

This is the peer reviewed version of the following article:

Incidence, prevalence and survival of biopsy-proven giant cell arteritis in Northern Italy during a 26-year period / Catanoso, Mariagrazia; Macchioni, Pierluigi; Boiardi, Luigi; Muratore, Francesco; Restuccia, Giovanna; Cavazza, Alberto; Pipitone, Nicolò; Mancuso, Pamela; Luberto, Ferdinando; Salvarani, Carlo. - In: ARTHRITIS CARE & RESEARCH. - ISSN 2151-4658. - 69:(3)(2017), pp. 430-438. [10.1002/acr.22942]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

20/04/2024 04:42

(Article begins on next page)

Incidence, prevalence and survival of biopsy-proven giant cell arteritis in Northern Italy during a 26-year period

Address for correspondence and reprint requests: Carlo Salvarani, MD, Unità Operativa di Reumatologia, Azienda Ospedaliera IRCCS di Reggio Emilia, Viale Risorgimento 80, 42123 Reggio Emilia, Italy. email: salvarani.carlo@asmn.re.it

*Catanoso Mariagrazia, MD; *Macchioni Pierluigi, MD; *Boiardi Luigi, MD; *Muratore Francesco, MD; *Restuccia Giovanna, MD; &Cavazza Alberto, MD; *Pipitone Nicolò, MD; § Mancuso Pamela, MD; §Luberto Ferdinando, MD; *Salvarani Carlo, MD

*Rheumatology Unit and &Pathology Unit, Azienda Ospedaliera IRCCS di Reggio Emilia, Reggio Emilia, Italy; § Interinstitutional Epidemiology Unit, Azienda USL di Reggio Emilia (Local Health Authority) and Azienda Ospedaliera IRCCS di Reggio Emilia, Reggio Emilia, Italy.

Running head: GCA epidemiology in Italy

Funding: This study was not sponsored .

Competing interests: None

Ethics approval: The study was approved by the Reggio Emilia Provincial Ethics Committee, and informed consent was obtained from all patients or their relatives.

Key words: giant cell arteritis; temporal artery biopsy; incidence rate; prevalence rate; survival; causes of death.

Words count: 3,850

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/acr.22942

© 2016 American College of Rheumatology

Received: Jan 20, 2016; Revised: Mar 26, 2016; Accepted: May 17, 2016

Abstract

Objectives. To investigate the epidemiology and mortality in patients with biopsy-proven giant cell arteritis (GCA) in Northern Italy.

Methods. All patients with incident temporal artery biopsy-positive GCA diagnosed between 1986 and 2012 living in the Reggio Emilia area were identified using pathology register and by reviewing all histopathological specimens. For each patient, we identified one comparison subject from the same geographic area matched for age and gender. Mortality rates and specific causes of death were reported.

Results. There were 285 incident cases of biopsy-proven GCA (210 women) during the 26-year study period. The overall age- and sex-adjusted incidence per 100,000 persons aged 50 years or older was 5.8 (95%CI: 5.1 to 6.5). Incidence was significantly higher in women (7.8, 95%CI: 6.7 to 8.9) than in men (3.3, 95%CI: 2.6 to 4.1) ($p < 0.0001$). Annual age- and sex-adjusted incidence rates significantly increased by 15.9% per 3 years from 1986 to 2000, then significantly fell by -4.8% per 3 years from 2001-2012. The prevalence of GCA on December 31, 2012 was 87.9 (95%CI: 75.8 to 101.4). No significant differences in the mortality rates were observed between GCA patients (4.9 per 100 person-year, 95%CI: 4.1 to 5.8) and non-GCA subjects (5.6, 95%CI: 4.7 to 6.6). No significant differences in causes of death were observed comparing GCA patients to non-GCA subjects.

Conclusions. This large population-based study of biopsy-proven GCA confirmed the lower incidence of GCA in Mediterranean countries and did not observe any increased mortality risk.

Significance and Innovations

1. The incidence of biopsy-proven GCA in Northern Italy is similar to that observed in other Mediterranean countries but lower than that reported in Northern European countries.
2. A distinct peak period in the incidence of GCA was observed in 1998-2000 suggesting the influence of an environmental trigger.
3. Survival in GCA was similar to that of non-GCA subjects.

