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Review

Revisiting the epidemiology of giant cell arteritis

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ABSTRACT

In this article, we review the epidemiology of giant cell arteritis (GCA), the most common form of vasculitis in older adults, which primarily affects large and medium-sized arteries. We discuss various epidemiological aspects of GCA, including its incidence, genetic factors, the potential role of seasonality, environmental influences, and infections as possible triggers. Additionally, we explore its association with polymyalgia rheumatica and the significance of major complications, such as the development of aneurysmal disease in GCA, and the decline in the frequency of visual loss. The impact of tocilizumab in reducing disease relapses has also been briefly discussed. Finally, we examine data on GCA-related mortality and outline future research directions and perspectives.

As populations age, the incidence of GCA is expected to rise, necessitating greater physician awareness for early diagnosis. Advances in diagnostics and genetics may improve understanding and treatment, while research on environmental triggers could aid in prevention. Identifying biomarkers and developing safer therapies remain priorities, with fast-track GCA clinics playing a key role in reducing visual complications.

Systemic vasculitides are heterogeneous disabling diseases characterised by chronic inflammation of blood vessels that can cause tissue destruction and organ failure (1, 2). Giant cell arteritis (GCA), formerly known as temporal arteritis, is the most common form of vasculitis in older adults and primarily affects large and medium-sized arteries (3, 4). Because it can lead to significant complications, such as permanent vision loss and stroke, understanding the epidemiology of this condition is critical for timely diagnosis and treatment.

Incidence and prevalence of GCA

GCA primarily affects individuals aged 50 years and older, with a sharp increase in cases as age advances (3). A meta-analysis of the epidemiology of GCA has confirmed that the incidence and prevalence of this vasculitis varies significantly based on geographic region and population ethnicity (3). A clear geographic variability with north-south gradient was observed in Europe, with higher incidence rates in northern countries like Sweden and Norway and lower rates in southern Europe and countries such as Italy or Spain (3).

Li *et al*. conducted an exhaustive meta-analysis of the epidemiology of GCA that included geographic areas from highest to lowest incidence (5). They described that incidence of GCA was threefold higher in Scandinavia relative to the rest of Europe and was 6 times higher in Scandinavia compared to East Asia (5). These authors confirmed the previously reported higher incidence in Scandinavian countries (21.57 cases per 100,000 people over 50 years old), followed by North and South America (10.89 cases per 100,000 people over 50 years old), Oceania (7.85 cases per 100,000 people over 50 years old), Southern Europe (7.26 cases per 100,000 people over 50 years old), Middle East (5.73 cases per 100,000 people over 50 years old), Africa (4.62 cases per 100,000 people over 50 years old), and East Asia (0.34 cases per 100,000 people over 50 years old) (5).

A relatively recent study on incident GCA cases in Denmark showed that in this Scandinavian country the incidence remained high and stable at 19-25 per 100,000 people aged >50 years

from 1996-2018 (6). This is very different from other regions of the world. In this regard, an intermediate incidence rate was reported in Aotearoa New Zealand (14.7 per 100,000 people over 50 years (95% confidence interval-CI: 12.7–16.6; most of them of European ancestry) (7) and in the Lugo region of NW Spain in the period 1981-2005 (10.13 (95% CI: 8.93–11.46) per 100,000 population aged 50 years and older) (8). Studies in Japan, Korea, and African countries report much lower incidence rates, often below 1 per 100,000 (3). With respect to this, a recent report on incidence of GCA in Shanghainese individuals residing in China over a 10-year period yielded a mean annual incidence of 1.91 cases per 100,000 persons (9).

In most studies the overall incidence of GCA has been increasing slightly due to aging populations, especially in Europe and North America (3,8). However, in the Danish study reported by Therkildsen *et al*. the incidence remained stable from 1996-2018 despite increasing use of diagnostic imaging (6). Therefore, more research is needed to establish whether environmental, genetic, or healthcare-related factors also play a role in the rising trend.

