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Infections Are Associated With Increased Risk of Giant Cell Arteritis: A Population-based Case-control Study from Southern Sweden

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ABSTRACT. ***Objective***. To investigate the association between infections and the subsequent development of giant cell arteritis (GCA) in a large population-based cohort from a defined geographic area in Sweden.

Methods. Patients diagnosed with biopsy-confirmed GCA between 2000 and 2016 were identified through the database of the Department of Pathology in Skåne, the southernmost region of Sweden. For each GCA case, 10 controls matched for age, sex, and area of residence were randomly selected from the general population. Using the Skåne Healthcare Register, we identified all infection events prior to patients' date of GCA diagnosis and controls' index date. With infection as exposure, a conditional logistic regression model was employed to estimate the OR for developing GCA. The types of infections contracted nearest in time to the GCA diagnosis/index date were identified.

Results. A total of 1005 patients with biopsy-confirmed GCA (71% female) and 10,050 controls were included in the analysis. Infections were more common among patients subsequently diagnosed with GCA compared to controls (51% vs 41%, OR 1.78, 95% CI 1.53–2.07). Acute upper respiratory tract infection (OR 1.77, 95% CI 1.47–2.14), influenza and pneumonia (OR 1.72, 95 % CI 1.35–2.19), and unspecified infections (OR 5.35, 95 % CI 3.46–8.28) were associated with GCA. Neither skin nor gastrointestinal infections showed a correlation.

Conclusion. Infections, especially those of the respiratory tract, were associated with subsequent development of biopsy-confirmed GCA. Our findings support the hypothesis that a range of infections may trigger GCA.

Key Indexing Terms: epidemiology, giant cell arteritis, infections, risk factors, vasculitis

Giant cell arteritis (GCA) is a large-vessel vasculitis that typically affects individuals over 50 years old. It is the most common type of vasculitis in adulthood and is more common in females than in males[1,2,3,4]. Incidence increases with age and peaks in the 70–79 age group[2,5], with 75 being the approximate mean age of diagnosis[2,6]. The incidence rate of GCA is higher in Scandinavian populations and in North Americans of Scandinavian descent[1,7,8,9] than in South European and Asian populations[3,4,10,11,12].

The etiology of GCA has not been established, but environmental factors and infectious agents may contribute to its pathogenesis[13,14]. It is considered to be an antigen-driven disease, although neither autoantigens nor antigens have unequivocally been identified yet[15,16,17]. Fluctuations in the incidence of GCA and an epidemic-like cyclical pattern have been reported, leading to the hypothesis that specific infectious agents could act as triggers[1,4,13,14,18]. Petursdottir, *et al*[1] conducted a study in Gothenburg, Sweden, reporting significant fluctuation in the number of positive temporal artery biopsies (TAB), with peaks in late winter and autumn. A previous study in California also demonstrated significant fluctuations in the number of positive

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The authors declare no conflicts of interest.

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TAB, with positive biopsies more likely in May through July[19]. A population-based study of Olmsted County in Minnesota found an apparent cyclical pattern, with peak periods every 7 years, providing further support to the hypothesis that an infection can trigger GCA[13].

Several infectious agents have been proposed as possible GCA triggers, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, parvovirus B19, and varicella zoster (VZV)[14,18,20,21,22,23]. This is based on observed GCA incidence peaks that are closely associated with infection outbreaks[14], and on detection of parvovirus B19 DNA[22] and VZV antigens in TAB specimens from patients with GCA[23]. These findings have not been confirmed by subsequent studies. Helweg-Larsen, *et al* observed no evidence of parvovirus B19, *C. pneumoniae*, or human herpes viruses in TAB of patients with GCA[24]. A recent immunohistochemistry analysis of 41 TAB and 47 specimens from ascending aortic resections found all to be negative for VZV[25]. The discrepancy between these and previous findings[23] may be due to problems in some studies with false-positive VZV antigen detection as a result of antibodies cross-reacting with myocytes and/or calcified tissue[26,27].