Giant cell arteritis (GCA) is a large vessel vasculitis of unknown etiology involving medium and large arteries affecting people aged 50 years or older (1). Epidemiological studies have shown that incidence rates increase with age and are higher in populations of Northern European origin than in those of Mediterranean countries (2-24).

Annual incidence rates were generally higher than 20/100,000 people in individuals ≥ 50 years in Scandinavian countries (3-11) and lower than 11/100,000 people in individuals ≥ 50 years in Mediterranean countries (14-20). Several studies have noted variations in the incidence of GCA over time (7-9,14,17).

Although its etiology is unknown, genetic, geographic and environmental factors have been implicated in the susceptibility to GCA (25,26). The cyclic pattern of yearly incidence rates (11,19,21,22,23) and the seasonal variations (7,13,18,23,24) reported by some studies support the hypothesis that an environmental cause, in particular an infectious agent, could play a role in the pathogenesis of GCA. Although most studies found that life expectancy of patients with GCA is comparable to that of the general population (18-20,22,27-30) some studies demonstrated an increased mortality (9,32-37).

The present study extends our previous epidemiologic observations, in particular we evaluated the prevalence and the variations in incidence rates of biopsy-proven GCA in the Reggio Emilia area over a 26-year period. Survival rate and causes of death were also studied in comparison with controls from the same geographic area.

PATIENTS AND METHODS

Study design and population.

In a retrospective cohort study, all patients with incident biopsy-positive GCA diagnosed over a 26-year period (from January 1, 1986 to December 31, 2012) living in the Reggio Emilia area (provincia di Reggio Emilia) were identified. All patients were required to have been living in the Reggio Emilia area for at least 12 months prior to diagnosis. Reggio Emilia Hospital (Arcispedale Santa Maria Nuova) is the only referral

center for the population of 519,480 individuals living at January 1, 2009 in the Reggio Emilia area.

The computerized pathology laboratory's register, which keeps a record of all temporal artery biopsies (TABs) performed at our institution, was searched for all the TABs performed between January 1, 1986 and December 31, 2012.

A total of 853 TABs performed in 836 patients were retrieved. The length of the temporal artery specimen after fixation was at least 0.5 cm in all cases. A pathologist (AC) with expertise in vasculitides who had no access to the clinical data or knowledge of the previous pathology report reviewed all TABs. A detailed description of this pathological series has been already reported by our group (38,39).

Two hundreds and eighty-five patients with positive TABs were living in the Reggio Emilia area (provincia) and entered in this inception cohort study.

Information about clinical manifestations, laboratory findings, and disease course were obtained through interviews and by reviewing the medical records of the patients by two of the authors (L.B and F.M.). Patients were followed from the time of diagnosis until either their death or until December 31st, 2013.

For each GCA patients, we identified one non-GCA subjects from the same geographic area who was matched for age and gender and was randomly extracted from the list of resident population.

Information on the date of death for the GCA patients and comparison subjects was obtained from the records of registry offices. Death certificate information for the population of Reggio Emilia area (provincia) are collected in the "provinciale" registry of deaths. The primary cause of death as documented by the treating doctor on the death certificate is recorded and coded according to the International Classification of Disease (9 and 10th revisions). Other diseases contributing to death may also be recorded by the treating doctor.

The study period was arbitrarily divided into nine 3-year periods (1986–88, 1989-91, 1992-94, 1995-97, 1998-2000, 2001-03, 2004-06, 2007-09 and 2010-12), in order to identify possible changes in the incidence rates.

We also checked the Reggio Emilia district database for rare diseases, which was created to identify all patients with rare diseases, including GCA, in order to exempt

patients from payment of disease-related medical costs. This source permitted us to evaluate if GCA patients living in Reggio Emilia area were followed within or outside this area. No GCA patients were diagnosed outside the Reggio Emilia area in the study period.

Statistical analysis.

The population distribution, according to age, sex and calendar time, was provided by the Statistics Office of Emilia-Romagna region that collects data of all municipalities in Emilia-Romagna region every year (40). The target population included the whole population of the Reggio Emilia area (provincia) during the 26-year study period.