Age and gender distribution in GCA

As previously discussed, GCA predominantly affects individuals over the age of 50, with the highest rates seen in those between 70 and 80 years of age with a mean age at disease diagnosis of 75 years in biopsy-proven GCA patients (3, 8).

The risk increases sharply with age, making GCA a condition closely associated with aging populations.

Women are more likely to be affected by GCA than men. Studies consistently show a female-to-male ratio of approximately 2:1 or 3:1 (3). This gender disparity is observed in different degrees across different regions and ethnicities, though the reason for this remains unclear (Fig. 1).

Genetic factors in GCA

The genetic basis of GCA has been extensively studied, making it one of the most well-researched forms of vasculitis in terms of genetics (10). The strongest genetic associations involve the *HLA class II* region (11), particularly *HLA-DRB1*04* alleles (*e.g. HLA-DRB1*0401* and *HLA-DRB1*0404*), which are linked to GCA regardless of phenotype. Additional associations include *HLA class I* alleles, the *MICA* gene, and polymorphisms in the *TNF* region (12).

Large-scale genetic studies, including immunochip and genome-wide association study (GWAS) analyses, confirmed the strong link between GCA and the *HLA* region while identifying additional risk markers like *PTPN22* that emphasise the role of antigen presentation and immune dysregulation in GCA pathogenesis (13). Moreover, these large scales studies confirmed the role of other genetic markers such as *PLG* and *P4HA2* that are involved in vascular remodelling and angiogenesis, suggesting a high relevance of these processes for the pathogenic mechanisms underlying this type of vasculitis (14). In this regard, a recent report described the largest GWAS on GCA to date, analysing genetic data from 3,498 patients and 15,550 controls of European ancestry (15). Researchers identified three novel risk loci (*MFGE8*, *VTN*, and *CCDC25*) linked to angiogenesis and neutrophil extracellular traps (NETs), along with associations in the *HLA* region and *PLG*. Functional analyses suggest these variants play key regulatory roles in immune cells. A polygenic risk score effectively identified individuals at increased GCA risk, and drug repurposing analysis highlighted potential new treatments, advancing the clinical translation of genetic findings (15).

The *NLRP1* gene, involved in inflammasome activation, has also been identified as a susceptibility factor. Variants in cytokine-related genes, such as *IL10*, *IL-4*, *IL-6*, and *IFN-γ*, play roles in immune regulation and inflammation, contributing to disease pathogenesis. Genes involved in innate immunity, including *TLR4, FCGR2A/FCGR3A, and MPO*, have also been implicated (10,12,16). Also, genetic studies have explored the relationship between endothelial function and GCA, highlighting associations with *ICAM1, NOS2A/NOS3, and MMP9*. However, many findings require further validation due to limited statistical power (10,12,16). Additionally, genetic markers have been linked to severe ischaemic manifestations, such as vision loss, with *VEGF* playing a key role in compensating for ischaemia (17).

Figure 1 shows the main genes that have been implicated in the pathogenesis of GCA.

The role of seasonality and environmental factors in GCA

Some studies suggest a possible seasonal pattern in the onset of GCA (3). In this regard, Salvarani *et al*. analysed the incidence of GCA in Olmsted County, Minnesota, USA, from 1950 to 1991 using Mayo Clinic records. Among 125 diagnosed cases (103 women, 22 men), the age- and sex-adjusted incidence rate for individuals aged 50 and older was 17.8 per 100,000, with higher rates in women (24.2) than men (8.2). The incidence increased with age and showed a significant upward trend over time, rising by 2.6% every five years. Notably, incidence appeared to follow a cyclic pattern, peaking approximately every seven years, suggesting a possible infectious trigger for GCA (18) (Fig. 1).

