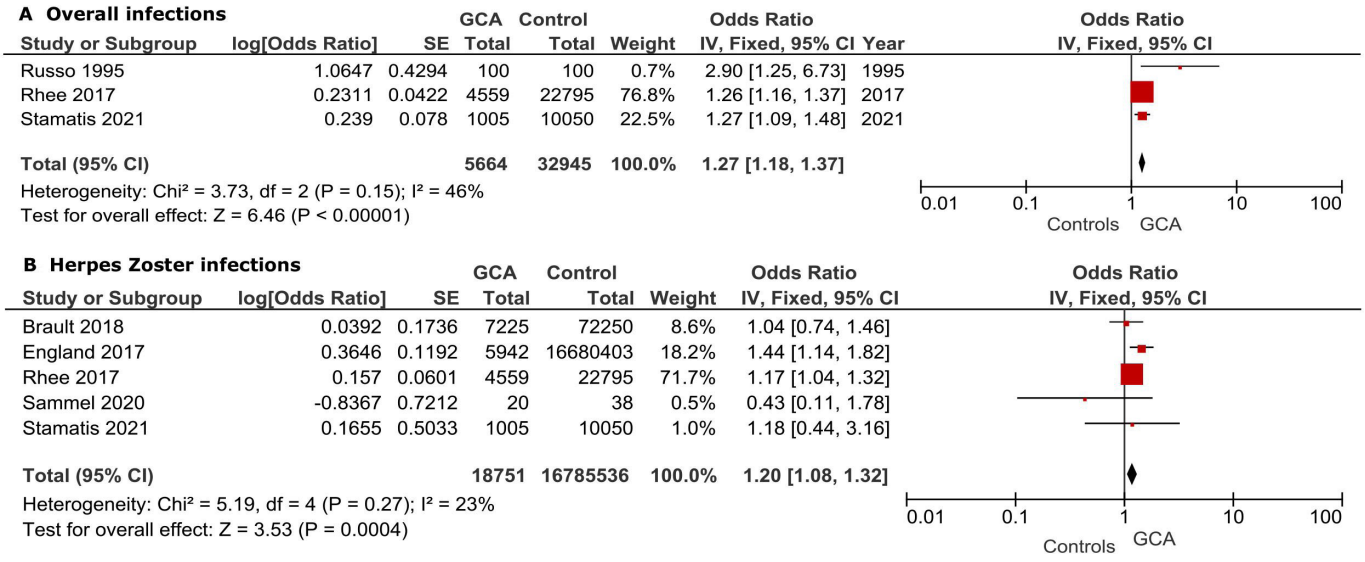

Figure 2 Forrest plot of studies about (A) overall infections and (B) Herpes Zoster infections, excluding infections 1 year prior index date from Brault *et al*, and defined by ICD-10 code by Rhee *et al*. GCA, giant cell arteritis.

lifetime assessment of HZ infection prior the index date. England *et al*[25] included only uncomplicated previous HZ infections without time restriction, defined by ICD code.

There was no significant heterogeneity (I^2 = 23%, p=0.27). Using a fixed-effect model, we found a statistically significant and positive association between GCA and HZ infections, with a pooled OR of 1.20 (95% CI 1.08 to 1.32) (Z=3.53, p=0.0004).

As previously mentioned, Brault *et al*[24] defined two mutually exclusive exposures periods: ≤1 year and>1 year before the index date. Rhee *et al*[27] used different definitions of HZ infection: defined either by ICD code or by ICD code associated with antiviral therapy within 1 month. Using either of those definitions did not change the sense of the associations, nor their amplitudes (online supplemental figure S2).

Studies not included in the meta-analysis

Four studies[4 21–23] were not included in the meta-analysis. Three of them used serology at diagnosis as the assessment for exposure,[21–23] while the last one used retrospective declaration (questionnaire).[4] Each explored a wide range of infections, partially detailed in table 1.

Duhaut *et al*[21] found a significant and positive association between Human Parainfluenza Virus positive serology at index date and GCA/PMR. Barrier *et al*[4] found a significant and positive association between urinary tract infection within the year prior diagnosis and GCA. All the other associations analysed were not significant, notably for parvovirus B19, Herpes Simplex Virus, Hepatitis B or Borrelia.

DISCUSSION

Our meta-analysis demonstrated significant and positive association between prior overall infections and prior HZ infections and further onset of GCA.