In Reggio Emilia population there is an annual surveillance of vital status and emigration out of Reggio Emilia area.

The Reggio Emilia population is predominantly of Caucasian origin (92.5%) with a yearly 1.4% increase from 412,525 inhabitants in 1986 to 534,598 in 2012 (40).

Age- and sex-specific crude incidence rates were calculated using the number of new cases observed as the numerator and the Reggio Emilia province population for each year from 1986 to 2012 as the denominator. Rates were reported as cases per 100,000 in the population.

In Italy the censuses are taken by ISTAT every 10 years when the last figure of the year is 1. Incidence rates were adjusted for age and sex using the 2001 Italian census population (41). We calculated 95% confidence intervals (CIs) assuming a Poisson distribution.

To study temporal changes, incidence rates for nine time periods (1986–88, 1989–91, 1992–94, 1995–97, 1998–2000, 2001–03, 2004–06, 2007–09 and 2010–12) were calculated separately using the population aged ≥ 50 years during the same period as the denominator.

Data regarding the season at diagnosis were analyzed to study possible seasonal variations in incidence of biopsy-proven GCA. The seasons were defined as follow: winter (December-February), spring (March-May), summer (June-August) and autumn (September-November).

Prevalence was estimated on December 31st, 2012. The prevalence rate was obtained by dividing the living number of patients who had the disease (active plus remitted) on December 31st, 2012 by the number of individuals in the population (Reggio Emilia Provincia 2012 population).

For each GCA patient we identified one non-GCA subject from the same geographic area matched for age, gender, and entry-time randomly extracted from the list of the resident of the population of the Reggio Emilia area. A random number generator was used to select one comparison subject for each GCA patient. Comparison subjects were included only if they had a last follow-up date at or beyond the date of disease onset for the GCA-patient. No non-GCA subject was used for more than one GCA patient. Due to the advanced age of the patients, the matching birth year was expanded by ± 1 year to identify the comparison subjects.

Survival was estimated with the Kaplan–Meier method, and a one-sample log-rank test was used to compare observed survival with survival of age- and sex-matched non-GCA subjects.

To study possible differences in survival according to age at diagnosis, the cohort was divided into three groups: age at diagnosis <65 years, between 65-79 years, and ≥ 80 years, respectively. We also evaluated possible differences in survival according to the disease duration considering death and causes of death in 4 time periods: 0-1, 0-2, 0-5, and 0-10 years.

Mortality rates (MRs) were calculated as the number of deaths per 100 person-years (PY). 95% CIs were calculated assuming a Poisson distribution.

Continuous data were described as mean \pm SD or median and interquartile range and categorical variables as percentage. Differences between the patients were analyzed using chi-square test or the Fisher's exact test whenever indicated for categorical variables. $p < 0.05$ was considered significant. Statistical analysis was performed using the SPSS statistical package, version 20.0 and STATA 13.

Joinpoint regression analysis was used to describe GCA trends over time, including the amount of increase or decrease for each time intervals (three years) (42,43). This method determines the number of significant joinpoints by performing several permutation tests. Each trend in the final model was described by a three years percentage change. The rate of change for each trend was tested to determine whether it was significantly different from zero. Observed age- and sex-adjusted total and age-adjusted gender-specific incidence rates are represented by symbols and predicted trends from the

jointpoint analysis are represented by solid lines in figures (Figure 1).

The study was approved by the local Ethics Committee and written informed patient/parent consent to perform the study was obtained.

RESULTS

From 1986 to 2012, 285 Reggio Emilia area (provincia of Reggio Emilia) residents (75 men and 210 women) were diagnosed with biopsy-proven GCA. American College of Rheumatology criteria for GCA classification were satisfied in 260/285 (91%). Mean±SD age at diagnosis was 74.4±7.3 years.

Supplementary Figure S1 shows the number of positive and negative TABs and the proportion of patients with a positive TAB during the study period. A progressive increase in the number of TABs was observed in the last part of the first 15 years of the study period, particularly starting from 1994. No substantial variations in the number of biopsy were noted after 2002. A peak in the total number of TABs was observed in correspondence to 1999-2002 incidence rates' peak period. The proportion of patients with positive TABs mainly oscillated between 30%-50% during the study period.