A retrospective study that analysed the incidence of biopsy-proven GCA in the Mid-Atlantic United States from 1994 to 2011showed that while the highest monthly incidence was observed in July and the lowest in October, a significant seasonal or annual trend was not confirmed (19). Another retrospective study examined the incidence and seasonal variation of biopsy-proven GCA in Northern California from 2003 to 2014. Analysing 174 temporal artery biopsies, the authors found that positive biopsies were more common in older patients (average age 76.4 years), with increasing odds of GCA with age. While more women underwent biopsies, they did not have a significantly higher risk of GCA than men. Notably, positive biopsies were significantly more likely to occur between May and July, suggesting a seasonal pattern. The findings indicate that age and summer months may be risk factors for GCA

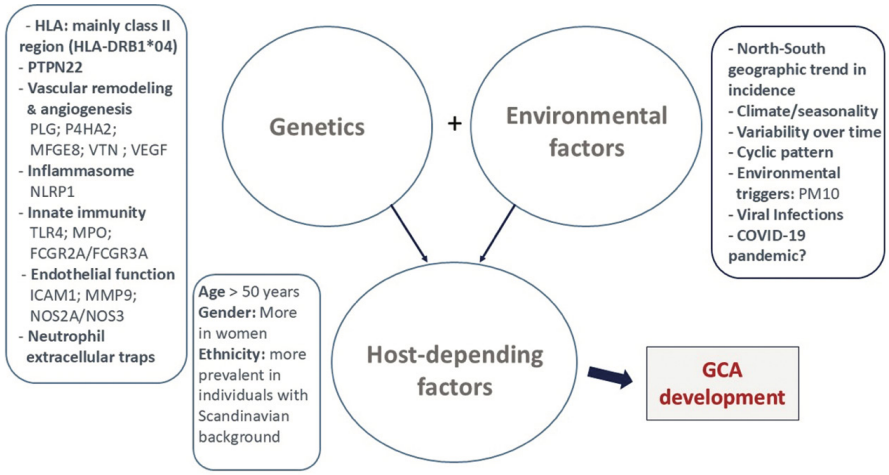


Fig. 1. Main factors implicated in the epidemiology of GCA.
PM10: particulate matter 10; COVID-19: COronaVIrus Disease-2019; GCA: giant cell arteritis.

in this region (20). A Danish study on biopsy-proven GCA also found a seasonal pattern, with higher incidence in summer compared to autumn (21). This could be related to environmental factors such as viral infections that might act as triggers for the disease (Fig. 1).

In line with the above, a study assessed the link between exposure to particulate matter (PM10) and the development of GCA and its ischaemic complications (Fig. 1). Conducted in northern Italy between 2013 and 2021, the authors analysed PM10 exposure using a Bayesian model and assessed its impact using conditional logistic regression. Among 232 patients, a 10-μg/m^3 increase in PM10 over 60 days was associated with a 27.1% higher risk of GCA. No significant associations were found for shorter exposure periods or ischaemic complications. The risk was notably higher in individuals aged 70 and older and those chronically exposed to high PM10 levels. Therefore, according to these results prolonged exposure to air pollution may contribute to GCA development, particularly in older adults (22). However, other studies did not demonstrate different distribution of the incidence rate across all four seasons (23). In this regard, a retrospective study of 161 biopsy-proven GCA cases in Northwest Spain (1981–1998) found no seasonal variation or incidence peaks. This study suggested that GCA onset in this population did not follow a specific seasonal pattern (24).

Infections as potential triggers of GCA

While the exact cause of GCA remains unknown, some researchers have suggested that infections (particularly viral) might initiate an abnormal immune response, leading to vasculitis (Fig. 1). However, this hypothesis is still under investigation (3, 25).

Several infectious agents have been proposed as potential triggers for GCA. A Danish study found a clustering of GCA cases during outbreaks of *Mycoplasma pneumoniae* and human parvovirus B19, suggesting a possible link between these infections and the disease (26, 27). However, serological studies found no significant differences in infection rates between GCA patients and controls for various viruses and bacteria, including *Chlamydia pneumoniae*, influenza, and herpes viruses (28). While one French study suggested a possible link between GCA and parainfluenza virus type 1 (29), other studies did not confirm this (3).