The risk of incident GCA was found to be higher among patients with prior overall infection in our meta-analysis. Here, the three studies included, as previously described, had heterogeneous period of exposure. Interestingly, Rhee *et al*[27] conducted different analyses according to the time period prior to index date, and showed that the association between infection and GCA onset was stronger when infection occurred during the first-year prior index date, then similar regardless of the time period in which the infection happened. When considering overall infections without excluding infections occurring the month before index date from Stamatis *et al*[30] the association was also stronger, with an OR of 1.78 (95% CI 1.53 to 2.07). Hospital and community-treated infections, taken separately, were only positively associated with the onset of GCA/PMR when the period of exposure chose from Brault *et al*[24] was ≤1 year prior the index date. This association was no longer found when we only considered the infections occurring>1 year prior GCA diagnosis.

The hypothesis of an infectious trigger for GCA/PMR was raised many years ago. In GCA, the inflammatory reaction within the artery wall could be suggestive of an antigen-driven disease,[8] potentially due to an infectious agent. Thus, infection could directly be responsible for the occurrence of GCA/PMR. Therefore, the timing between the infection and the occurrence of GCA/PMR is a central question. Thus, infections occurring close to the diagnosis, if not acting as a trigger, might be misclassified and be one of the first sign of GCA/PMR: this raises the question of reverse causation bias. In addition, as only one study included the use of glucocorticoids in the case definition[27] (but not for the index date), we cannot exclude that patients were taking glucocorticoids during the beginning of exposure period, which could increase the risk of infections.

