Title page

Trajectory of Healthcare Resources Utilization in Giant Cell Arteritis – A Population-Based Study

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Conflict of interest
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Abstract

Purpose: To estimate the healthcare resource utilization (HRU) in patients with giant cell arteritis (GCA) compared with the general population in southern Sweden.

Methods: The study sample comprised 653 GCA patients along with ten age-, sex-, and residency-area-matched reference subjects per patient. Data on public and private healthcare consultations and hospitalizations were extracted from the Skåne Healthcare Register. We assessed trajectories of primary and specialist healthcare visit, as well as hospital admissions, and inpatient days from three years before through five years after the date of GCA diagnosis for patients and matched references. HRU was analysed using generalized estimating equations adjusted for sex, age at the index year, calendar year of diagnosis, education, income, marital status, place of birth, and Charlson comorbidity index. Inverse probability weighting was used to account for drop-out during study.

Results: GCA patients had higher rate of healthcare visits than the references from the year before GCA diagnosis up to four years after diagnosis with the largest relative (rate ratio [95% CI]: 1.85 [1.68, 2.05]) and absolute (mean difference [95% CI]: 10.2 [8.1, 12.3] visits per-person) differences in the year of diagnosis. Similar trajectories were observed for primary and specialist healthcare visits. For hospital admissions and inpatient days, the differences disappeared one year after diagnosis date.

Conclusions: Patients with GCA utilized health care services at a significantly higher rate than a reference population. The increased utilization among Swedish patients with GCA was evident one year before and prolonged up to four years after diagnosis date.

Introduction

Giant cell arteritis (GCA) is a primary systemic vasculitis of unknown aetiology affecting large arteries, especially the aorta and its main branches (1). GCA presents a female: male ratio of 3:1 (2) and rarely occurs before age 50, with incidence rising rapidly after 50 years. GCA is most common in populations of Northern European ancestry. The reported incidence of biopsy-verified GCA in Sweden is 14.1 to 22 per 100,000 inhabitants aged ≥50 years (2, 3). Common clinical presentations include new-onset headache, scalp tenderness, fever, and constitutional systemic signs (4-6). The most feared complication is vision impairment or irreversible blindness due to involvement of the arteries supplying the optic nerves (7, 8). The diagnosis of GCA is based on clinical characteristics and is usually confirmed by temporal artery biopsy demonstrating vasculitis. In recent years diagnosis of GCA has also been based on imaging studies, especially PET/CT-scans, revealing the presence of inflammatory changes in large blood vessels (9). Glucocorticosteroids are the cornerstone in the treatment of GCA, often requiring high to moderately high doses for a long duration to achieve and maintain remission (10, 11). Prolonged exposure to glucocorticosteroids and high cumulative doses are well-known risk factors for comorbidities including osteoporosis, diabetes, cardiovascular diseases and infections(12) and is associated with increased healthcare cost(13).

Previous studies have demonstrated that patients with GCA suffer a higher rate of cardiovascular disease, severe infection, and venous thromboembolic disease compared to the background population (14, 15). GCA and associated comorbidities are believed to produce a substantial societal and health economic burden, but few studies of the economic consequences of GCA are available. Studies have shown that patients with GCA consume health care resources to a greater extent than the background population (16, 17). A recently published study by Valent et al. has demonstrated a high burden of GCA in terms of

healthcare resource utilization and that healthcare cost of GCA was comparable to more common chronic diseases as diabetes(18). The majority of published reports originate from estimates by pharmaceutical industries relying on administrative registries in confirming the diagnoses or are limited to hospitalization costs (16, 19, 20). However, no studies have assessed the consultation rates in Sweden of patients with GCA. In this population-based study we aimed to estimate the rate of healthcare resource utilizations in a large cohort of patients with biopsy-confirmed giant cell arteritis compared to the background population in southern Sweden. Furthermore, we aim to shed a light on the pattern and trajectories of HRU over longer time period prior to and after disease onset to account for the impact of both disease factors and its treatment on the rate of HRU.