In our large population-based case-control study, we aimed to determine whether infection is associated with risk of future development of GCA. We also investigated whether GCA risk is affected by infection type, frequency, or severity.

MATERIALS AND METHODS

Patients. All patients diagnosed with TAB-positive GCA during the years 1997–2016 were eligible to be included in the study. Patients were identified from a database by the Department of Pathology in Skåne, which operates at 4 hospitals in the area: Skåne University Hospitals in Lund and Malmö, Helsingborg Hospital, and the Central Hospital in Kristianstad. Case identification and retrieval of information pertaining to patients with biopsy-confirmed GCA was previously described by Mohammad, *et al*[2]. The database search was performed using topographic codes relating to "temporal artery biopsy." All histopathology reports were reviewed by 2 of the authors (AJM, PS) to ascertain the diagnosis of biopsy-confirmed GCA. In cases of borderline diagnosis, a consensus was reached by 3 authors to confirm the diagnosis of GCA (AJM, CT, PS). Patients were recorded as having GCA if the pathology report stated the diagnosis of "giant cell arteritis," "temporal arteritis," "granulomatous arteritis," or when the report clearly indicated the infiltration of mononuclear cells into the arterial wall, with or without giant cells. The presence of multinucleated giant cells was not required for GCA diagnosis. In total, 1202 patients (864 females, 72%) had positive TAB diagnoses of GCA. The index date for patients was the date of GCA diagnosis.

Skåne Healthcare Register. The Skåne Healthcare Register (SHR) is a comprehensive administrative register that contains information regarding healthcare services in the region of Skåne, Sweden, since 1998. Visits to physicians, nurses, and other healthcare professionals, along with a record of all health care provided, are registered by the patient's unique 10-digit personal identity number (PIN). Diagnoses are reported in the SHR using the International Classification of Diseases, 10th revision (ICD-10). Up to 8 diagnostic codes for each individual per healthcare contact are registered. In addition to diagnostic codes, the SHR contains visit-related information on sex, age, place of residence, date of visit, and information regarding the healthcare provider. These entries constitute the basis for monetary reimbursement[28,29]. Every citizen who has obtained a Swedish PIN and every European citizen who holds a European Health Insurance Card is entitled to health care at the standard patient fee, with some exceptions depending on taxpayer status. Persons over 65 years old, pregnant women, and persons with certain underlying diseases are recommended to receive the annual influenza vaccination that is offered free of charge. Vaccinations against pneumococcal infections are also recommended for certain risk groups and are available at no cost to the patient[30].

Controls. For each patient with GCA, 10 controls matched for age, sex, and area of residence were randomly selected from the general population. The controls were identified from the SHR database after it was confirmed that they did not have GCA on the date that their respective GCA-positive case was diagnosed, and that they had consulted a physician at some point in the same year. Each control was assigned an index date that corresponded with the date of diagnosis for their respective GCA case.

Exposure. Exposure was defined as any episode of infection that had been diagnosed by a physician, either in an outpatient consultation or during hospitalization, and assigned an ICD-10 code for infection prior to the date of GCA diagnosis/index date. Since the SHR contains data on diagnoses from the beginning of 1998, in order to allow at least a 2-year period during which both cases and controls could potentially contract an infection, we excluded from analysis all patients diagnosed with GCA before January 1, 2000.

Statistical analysis. Conditional regression analysis was performed to calculate the OR with 95% CI as a measure of infection associated with the subsequent development of GCA. In patients and controls with more than 1 infection prior to the index date, only the infection nearest in time to the index date was included in our analysis.