Conflicting results exist regarding *C. pneumoniae*, with some studies detecting it in GCA patients while others did not. Ultimately, *C. pneumoniae* does not appear to explain the high prevalence of GCA in Scandinavian women (30). It was also the case for varicella zoster virus. In this regard, a study of biopsy-positive temporal arteries, using immunohistochemical and polymerase chain reaction techniques, did not reveal varicella zoster virus antigen or DNA in any of the subjects (31).

More recent reports suggest a potential temporal correlation between the onset of GCA and COVID-19 infection (32), as well as new cases of GCA following COVID-19 mRNA vaccination (33). However, further research is needed to establish a causal relationship and understand the underlying mechanisms.

Associated conditions and important complications in GCA

A strong association exists between GCA and polymyalgia rheumatica (PMR), a condition characterised by muscle pain and stiffness, particularly in the shoulders and hips (34). Up to 50-60% of patients with GCA also have PMR, and 10-20% of patients with PMR will develop GCA (34). Moreover, the use of imaging techniques, in particular the use of positron emission tomography-computed tomography (PET-CT) has been demonstrated the presence of extracranial large vessel vasculitis in approximately a third of individuals presenting with isolated PMR (35). This fact raises the question of when we should suspect an underlying, often silent, extracranial large vessel vasculitis in a patient presenting with PMR (36). Situations such as PMR with predominant inflammatory low back pain, significant pelvic girdle involvement, bilateral diffuse pain in the lower extremities, a marked inflammatory response, and an inadequate or incomplete response to 20 mg/day of prednisone warrant the use of imaging techniques to exclude the presence of an underlying large vessel vasculitis (36, 37). Moreover, close follow-up of patients diagnosed with isolated PMR is essential. Some patients initially classified as having isolated PMR, due to the absence of clinical evidence of GCA at diagnosis and a prompt, complete response to low-dose glucocorticoid therapy, may later experience an arteritic relapse. During follow-up, some of them may develop typical craniofacial symptoms or signs of upper extremity vascular insufficiency, ultimately leading to a diagnosis of large-vessel GCA (38).

Visual loss is the most serious and feared complication of GCA (39, 40). It is more commonly seen in patients

with the classic cranial phenotype of GCA (40). In contrast, it is uncommon in those with the predominant extracranial large-vessel vasculitis phenotype (41, 42). The frequency of visual loss in GCA has shown a decreasing trend over the years, likely due to earlier diagnosis and prompt treatment with glucocorticoids (39). Historically, 15-20% of untreated GCA patients developed permanent visual loss, often due to anterior ischaemic optic neuropathy or less commonly as a result of central retinal artery occlusion (8, 39, 40, 43). However, it is noteworthy that a statistically significant progressive decline in the number of patients with visual ischaemic manifestations was observed in the Lugo region of northwest Spain over a 25-year study period (8, 39). Moreover, unlike data from series in the past century, more recent studies show a lower incidence of visual ischaemic manifestations, around 5-10%, with an even lower frequency of permanent visual loss (44). This is likely due to improved physician awareness and early intervention (39). In this regard, advances in diagnostic tools such as colour Doppler ultrasound, and PET-CT scans allow for earlier detection of GCA. Prompt glucocorticoid therapy significantly reduces the risk of irreversible vision loss. Also, the use of new therapies such as the anti-IL-6 receptor inhibitor tocilizumab has improved disease control and reduced dependence on high-dose glucocorticoids, potentially lowering the risk of vascular complications.

Patients with GCA may also develop strokes, typically affecting the vertebrobasilar territory more than the carotid territory, usually occurring soon after or within the first few weeks of diagnosis (45, 46).