The age- and sex-adjusted annual incidence rate of biopsy-proven GCA was 5.8 (95%CI: 5.1-6.5) per 100,000 population aged 50 years and older. The overall incidence rate in women (7.8, 95%CI: 6.7-8.9) was double than in men (3.3, 95%CI: 2.6-4.1). The difference was highly significant ($p<0.0001$). Figure 2 shows the annual incidence per 100,000 population of biopsy-proven GCA in the total population of Reggio Emilia area, by sex and by age group. The total annual incidence rates increased with advancing age to a maximum in the 80-84 age group (16.7, 95%CI: 12.9 to 21.4). The age-specific incidence rates were higher in women of all age groups compared to those observed in men, excepted for the 90-94 age group. The highest incidence rate was observed among

women in the 80-84 age group (21.0, 95%CI: 16.1 to 28.3), after which the incidence rate fell. The highest incidence in men was observed in the 75-79 age group (11.0, 95%CI: 7.2 to 16.3), after which the incidence progressively decreased.

Table 1 compares age-adjusted annual incidence rates per 100,000 population age ≥ 50 years for 9 time periods from 1986 to 2012. A progressive increase in total incidence rates and in incidence rates among women was observed from 1986 to 2000. Subsequently, no substantial variations in incidence rates were observed. Variations in incidence rates over time without a distinct trend were observed among the men, however a peak in the incidence was observed in 1998-2000.

Age at onset of GCA did not varied during the study period. Mean age at incidence of GCA was 73.7 ± 6.2 years in the first decade of our study (1986-1995) compared to 73.5 ± 8.0 years in the last decade (2003-2012) ($p=0.879$).

In Figure 3, annual total and gender-specific incidence rates per 100,000 population are plotted to illustrate trends over the entire study period. A peak period (1999-2002) was observed for both women and men, subsequently some fluctuations in the incidence were observed.

Joinpoint analysis identified a significant increasing trend ($p < 0.05$) in total age- and sex-adjusted incidence rate between 1986 and 2000 with an average increase of 15.9% per 3 years followed by a significant 3-year decline ($p < 0.05$) of -4.8% for 2001-2012 (Figure 1A). The incidence rate peaked in 1998-2000, at 10.5 incident cases per 100,000 aged 50 years and older. A significant increasing trend ($p \leq 0.05$) in the age-adjusted female incidence rate between 1986 and 2000 (17.9% per 3 years), followed by a significant ($p \leq 0.05$) decline (-4.8% per 3 years) for 2001-2012 was also observed (Figure 1B). In males there was a continuous, not significant, increase of 1.3% over time (Figure 1C).

The number of patients with biopsy-proven GCA grouped by season was: 64 patients (22.5%) in winter, 76 patients (26.7%) in spring, 76 patients (26.7%) in summer, and 69 patients (24.2%) in autumn. The seasonal distribution of the diagnosis of biopsy-proven GCA did not differ significantly ($p=0.696$).

As of December 31, 2012, the prevalence of active or remitted cases of GCA was 30.4 (95%CI: 25.9-35.6) per 100,000 for general population and 87.9 (95%CI: 75.8-101.4)

per 100,000 population aged 50 years or older. The disease was significantly more prevalent in females (45.3 per 100,000; 95%CI: 37.6-54.1) than in males (14.9 per 100,000; 95%CI: 10.5-20.4).

The mean duration of follow-up from diagnosis (entry-time for comparison subjects) to 31 December 2013 or death was 96.1 ± 58.8 months for GCA patients and 95.7 ± 62.0 months for comparison subjects ($p=0.937$). 120 patients (85 women) died during this follow-up period. For all GCA patients the absolute survival rate was 97.5% at 1 year, 95.4% at 2 years, 87.2% at 5 years and 63.5% at 10 years. The corresponding rates for men were 95.9%, 91.8% and 81.3%, 59.8%, respectively, and for women, 98.1%, 96.6%, 89.2%, 64.7% respectively. No significant differences were present comparing men and women.