We also performed 3 sensitivity analyses. First, to minimize the risk of misclassification bias since signs and symptoms of GCA could be misinterpreted as infection symptoms (fever, fatigue, high erythrocyte sedimentation rate, or C-reactive protein), all unspecified infections assigned prior to the GCA diagnosis/index date were excluded. To minimize the risk of reverse causality in the second analysis, all infection events occurring within 30 days prior to GCA diagnosis/index date were excluded. The selection of the 30-day time period was based on a previous study of the same cohort showing that the median duration of time from symptom onset to GCA diagnosis (diagnosis delay) was 24 days[31]. In the third sensitivity analysis, patients with prior diagnoses of polymyalgia rheumatica (PMR) who might be receiving glucocorticoids, and hence might be prone to infection, were excluded.

In order to quantify a possible dose-response relationship of infection with GCA risk, the OR for development of GCA per number of previous infections was analyzed in a separate logistic regression model. In the analysis, we categorized the number of infections into 4 groups: no infection (reference), 1 infection, 2–4 infections, and ≥ 5 infections. In addition, we investigated whether the severity of infection affected the risk of future GCA development through analyses with an independent variable of 3 categories: no infection (reference); nonhospitalized infection; and hospitalized infection, assuming infections requiring hospital stay longer than 1 day were severe.

For continuous and normally distributed variables, data are presented as mean (SD). Continuous, abnormally distributed data are presented as median (IQR). We presented inferential results as OR with 95% CI. Statistical analyses were performed using the Statistical Package for the Social Sciences, SPSS 25.0 for Macintosh (IBM SPSS 25.0.0).

Ethics. Our study was performed in accordance with the principles of the Declaration of Helsinki. The Regional Ethical Review Board (ERB) in Lund, Sweden, approved the study (Dnr 2010-517). No informed consent was obtained, as it was not required by the ERB.

RESULTS

Infections prior to GCA. A total of 1014 individuals with GCA were eligible to be included in the study. We were unable to verify records for 9 patients with GCA. Accordingly, 1005 patients

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with GCA (714 females, 71%) and 10,050 (7140 females, 71%) controls were included in the final analyses. Demographics and principal characteristics of the study population are summarized in Table 1. Supplementary Figure 1 (available with the online version of this article) illustrates the identification of all infection events prior to diagnosis/index date for GCA patients and their controls.

In total, 517 (51%) patients with GCA and 4084 (41%) controls were diagnosed with at least 1 infection prior to GCA diagnosis/index date. For patients with GCA, the median time from infection to GCA diagnosis was 7.7 months (IQR 0.7–40.1); the corresponding figure for controls was 24.4 months (IQR 9.1–53.5) from infection to index date (Table 1).

Table 1. Demographics and main characteristics of study population.

	Cases	Controls
N	1005	10,050
Age, yrs, mean (SD)	75.2 (8.03)	75.2 (8.03)
Age, yrs, median (IQR)	76 (70–81)	76 (70–81)
Sex, female, %	71	71
Infection episodes, n	1602	13,037
≥ 1 infection prior to GCA diagnosis/ index date, n (%)	517 (51)	4084 (41)
Only 1 infection prior to GCA diagnosis/ index date, n (%)	195 (19)	1567 (16)
Median time from infection to index date, mos, (IQR)	7.7 (0.7–40.1)	24.4 (9.1–53.5)
Infection episodes required hospitalization, n	180	1612
≥ 1 hospitalization due to infection, n (%)	125 (12)	1011 (10)
Days in hospital, median (IQR)	6 (3–11)	5 (3–9)

GCA: giant cell arteritis.

Infections were more common among patients who subsequently developed GCA compared to controls (51% vs 41%; OR 1.78, 95% CI 1.53–2.07). There was an increased risk of GCA in individuals with acute upper respiratory tract infections (OR 1.77; 1.47–2.14), influenza and pneumonia (OR 1.72, 95% CI 1.35–2.19), and unspecified infections (OR 5.35, 95% CI 3.46–8.28), but not in those with urinary tract infections (OR 1.21, 95% CI 0.92–1.58). OR for these and other infections are presented in Figure 1.