Methods

Study area and population

The study area included Skåne, the southernmost region in Sweden, with a population of 1.3 million (36% >50 years). The study area and population have been described in detail (2). Women made up 50.4% of the study population. The age distribution was 0–14 years, 18.8%; 15–54 years, 54.6%, and >55 years, 26.6% (www.scb.se). The healthcare system in Skåne comprises both public and private providers. The Region Skåne, the administrative body, manages the public healthcare. All residents in Sweden are covered by healthcare insurance. The maximum cost for each individual per annum is 1150 SEK for healthcare and 2300 SEK for drugs. After these limits, all care and pharmaceuticals are provided by the Region at no cost for the individual.

The Skåne Healthcare Register

The Skåne Healthcare Register (SHR) is a central database into which all information on healthcare contacts and diagnosis codes is transferred. The SHR receives data from primary outpatient care, private clinics, and specialized in-hospital care. Each single healthcare consultation (public or private) at any level (physician or paramedic) generates a data entry by the provider that is transferred to the SHR(21). Data in the SHR are available from January 1998 and include records of all consultations with physicians and other healthcare personnel as well as hospitalizations with admission and discharge dates. All physicians report diagnoses according to the assigned International Classification of Diseases, Version 10 (ICD-10 codes). The proportion of assigning diagnosis codes in relation to consultations varies depending on level of healthcare and type of consultation, and it is close to 100% for in-patient care. For specialist care consultations was increased from around 60% in 2001 to reach 100% in 2017. The proportion of consultation assigned diagnosis codes was lowest for primary care but successively increased after 2004 to reach 100% for consultations with a physician and 66% for all consultations in 2016(21).

Study population

Patients with incident biopsy-verified GCA from 1997 through 2016 in Skåne make up a GCA cohort that has been extensively studied by (2, 14, 22, 23). The case identification was carried out using the registries of the Department of Pathology in Skåne by examining reports of all temporal artery biopsies from 1997 (2). As data in the SHR are only available from 1998, and the study was designed to include HRU three years prior to, through five years after, diagnosis date of GCA, only patients diagnosed from January 1st 2001 through December 31st 2011 were included in the current study.

For each patient with GCA, 10 reference subjects from the general population in Skåne, matched for age (±1 years), sex, and residency area (parish) were randomly selected from at risk population. All reference subjects had at least one clinic visit during the same calendar year as their respective cases with any diagnosis made by any physician in the Skåne region. The date of enrolment in the study was defined as the date of diagnosis of GCA. The same date was assigned to each matched reference subject. The observation period was defined relative to the index date (i.e. the first 365 days from the index date was defined as the index year). In this study, the term "reference subjects" was preferred over "controls" as this was not a case-control study in the strict epidemiologic definition but an exposure-matched.

Linking of the GCA cohort and reference population to data sources

The cohort of the GCA and the reference subjects were linked to the databases and registries used via personal identification numbers (Table 1) in order to identify all data relevant to assessment of HRU.

Definition of healthcare resource utilization

Healthcare resource utilization was defined as the number of consultations with healthcare facilities including primary healthcare centres, hospital services for outpatient clinics, and inpatient departments in both public and private sectors. Healthcare resources were classified as *primary healthcare consultations,* defined as all registered physical visits to primary health facilities in Skåne; s*pecialist care consultations*; and *hospital admissions*. Healthcare utilization was assessed from three years prior to, through five years after, the date of GCA diagnosis/index date. In addition to hospital admissions, we calculated total days in hospital.

Registries and databases

The registries and databases used in this study are summarized in Table 1.

Study period

Data from 1998 through 2016 were obtained from the SHR. Healthcare utilization was assessed from three years prior to diagnosis date of GCA through five years following this date. Accordingly, patients diagnosed from 2001 through 2011 were included in the study.

Statistical analyses

We used generalized estimating equations (GEE) (24) to compare trajectories of healthcare utilization in the GCA and the reference cohorts over 8 years observation period (from three years prior to five years following the index date). GEE take into account the dependencies of observations for each individual. Since we had count data, we ran GEE with Poisson and negative binomial distributions and log link function. Based on the QIC selection criterion (25), an independent covariance matrix with negative binomial distribution provided the best fit to the data for all, primary, specialist, and inpatient days. For hospital admissions, an unstructured covariance matrix with Poisson distribution was the preferred model. From these models, the differences in healthcare utilization between two cohorts were reported as rate ratio with 95% confidence interval (CI). We used "margins" command in Stata 15 to obtain the predicted annual mean number of healthcare visits per-person and the annual mean differences per-person between two cohorts with 95% confidence interval (CI). To assess between- and within-cohort differences in healthcare visits, we introduced an interaction term between GCA and year of observation (spanning over 8 years). To minimize the effect of possible confounding factors, all models were adjusted for sex, age at the index year, calendar year of diagnosis, socioeconomic status (education, income, marital status and place of birth), and Charlson comorbidity index(26). Education, income, and marital status were registered at the start of observation, i.e. three year prior to the index date and Charlson comorbidity index

was calculated based on three-year data before index date (i.e. from the start of observation up to the index date).