Another important complication that may arise is the development of aortic aneurysms and dissections, particularly in the thoracic and abdominal aorta and its major branches. A unique scenario arises in elderly patients with advanced atherosclerosis who are newly diagnosed with GCA, where aneurysm formation may be triggered by a dual mechanism. The difference between aneurysms related to GCA and those associated with atherosclerotic disease lies in several key aspects, including their location, pathophysiology, and risk factors. In this regard, GCA is more commonly associated with thoracic aortic aneurysms, especially in the ascending aorta (47). They can occur at the aortic arch, affecting branches like the subclavian or brachiocephalic arteries (48). This is likely due to the inflammation and vasculitis caused by GCA, which can affect large vessels such as the aorta, particularly the aortic arch and ascending aorta. The abdominal aorta is more commonly affected in atherosclerotic aneurysms. In GCA, the inflammation is driven by immune-mediated vasculitis, which causes granulomatous inflammation in the walls of large arteries. This leads to vascular damage and wall thinning, increasing the risk of aneurysm formation. The inflammation tends to target large and medium-sized vessels, including the aorta.

Aneurysms are more commonly observed several years after the initial diagnosis of GCA, typically within 5 to 10 years. This delayed occurrence results from chronic inflammatory damage that progressively weakens the arterial walls, leading to aneurysm formation over time. Therefore, long-term follow-up of GCA patients is essential to detect this potential complication early (47, 49, 50).

Table I. Future directions and perspectives in the epidemiology of GCA.

1. **Improvement in genetic and molecular insights**
   - Genetic studies (including genome-wide association studies) to identify markers in high-risk populations (Scandinavian/Northern European descent).
   - Research on inflammasomes and immune system dysregulation in GCA.
   - Development of biomarkers for early detection and monitoring disease activity.
2. **Epidemiological data and geographic variability**
   - Expanding studies in under-researched regions like Asia and Africa to understand geographic and environmental influences.
   - Long-term studies to track GCA incidence, prevalence, and trends in specific regions/ethnic groups.
3. **Early diagnosis and screening**
   - Development of non-invasive, sensitive diagnostic methods (advanced imaging, genetic testing).
   - Implementation of screening programs in high-risk populations (older individuals and those with Scandinavian background).
4. **Environmental and lifestyle factors**
   - Research on environmental triggers (infections, pollutants, diet).
   - Studies on the impact of climate, latitude, and geography on GCA incidence.
5. **Treatment advances and management**
   - Advancements in targeted therapies (such as biologics) to reduce long-term glucocorticoid use and its side effects.
   - Focus on personalised medicine.
   - Assessment of long-term outcomes (reducing blindness and aortic aneurysms).
6. **Patient-reported outcomes and quality of life**
   - Studies on quality of life and psychosocial impact of GCA on patients.
7. **Public health initiatives**
   - Awareness campaigns to increase recognition of GCA.
   - Improvements in health systems and access to care for affected individuals.

GCA: giant cell arteritis.

Relapses of GCA and beneficial impact of tocilizumab

Relapses are common in patients with GCA, even with treatment. They usually occur when the dose of prednisone is tapered, or the glucocorticoid therapy is discontinued. Studies from the prebiologic era showed a high rate of relapses, with 40% of patients experiencing recurrences (51). In contrast, more recent studies with the use of the anti-IL-6 receptor tocilizumab showed significantly lower relapse rates (52). As observed in open label studies based on clinical practice (53), the Giant-Cell Arteritis Actemra (GiACTA) trial confirmed important findings regarding the effectiveness of tocilizumab in achieving long-term, glucocorticoid-free remission for GCA patients over a 52-week period (54). In this regard,

56% of patients in the weekly tocilizumab group achieved sustained remission (54). Moreover, the rate of relapses was much lower compared to placebo groups (54). Long-term studies have confirmed that tocilizumab helps maintain remission, reduces the use of glucocorticoids, and significantly lowers relapse rates (55, 56). Additionally, a retrospective analysis from North America also found low relapse rates in GCA patients treated with tocilizumab (57). These findings suggest tocilizumab is effective in reducing GCA relapses, and its use as first-line therapy is recommended.