When we excluded unspecified infections, the results were similar, with infections more common in those individuals who later developed GCA (OR 1.61, 95% CI 1.38–1.87; Figure 2). Similarly, when we excluded infections that occurred within the 30 days prior to GCA diagnosis/index date, a significant association between infection and development of GCA remained (OR 1.27, 95% CI 1.09–1.47; Figure 3). The OR for various types of infections occurring ≥ 30 days prior to index dates are shown in Figure 3. Gastroenteritis arose as a significant risk factor when we excluded infections occurring in the 30 days prior to diagnosis (OR 2.12, 95% CI 1.05–4.29; Figure 3) but not when the unspecified infections were excluded (OR 1.96, 95% CI 0.98–3.93; Figure 2). The results were similar when the analyses were restricted to infections occurring 1–6 months prior to index date (Supplementary Table 1, available with the online version of this article).

Of the patients with GCA, 17% had been diagnosed with PMR before the GCA diagnosis, compared to 2% of controls before the index date. When these individuals were excluded from the analysis, results were similar to the results of the main analysis (OR 1.69, 95% CI 1.43–1.99). Rates of other major comorbidities, including diabetes mellitus, obstructive lung disease, malignancies, hypertensive disease, ischemic heart disease, and thromboembolic disease, are presented in Table 2.

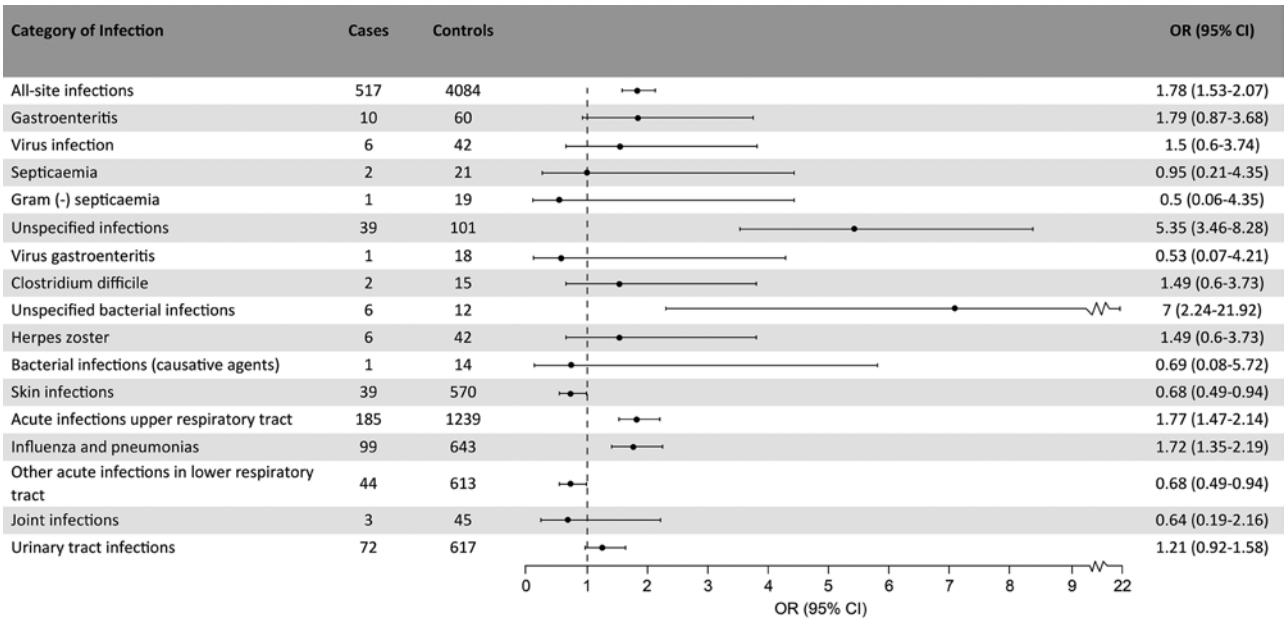

Figure 1. OR with 95% CI for developing GCA relative to prior infection. GCA: giant cell arteritis.