To account for drop-out during the observation period, we used inverse probability weighting. We used logistic regression to predict probability of drop-out for each year after the index date (by study design, people could not drop out of the study before the index date) based on participants' GCA status, sex, age at the index year, socioeconomic status, comorbidity index, and calendar year of diagnosis. Then, these probabilities were multiplied to generate one probability per person and inverse of this probability (1-probability) was used as weight for people with non-complete (complete) data in GEE models. Furthermore, we included the length of follow-up time in each year as offsets in our models.

Ethical approval: The study is based on registry data that were linked through use of a personal identifier. Ethics approval was provided by the Ethical Review Board in Lund (Dnr. 2010/517, 2013/720, and 2017/298)

Results

Patients and reference subjects

Patients with biopsy-verified GCA from the Skåne region diagnosed from January 2001 through December 2011 were included in the study. This comprised 653 patients (female 479, 73.4%) with 58% diagnosed at age ≥75 years [mean (SD) 75.3 (8.3) years] and 6571 reference subjects (4825 female, 73.4%). Table 2 summarizes the primary demographic characteristics of patients and reference subjects.

Healthcare resource utilization

The mean number of healthcare visits in the reference cohort rose slightly from 10.1 visits per-person in year -3 to 11.2 in index year and was stable thereafter (Figure 1). In GCA group, this figure increased from 9.7 in year -3 to 21.5 in index year and declined to 12.8 in year 4. In both groups, primary care visits constituted more than half of all healthcare visits in all study years (except for the GCA group in the index year). Hospital admissions for infectious diseases (5.6% vs. 3.4%), mental and neurological diseases (8.2% vs. 6.1%), and musculoskeletal disorders (12.1% vs. 7.9%) constituted a larger proportion of total hospital admissions in the GCA group compared to the reference cohort (Figure S1 in supplementary). The results of GEE showed that while two cohorts had comparable healthcare visits in the first two years of observation (RR 0.90 [95% CI: 0.78, 1.02] and 1.01 [0.87, 1.14] for year -3 and -2, respectively), the GCA patients started to have more healthcare visits from the year before (RR 1.39, 95% CI: 1.19, 1.60) until four years after the index date (Figure 2). The similar patterns were observed for primary and specialist care visits, while for hospital admission and inpatient days the differences were only evident for one year before and one year after the index date. In particular, the RR for hospital admission reached its highest level during the year before the index year (2.24 ,95% CI 1.92-2.56, Figure 2).

After adjustment for all covariates, the GCA patients had 9.8 (95% CI, 8.6, 11.1) healthcare visit per-person at the year -3 (Figure 3) compared with 10.9 (10.4, 11.5) healthcare visits per-person in the reference (a mean difference of 1.1 [-0.3, 2.5] per-person, Figure 4). While the corresponding number in the reference slightly increased at the index year (11.9 [11.0, 12.3] visits per-person), this number rose more than double in the GCA cohort (22.0 [20.0, 24.1] visits per-person). The mean differences (95% CI) per-person for different type of health care

visits at the index year were as follow: primary care 3.5 (2.7, 4.4), specialist care 6.0 (4.5, 7.6), hospital admission 0.4 (0.3, 0.6), and inpatient days 9.9 (6.5, 13.3). The mean differences in healthcare use generally rose up to the index year and declined thereafter. It also should be noted that while the mean difference in hospital admission was slightly greater in the year -1 than in the index year, the greatest difference in inpatient days was observed in the index year.