Mortality in GCA

Population-based studies conducted in countries such as Norway, Spain, and the U.S. state of Minnesota suggest that overall survival in GCA patients is similar to the general population (58-60). This is reassuring and highlights the positive impact of early diagnosis and effective treatment. These studies suggest that GCA itself does not significantly increase mortality, as long as complications, such as like blindness, stroke, or cardiovascular events due to aneurysmal disease, are avoided or managed.

Crow *et al*. performed a comparative analysis of GCA mortality and found that most studies report no significant increase in mortality in GCA patients compared to the general population (61). However, in their retrospective chart review of 44 patients, they observed a significantly lower 5-year survival rate in GCA patients compared to a control group (61). This suggests that there may be some subgroup of GCA patients, possibly those with more severe disease, delayed diagnosis, or untreated disease, who are at an increased risk of mortality.

It is important to note that most classic studies assessing mortality in GCA were conducted on patients with the classic cranial GCA phenotype of the disease. In this context, the outcomes related to large artery involvement among patients with GCA may differ from those with the classic phenotype of GCA without large vessel involvement. To address this, Elfishawi *et al*. performed a study including residents of Olmsted County, Minnesota, USA, with incident GCA between 1950 and 2016, with follow-up through December 31, 2020, death, or migration. The cohort included 289 patients (77% female, 81% temporal artery biopsy positive), 106 of whom had large artery involvement (62). A population-based, age- and sex-matched comparator cohort without GCA was assessed. GCA patients had a higher risk of large artery involvement compared to non-GCA individuals. Thoracic aortic aneurysms, but not abdominal aneurysms, were increased in GCA versus non-GCA patients. All-cause mortality in GCA patients improved over time (hazard ratio 0.62 in 2000-2016 versus 1950-1974) but remained significantly elevated in those with large artery involvement. The authors concluded that large artery involvement in GCA increased over time. Notably, mortality was higher in patients with GCA and large artery involvement, highlighting the need for continued surveillance (62).

We believe that if GCA is diagnosed late, the disease may have already caused significant damage, leading to complications such as stroke, blindness, or aortic aneurysms, which can impact long-term survival. Additionally, patients with GCA may have underlying comorbid conditions, such as cardiovascular disease or diabetes, that could contribute to a higher risk of mortality. Long-term glucocorticoid use may also result in significant side effects, such as osteoporosis, infections, and cardiovascular problems, which could further reduce survival. Moreover, in line with Elfishawi *et al*. (62), we advocate for long-term follow-up of GCA patients to monitor for large artery involvement, particularly the development of aortic aneurysms, especially in those with other cardiovascular risk factors, such as hypertension.

Future directions and perspectives in GCA

As populations in many parts of the world, particularly in Europe and North America, continue to age, the incidence of GCA is expected to rise. Therefore, high physician awareness will be required to identify this vasculitis early. Additionally, advancements in diagnostic techniques may contribute to earlier detection, potentially reducing complications. Further research into the genetics of GCA could improve our understanding of the disease's genetic predisposition and lead to more effective therapeutic targets. Investigating the role of environmental triggers may also provide valuable insights into potential preventive strategies for high-risk populations. Ongoing research will focus on identifying biomarkers for earlier detection and developing safer, more effective treatments. The increasing use of fast-track GCA clinics may also further reduce visual complications through rapid assessment and management.

Table I enumerates future directions and perspectives in the epidemiology of GCA, including others that may improve our understanding of the disease.

Competing interests

M.A. González-Gay received consultation fees/participated in company-sponsored speaker's bureau from GSK, Otsuka, Sanofi, Amgen, and Novo Nordisk.

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