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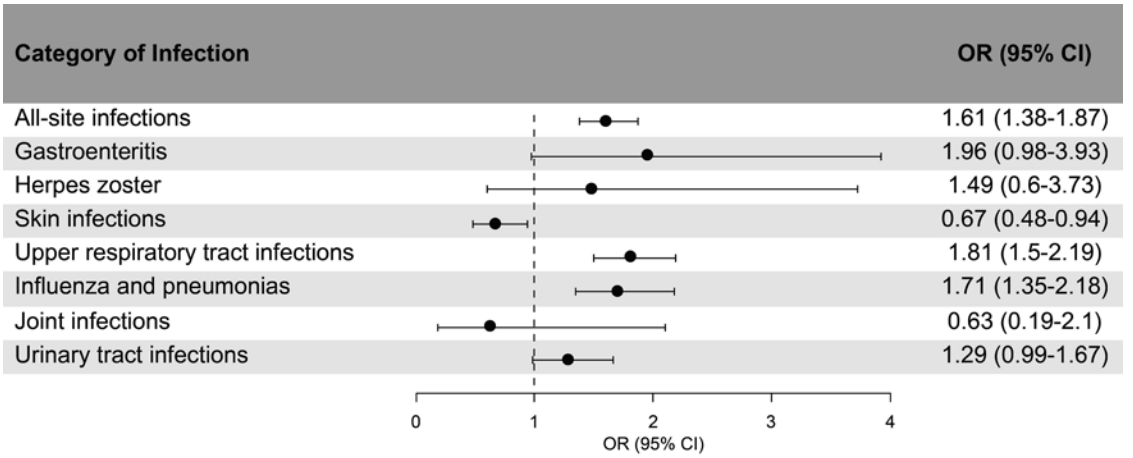

Figure 2. OR with 95% CI for developing GCA relative to prior infection. Unspecified infections excluded. GCA: giant cell arteritis.

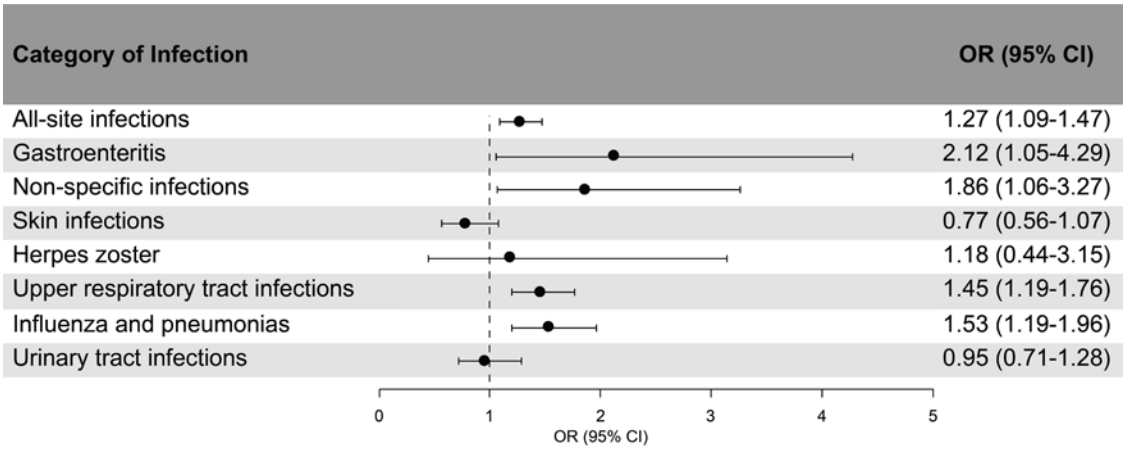

Figure 3. OR with 95% CI for developing GCA relative to prior infection. Infections occurring within 30 days prior to positive TAB excluded. GCA: giant cell arteritis; TAB: temporal artery biopsies.