Discussion

The results of this study demonstrated a higher rate of healthcare utilization for GCA patients relative to the general population at all levels of the healthcare system. Patients with GCA showed higher mean numbers of ambulatory visits, specialist visits, hospitalizations, and inpatient hospital stays compared to reference subjects. The differences were evident in the year before GCA diagnosis and up to four years post-diagnosis. Previous studies of HRU in patients with vasculitis are scarce.

These findings were consistent after adjustment for a number of covariates that may have important impact on the extent of health resources utilizations. The healthcare use among persons with GCA was higher compared to the background population after adjustment for sex, age, Charlson comorbidity index, and socio-economic factors. Adjustment was also made for dropout after diagnosis/index date.

In addition to the higher rate of outpatient healthcare use, patients with GCA also showed greater duration of hospitalization compared to the general population. The rate ratio of all-cause hospital admission was high in GCA compared to the general population and reached its highest level the year before diagnosis to 2.24 (95% CI 1.92-2.56), a higher estimate than that of a large study in the United Kingdom that demonstrated a RR of 1.7 (95% CI 1.6-1.8)

(27). The rate of hospitalization reported has varied among countries and is difficult to compare directly for reasons including differences in treatment and access to healthcare services. Mounié et al. has recently demonstrated an additional increased cost of GCA with polymyalgia rheumatica (PMR) compared with GCA without PMR mainly due to increased cost of in-patients stay, drugs and increased paramedic care (28). Similarly, the rate of inpatient hospital admissions for the investigation of GCA and PMR in the UK increased during a period from 2002–2013 (29). However, a recent study using the Swedish Inpatient Registry demonstrated a substantial decrease from 1998 to 2016 in the absolute and relative burden of hospitalization due to systemic connective tissue disease including vasculitis, possibly reflecting improvements in disease management in Sweden (30). Healthcare resource utilization after diagnosis of GCA may have been influenced by the higher rate of comorbidities in patients with GCA. It has been previously shown that patients with GCA have a significantly higher rate of ischemic heart diseases, stroke and traditional risk factors for cardiovascular events, a two-fold higher occurrence of venous thromboembolic disease, a nearly two-fold increase in rate of severe infections and septicaemia(14, 23, 31, 32). This increase in comorbidity rates may partially explain the higher rate of HRU seen in this study at least after GCA onset. However, disease specific factors may have an important impact as well, as we also demonstrated similar findings of increased HRU during the year before GCA onset, even after adjustment for comorbidities. We have recently shown that patients with GCA had a higher rate of infections prior to disease onset compared to the background population(33). Possibly, another contributing factor could be that the treating physician may have an increased tendency to admit patients with GCA to hospital for mild illness or to prolong hospital stays. However, this bias is unlikely to have occurred prior to the diagnosis of GCA.

Few studies have assessed the economic consequences of vasculitides. The majority have originated from estimates obtained with the aid of pharmaceutical companies, relying largely on patient administrative registries in the United States, and were limited to quantification of hospitalization costs, and, perhaps most importantly with respect to our study, are not representative of Swedish hospital practices and costs (16, 19, 20). Not only are these diseases debilitating for the individual, but they also give rise to a substantial health-related economic and societal burden. Many of these comorbidities are the direct result of GCA treatment, including long-term exposure to glucocorticosteroids. It is therefore important to consider using lower doses of glucocorticosteroids and/or shorter duration of treatment. It is also essential to increase healthcare awareness in patients at risk of developing comorbidities and expand the use of preventative measures in patients with GCA. Studies of procedures aiming to decrease the risk of comorbidities in vasculitis should also be encouraged by healthcare providers and granting agencies, as these would impact not only the well-being of individual patients, but also the resources of the community.

Strengths of this study include the use of a large population-based cohort of patients with GCA with no selection bias. The study utilized validated sources of diagnosis and healthcare contacts and covered a period of 10 years. Limitations include that the study totally relies on data from the Skåne Healthcare Register, and no clinical data have been collected from case records. However, in a previous study from same cohort, we found that 10% of the patients had visual complications and almost 98% of cases fulfilled the American College of Rheumatology 1990 classification criteria for GCA (23, 34). Furthermore, comorbidity data on first 840 patients in the cohort have been previously published (14). The cohort only includes patients diagnosed with positive temporal artery biopsy and may not be fully representative for patients with other disease phenotypes within GCA, such as those with isolated large vessel disease. Finally, the comparator in this study consisted of reference

subjects from the general population. Further studies, comparing HRU in patients with GCA to that in patients with other chronic diseases would be of interest.