The mortality rate for GCA was 4.9 (95%CI: 4.1 to 5.8) per 100 person-years compared to 5.6 (95%CI: 4.7 to 6.6) in the non-GCA subjects. The difference was not significant. The mortality rate ratio (MRR) was 0.87 (95%CI: 0.67-1.13). No difference in MRR between GCA patients and non-GCA subjects was observed in both males [MMR 0.87 (95%CI: 0.64-1.20)] and females [MMR 0.89 (95% CI: 0.61-1.11)].

The Kaplan-Meier survival curves for GCA patients compared with sex- and age-matched non-GCA subjects are shown in Fig. 4. Survival in patients with GCA was not different from that observed in the non-GCA subjects. No differences were observed in the first year, in the first 2 years, or during the first 5 years or 10 years after GCA diagnosis comparing groups of patients with different ages at disease diagnosis (50-64 years, 65-79 years and over 80 years) with age-matched non-GCA subjects (data not shown).

Table 2 shows the causes of death in GCA patients and in the non-GCA subjects. Three males and 3 females in GCA and 4 males and 15 females in non-GCA subjects were lost at the end of follow-up. All causes of death were identified. The most frequent causes of death were diseases of circulatory system, neoplasms, and diseases of respiratory system. Infections as cause of death in our GCA patients were rarely observed. No significant differences for causes of death were observed comparing GCA patients and the non-GCA subjects.

DISCUSSION

Herein, we showed that GCA is more common in women and in persons more than 70 years of age, in keeping with the results of earlier studies (1-13, 15-24). As reported by Rajala et al (4), we observed sex differences in age-related peaks of incidence with a younger age in males than females. In agreement with other studies (9,14), we also observed a decline in incidence in the oldest patients (80 and older for males and 85 years and older for females). Differently from a recent population-based study (44), we did not find an increase in the age at onset of GCA during the study period.

In a previous study we investigated the epidemiology of GCA in Reggio Emilia area over a 9-year (1980-1988) period, considering both TAB-positive and –negative patients (15,16). We found an average annual incidence of 6.9/100,000 in a population aged 50 years or older. In this study over a 26-year period, considering only biopsy-positive patients, we observed a similar average incidence rate of 5.8 per 100,00 population aged 50 years and older.

Our incidence rate is comparable to that reported from other Mediterranean countries (14). Incidence rates of 10.1 and 9.5 per 100,000 population aged 50 years or older were reported for biopsy-positive cases in Spain (14) and Jerusalem (19), respectively. Our data confirm that incidence of GCA in Northern Italy is lower as compared to northern European countries (3-12) and Minnesota (21-22), which is primarily home to people of Northern European descent. The incidence of GCA in Olmsted County, Minnesota (18.8 per 100,000 in people ≥ 50 years) was almost identical to that reported in Göteborg, Sweden (22.2 per 100,000 in people ≥ 50 years) (7-22). Low or very low incidence rates of GCA were reported in South Australia (3.2 per 100,000 populations aged ≥ 50 years), Japan (1.5 per 100,000 populations aged ≥ 50 years), Turkey (1.1 per 100,000 population aged ≥ 50 years), and Arab population (only 7 positive biopsies over a period of 22 years in a tertiary referral eye centre in Saudi Arabia) (20,24,45,46). The north-south gradient of incidence observed in European studies, with an increased prevalence of GCA at higher latitudes, is evocative of environmental causes, but could

also reflect a genetic or ethnic influence. However, independently of the differences in the incidence rates, the overall clinical spectrum of GCA at diagnosis is similar in the different geographic areas (47).

A progressive increase in incidence rates was observed from 1986 to 2000. Subsequently, no substantial variations in incidence rates were observed. These findings may be related to the increased awareness of GCA among clinicians in Reggio Emilia area over the first 15 years of the study period. Afterward, the awareness of GCA became stable throughout the last 12 years. In keeping with this interpretation, supplementary Figure S1 shows a parallel progressive increase in the number of TABs in the last part of the first 15 years of the study period, particularly starting from 1994, with no substantial variations in the number of TABs after 2002. The increased diagnostic awareness among clinicians for GCA is probably related to the different organization of the rheumatological care in the Reggio Emilia area. The Division of Rheumatology at Arcispedale Santa Maria was established in 1997 and since then TABs have been performed in all patients with suspected GCA. In the Reggio Emilia area general practitioners refer all the patients with suspected GCA to rheumatologists for consultation. Furthermore, since 1997 we started to provide rheumatological consultations outside the hospital in the 6 districts of the Reggio Emilia area and we extensively provided training courses on GCA and polymyalgia rheumatica to specialists and general practitioners working at Reggio Emilia Hospital and in the Reggio Emilia area.