Dose-response effect. With respect to a potential dose-response relationship, we observed a significantly increased risk of future GCA diagnosis in all frequency categories of infection compared to those without infection, but estimates for the 3 categories did not differ (OR 1.71, 1.85, and 1.78 for 1, 2–4, and ≥ 5 infections, respectively), suggesting no dose-response correlation with respect to frequency of infection.

In terms of the severity of infection, the 125 individuals (12%), who later developed GCA, had been hospitalized for infection prior to their GCA diagnosis date, exhibiting a total of 180 severe infection events, according to the study definition. The corresponding numbers for the controls were 1011 individuals (10%) with 1612 severe infections. The median time of hospitalization was 6 days (IQR 3–11 days) for individuals who subsequently developed GCA and 5 days (IQR 3–9 days) for controls. Compared to those without infections, the OR for developing GCA was 1.82 (95% CI 1.54–2.14) for infections without hospitalization and 1.70 (95% CI 1.35–2.13) for infections requiring hospitalization.

DISCUSSION

From our large population-based, matched case-control study, enrolling more than 1000 patients with biopsy-confirmed GCA, we can conclude that upper respiratory tract infections, influenza, pneumonia, and unspecified infections may be associated with the future development of GCA. Some types of infection were linked to a ≥ 70% risk of patients subsequently developing GCA. These results were similar when patients with a prior diagnosis of PMR were excluded from the analysis and when unspecified infections and infections occurring within 1 month prior to index date were excluded. Sensitivity analyses confirmed the robustness of our findings; however, neither the severity nor the frequency of infection showed an association with the occurrence of GCA.

Our findings are in agreement with previous studies[14,22,23,32,33], including the implication of an association between pathogens of the respiratory tract and GCA[14,22,23]. A direct comparison between our study and those cited is not possible due to differences in variables, such as patient populations, definitions, and

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Table 2. Diagnostic codes assigned to GCA patients and controls prior to index date, indicating major comorbidities.

	ICD-10 Codes	GCA Cases	Controls
N	NA	1005	10,050
Diabetes	E8–E14	103 (10.2)	1330 (13.2)
Type 1 diabetes	E10	24 (2.4)	374 (3.7)
Obstructive lung disease	J42–J46	110 (10.9)	1081(10.8)
Malignancies	All C codes	163 (16.2)	1880 (18.7)
Polymyalgia rheumatica	M353	172 (17.1)	203 (2.0)
Ischemic heart disease	I20–I25	140 (13.9)	1596 (15.9)
Hypertensive disease	I10–I16	405 (40.3)	3728 (37.1)
Venous thrombosis	I26, I80, I82, O08, O22, O87, I81	66 (6.6)	616 (6.1)
Arterial thrombosis	I74, I75, I63, K55, H34, N28	88 (8.8)	8198 (8.1)
Immunodeficiency	D80–D84, D89	0 (0.0)	16 (0.2)

Values are n (%) unless otherwise stated. GCA: giant cell arteritis; ICD-10: International Classification of Diseases, 10th revision; NA: not applicable.

methodology. We were unable to precisely calculate the association of GCA with herpes zoster infections due to wide CI; nevertheless, our results contradict findings from some previous studies regarding herpes zoster[23,33].

The association between unspecified infections and the future development of GCA may reflect a level of diagnostic uncertainty in the early phases of GCA. General systemic manifestations of GCA, such as fever, asthenia, and fatigue, in combination with elevated inflammatory markers, may blur the lines between infection and GCA. However, when the diagnosis of unspecified infection was removed from the regression model, the association of infection with future diagnosis of GCA displayed similar magnitude. The OR of site-specific infections were also similar to those of the main analysis.