Based on a large population-based study, we demonstrated, for the first time in Sweden, that patients with biopsy-verified GCA accessed healthcare resources at a significantly higher rate compared to a general population adjusted for factors including sex, age, year of diagnosis, socioeconomic factors, and dropout after index date. The increase in healthcare resource utilization was evident at all levels of healthcare contact one year prior to the diagnosis of GCA and up to four years following diagnosis. These results should be taken into consideration in planning for care of patients with giant cell arteritis, especially as novel therapeutic interventions beyond the traditional glucocorticosteroids become available.

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Table 1. Registries and databases utilized in this study.

Registry	Description	Role
Skåne Healthcare Register (SHR)	A central database in which all levels of health care are reported. The diagnoses in the SHR are registered using the ICD-10.	The SHR was used to identify all diagnosed comorbidities of interest.
The Swedish Population Register	***A nationwide register c***ontaining current information on all residents of Sweden including residential address and dates of immigration to and emigration from Sweden.	***To obtain residency information of surviving subjects***
The LISA* register	A central database since 1990 integrates existing data from the labour market, educational and social sectors and is updated each year with a new annual register.	***To obtain data on socioeconomic status***

ICD-10: The International Classification of Diseases, Version 10.
*LISA: Longitudinal integrated database for health insurance and labour market studies

Table 2. Characteristics of Giant Cell Arteritis (GCA) patients and reference subjects

	GCA n = 653	Reference subjects n = 6571
Female, n (%)	479 (73.4)	4825 (73.4)
Age at diagnosis, mean (SD)	75.3 (8.3)	75.3 (8.3)
Age groups, n (%)		
48-64 years	74 (11.3)	728 (11.1)
65-74 years	198 (30.3)	2012 (30.6)
75-84 years	302 (46.3)	3037 (46.2)
85-95 years	79 (12.1)	794 (12.1)
Charlson Comorbidity Index, %		
0	41.8	61.2
1	35.2	18.7
>1	23.0	20.1
Education, %		
0-9 years	47.3	49.5
10-12 years	*35.5*	*33.1*
13 years and more	14.9	15.2
Missing	2.3	2.2
Born abroad, %	8.6	11.4
Marital status, %		
Never married	8.0	6.2
Previously married	39.4	39.2
Married	52.7	54.6
Lost during follow-up, n(%)		
Died	141 (21.6)	1354 (20.6)
Moved out from Skåne	12 (1.8)	87 (1.3)