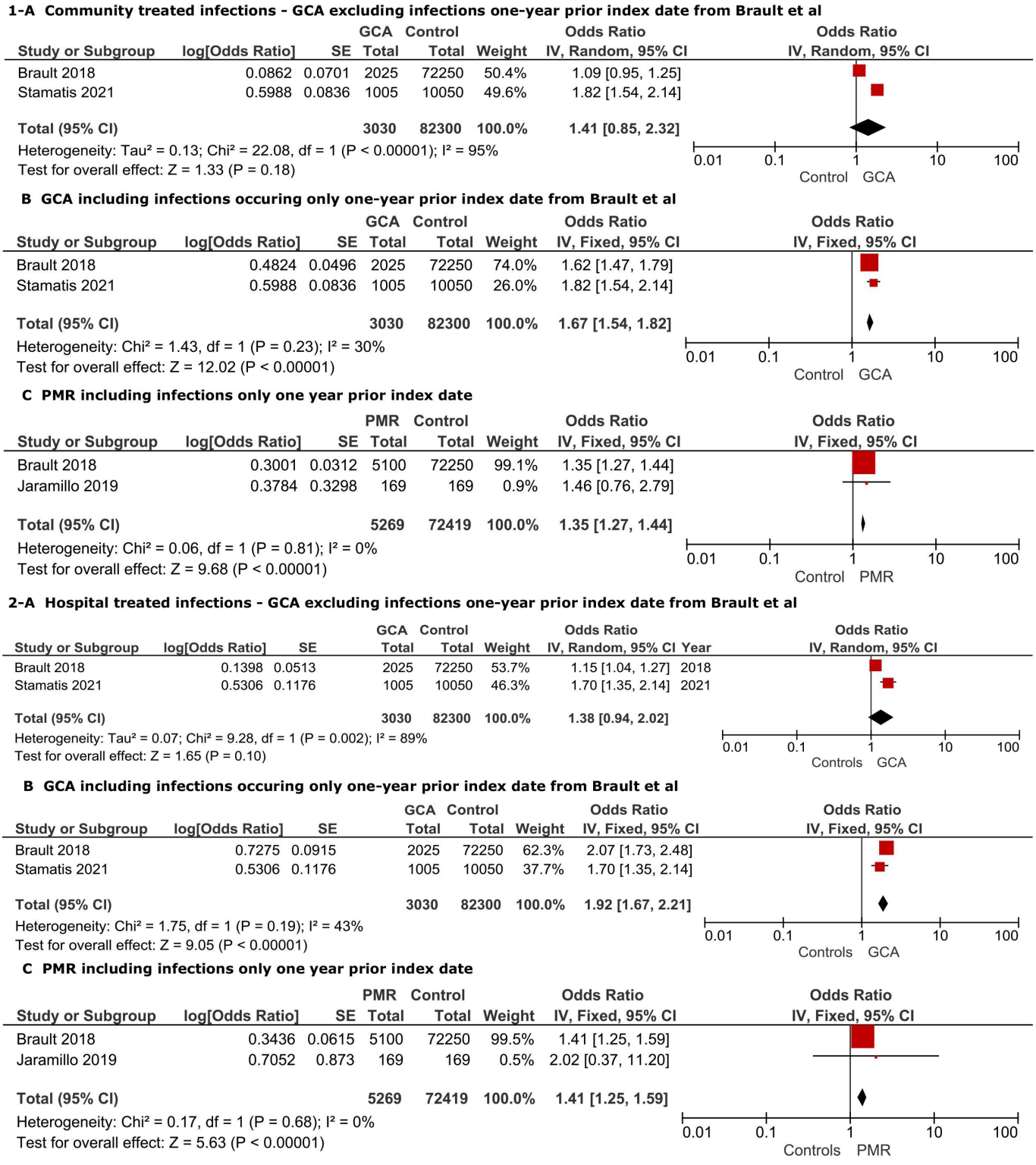

Figure 3 Forrest plots of studies about (1) community-treated infections and (2) hospital-treated infections, (A) GCA excluding infections 1 year prior index date from Brault *et al*, (B) GCA including infections occurring only 1 year prior index date from Brault *et al* and (C) PMR including infections only 1 year prior index date. GCA, giant cell arteritis. GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

Another possibility is that GCA patients present an altered immunity, responsible for these infections. Thus, regarding our results, two periods can then be considered: a long-term period as the overall infection risk seems to be higher anytime, and a short period before diagnosis (less than 1 year), related to a 'pre-ACG/PPR' state when the risk seems even greater. Nevertheless, our results do not allow to conclude whether infections really act as a trigger or only are an indicator of immune dysfunction.

In our meta-analysis, the risk of incident GCA was found to be higher among patients with prior HZ infections. Many histopathological studies previously aimed to identify VZV antigen in temporal artery biopsies (TAB), with contradictory results. Some of them[12 13] found VZV antigen in a great part of TAB of patients with GCA, whereas it was significantly less observed from TAB of patients without GCA, in contrast to other studies that found no such an association.[14 31–33] One possible explication for these discrepancies is the variable use either of PCR, either immunohistochemistry or both to assess the presence of VZV antigen. Ostrowski *et al*[15] performed a synthetic review about it in 2019, leading to the conclusion that there is insufficient evidence to support a direct causation theory. In our meta-analysis, we assessed the risk of HZ infections defined by clinical events. Exposure period was heterogeneous among the five included studies. However, we tried to limit the reverse causation bias by excluding infections close to the index date whenever it was possible.[24 27 30] Nevertheless, using different exposure period from these studies did not change the results. Interestingly, looking at study by study, the risk of incident GCA was not significantly different when comparing the exposure periods considering or not the infections close to the diagnosis. Moreover, when stratifying by time period prior the index date, Rhee *et al*[27] did not find a stronger association the first year prior. Therefore, despite the association between HZ infection and onset of GCA, there is a lack of a strong temporal link supporting the direct pathogenic role of VZV. However, a latent VZV infection might be responsible, which could not be demonstrated by this meta-analysis. Here again, we can hypothesise that patients with GCA present an intrinsic altered immunity, favouring the risk of HZ infection.

Our study has some limitations. First, we included two outcomes, GCA and PMR. However, outcomes were interpretated independently and as previously stated, both diseases are often associated suggesting a common physiopathological mechanism. Second, the included studies were heterogeneous regarding cases and exposure's definitions. However, only studies assessing the same exposure have been included in the meta-analysis. We also separately analysed different periods of exposure when possible. Third, only a small number of studies could be included, despite our large inclusion criteria. Indeed, many excluded studies evaluated infections by serologies, but after the diagnosis of GCA or PMR diagnosis, making the temporality of the infection impossible to assert.

Nevertheless, our study has some strengths. To the best of our knowledge, it is the first meta-analysis of observational studies evaluating the association between different type of infections and the onset of GCA/PMR. Literature screening, data extraction and quality assessment were simultaneously performed by two independent authors. Despite a small number of included studies, we could analyse a large number of subjects, and eight of 11 studies had a low risk of bias. The results of the meta-analysis about overall infection and HZ were stable when different period of exposure and/or different case definitions were used.

In conclusion, our study showed a significant and positive association between overall infections and the onset of GCA with an even greater risk when the infection occurred the year before index date. We also found a positive association with prior HZ infections regardless of the timing of the infection. Results about hospital-treated and community-treated infections were less clear, as the risk was significantly increased only when the infection occurring close to the index date was considered, which may reflect a reverse causation bias. Thus, rather than playing the role of trigger, those infections might be the reflect of an altered immunity among GCA patients.

Contributors LP, RS and YN designed the study. LP and YN were responsible for statistical analyses. LP, RS and YN analysed and interpreted the data. LP wrote the first version of the manuscript. YN accepts full responsibility for the work, had access to the data, and controlled the decision to publish. All other authors approved the final version of the manuscript.

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