In our previous study, we found the median amount of time between the onset of symptoms suggestive of GCA and a positive TAB to be 24 days[31]. Consequently, in a sensitivity analysis, we excluded infections that had occurred within 30 days prior to GCA diagnosis/index date. In this analysis, the size of the association between all-site infections and incidence of GCA was slightly attenuated from 1.6 to 1.3. This suggests that some infections near the index date might have been inaccurately diagnosed on the basis of early, nonspecific GCA symptoms. Our data from this sensitivity analysis may also suggest that gastroenteritis is a risk factor for GCA, although CI are wide and do not permit drawing firm conclusions.

It could be hypothesized that the GCA cases in our study had a higher risk of infection, since 17% had been diagnosed with PMR prior to GCA diagnosis, whereas the corresponding rate in controls was 2%. Patients with PMR show an elevated risk of infection, mainly due to the use of glucocorticosteroid therapy[34]. However, when we excluded all cases and controls with PMR prior to index, infection remained more common in patients who subsequently developed GCA and was nearly at the same level as when PMR was included.

We observed no association between multiple previous infections and the risk of future development of GCA, nor did the severity of infection affect the risk of developing GCA. The risk estimate for those hospitalized due to infection was similar to those with nonhospitalized infections. This suggests that the observed association between infection and GCA is not due to underlying immune deficiency, which would be expected to lead to multiple infections or increased hospitalizations.

With respect to infection as a potential trigger of GCA, several studies have shown that dendritic cells (DC) in the adventitia-media border play a key role in GCA pathogenesis[35,36,37,38]. A plausible hypothesis is that pathogen- or damage-associated molecular patterns from 1 or more infectious agents, introduced through the circulatory system or of local origin, may reach the adventitia-media border through the vasa vasorum[36,38]. In elderly individuals predisposed to GCA, impaired DC [e.g., with polymorphisms in the toll-like receptors (TLR)][39,40] may be activated by the presence of these danger signals, gaining T cell stimulatory capacity[35,37,38]. In the metanalysis by Song, *et al*[39], the TLR4 polymorphisms associated with GCA were found to confer attenuated signaling of TLR4 in the presence of liposaccharides (LPS)[41]. It could be hypothesized that danger signals other than LPS could play a crucial role in the activation of TLR4 in DC in cases of GCA. The activation of DC is known to result in DC migration into the media, where they produce chemotactic factors, which in turn stimulates the migration and activation of T cells and macrophages[35,36] and contributes to the granulomatous infiltrate seen in GCA[35,36,42].

Our study had several limitations. First, our cohort consisted only of patients with biopsy-confirmed GCA; thus, we cannot generalize our results to GCA patients without a positive biopsy or to those with the dominant large vessel vasculitis phenotype. However, 98% of the patients in our cohort fulfilled the ≥ 3 ACR 1990 criteria in a previous study of the same cohort[31,43]. Second, we relied on the assigned ICD-10 codes for infections without verifying the accuracy of the diagnoses. Third, data on vaccinations and smoking history, 2 factors that directly affect the risk for infection, especially of the upper respiratory tract, were not available.

Strengths of our study include the use of a large population-based cohort from a defined geographic area. The data source is validated and employed by practitioners at all levels of healthcare in the region. Several studies have validated the diagnoses in SHR and shown a high level of accuracy and agreement between the medical records and the SHR[28,29,44,45,46]. Between 1998 to 2017, nearly 100% of all in-patient consultations were assigned a diagnostic code[47]. The corresponding figure for primary care consultations was significantly lower but has increased steadily, especially after 2004, reaching close to 100% coverage in 2017 with respect to physician visits[47]. The fact that the entries in the SHR constitute the basis for reimbursement and that it is a part of the well-validated national patient register add strength to the validity of the SHR[48,49,50].

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Our study suggests that infection, especially upper respiratory tract infections, influenza, pneumonia, and unspecified infections, are associated with subsequent development of GCA. Our findings support the hypothesis that infections may trigger GCA, possibly through modulation of the immune system.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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