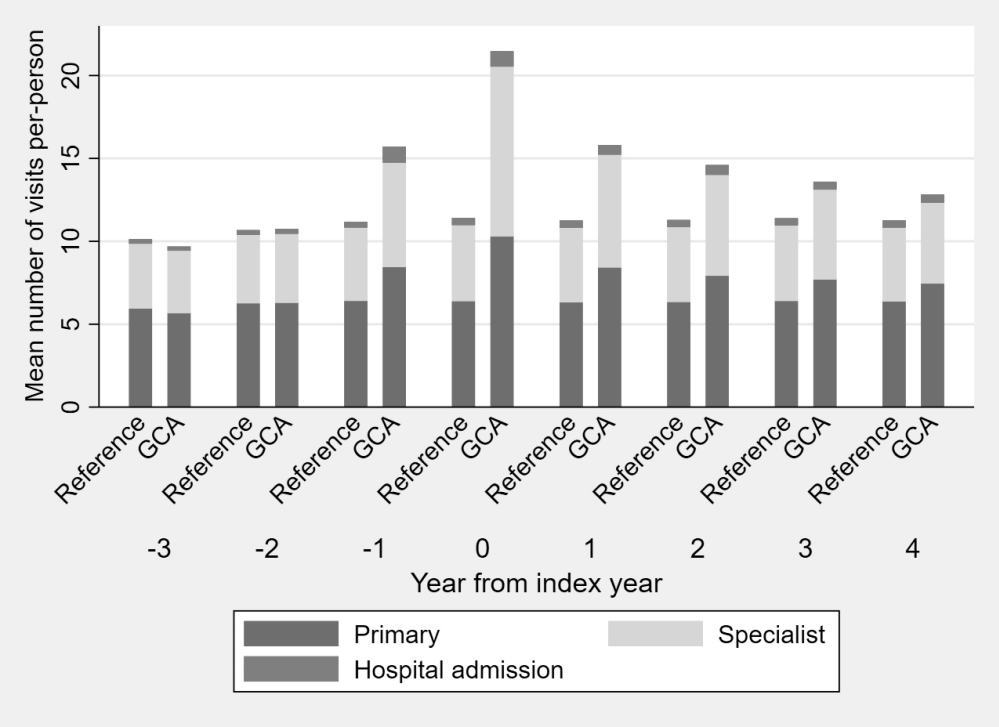

Figure 1. The mean healthcare visits per-person in GCA and reference population during the study time.

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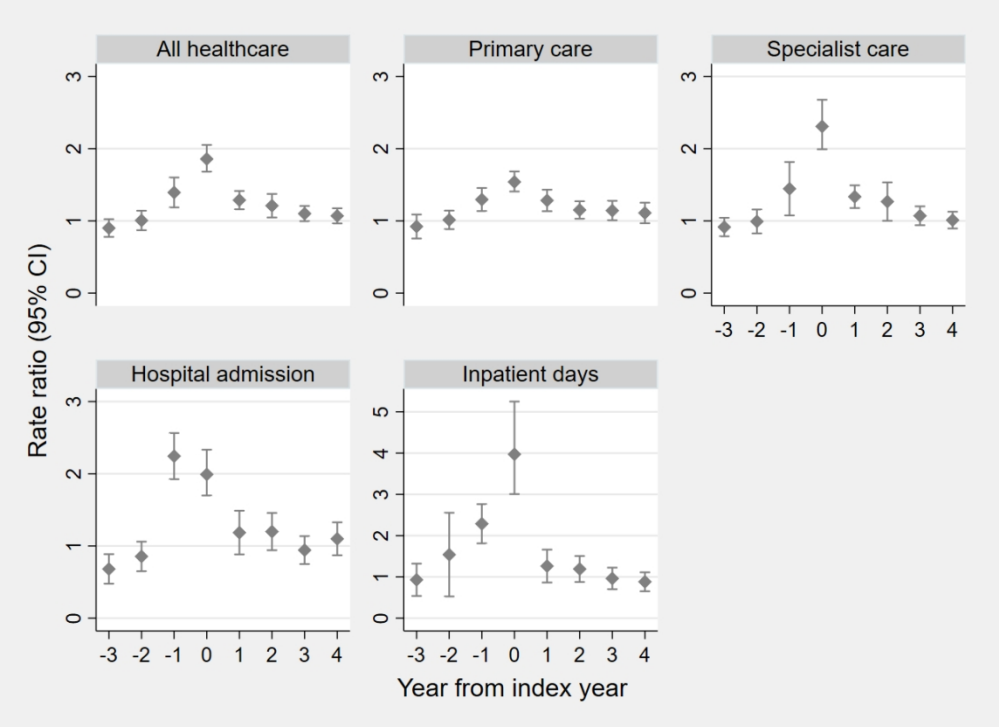

Figure 2

Figure 2. Rate ratio (95% confidence interval) of healthcare visits over 8 years of observation in giant cell arteritis compared with the reference subjects estimated from generalized estimating equations.

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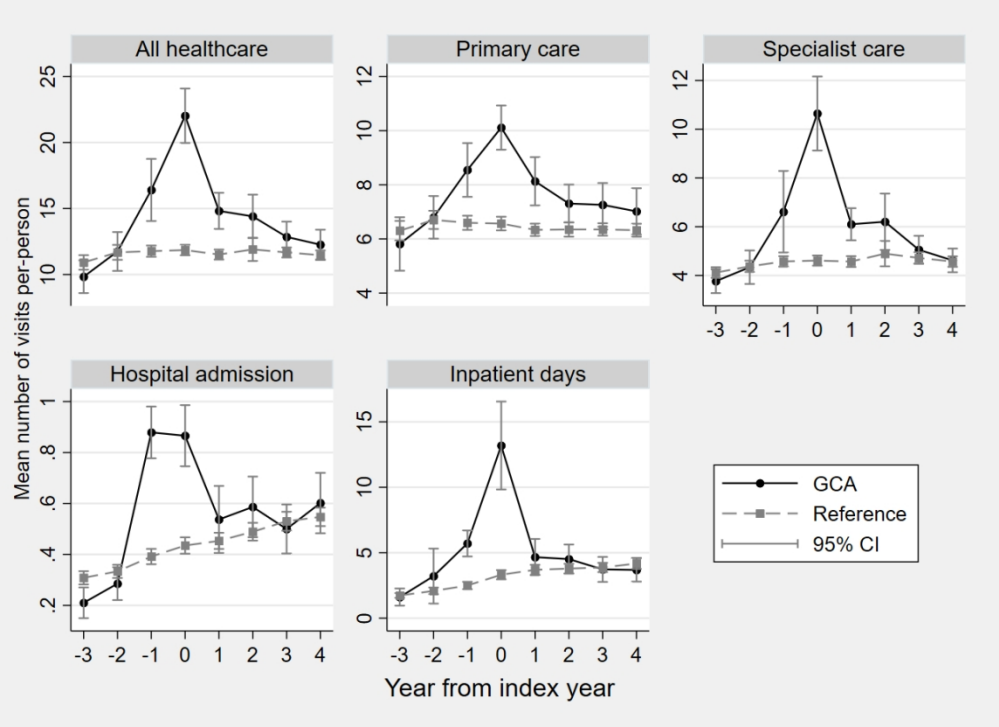

Figure 3

Figure 3. Mean number of healthcare visits per-person in giant cell arteritis compared with the reference over 8-year observation period estimated from the generalized estimating equations.

450x327mm (72 x 72 DPI)

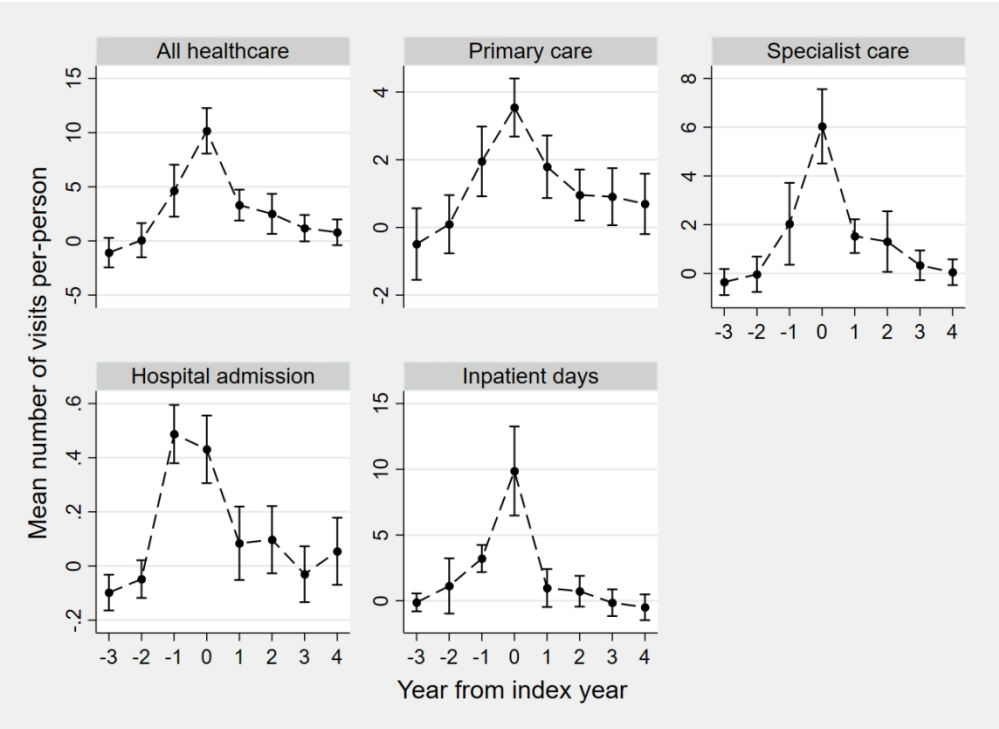

Figure 4
Figure 4. Mean differences in healthcare visits per-person in giant cell arteritis compared with the reference over 8-year observation period estimated from generalized estimating equations.

450x327mm (72 x 72 DPI)