The 26-year long study period allowed us to evaluate possible fluctuations in the incidence of this vasculitis in Reggio Emilia area. Cyclic fluctuations of yearly incidence rates (11,19,21-23) and seasonal variations (7,13,18,23,24) reported by some studies might suggest an environmental/infectious etiology for GCA. We observed a distinct peak period that lasted about 3 years in 1998-2000. This peak was significant in females, but not in males, probably owing to the much smaller number of cases occurred in men. In an analysis of the trends in incidence rates of GCA over a 42-year period in Olmsted County, Minnesota, the authors observed 5 epidemic-like, cyclic fluctuations (21). Each peak, as our peak, lasted about 3 years, and the peaks occurred approximately every 7 years. Cyclic fluctuations of GCA incidence with 3 distinctive peaks, 8-10 years apart, were also observed in the Jerusalem population (19). Finally, incidence peaks of GCA were observed by Elling et al in Denmark and Abdul-Rahaman et al in New Zealand (11,23). A

close concurrence between the observed incidence peaks of polymyalgia rheumatica/GCA and epidemics of *Mycoplasma pneumoniae*, parvovirus B19, and *Chlamydia pneumoniae* were found in different areas of Denmark (11). However, other studies failed to observe cyclic fluctuations or peaks in the incidence rate of GCA (7,9,14).

In this study, no seasonal variations were found, similarly to the results recently provided by two studies from Spain and Sweden, respectively (9,14). In contrast, several other studies have found seasonal variations in the diagnosis of GCA. However, there was a large variability in the months with peaks. In some studies more patients were diagnosed during the warmer-summer months, while in others in winter and autumn months (7,13,18,23,24). Therefore, although some epidemiological findings suggest a possible infectious etiology for GCA, the cause of GCA remains at the moment unknown and more studies about the role of infections in GCA are needed.

As reported by the majority of the studies (4,22,27-31), in our population-based cohort study we did not observe any increased mortality in patients with biopsy-proven GCA. The mortality rate was similar in GCA patients and non-GCA subjects and no differences in MMR among GCA patients and non-GCA subjects were observed in males and females. Five studies (9,32,33,35,36) found a significant higher standardized mortality rate (SMR) in GCA patients as compared to general population. Two studies have observed a higher SMR only in the first year after diagnosis (9,36), one during the first 5 years (33) and another study in the first two years and >10 years after diagnosis (32). Mohammad (9) estimated an excess mortality in patients aged ≤ 70 years and in women. Bisgard (35) observed an excess mortality only in men, while Udhammar (34) and Graham (37) only in women. We did not observe any differences in survival after stratifying patients according to the age of disease onset, sex, and follow-up duration. Of note, the studies showing increased mortality were prevalently hospital-based series and most of them included small number of patients, whereas the majority of population-based studies found no excess mortality in GCA patients.

Some studies defined the causes of death among patients with GCA. Neshet et al (36) and Ninan et al (27) reported an excess mortality in the first year of disease caused by steroid-related infections, while other studies (32), confirming our results, did not find an increased risk of death related to infection. In a nationwide Danish population-based

cohort study Baslund (32) observed an increased risk of cardiovascular deaths during the first 2 years of disease and after 10 years. An increased risk of death due to diseases of the gastrointestinal tract compared to controls was also observed in the periods 0-2 and 2-10 years after diagnosis. An excess of death due to aortic aneurysm rupture was only observed in GCA patients during the first 2 years after diagnosis (32). Uddhammar (34) observed a significant increase of death due to cardiovascular disease in both women and men, mainly due to ischemic heart disease. However, a more recent population-based study from Spain did not show an increased mortality due to ischemic heart disease in patients with GCA (48). We were unable to find any difference in the causes of death comparing patients with the non-GCA subjects, nor did we observe differences in the causes of death during the first years after diagnosis compared to the following years (data not shown). The most frequent causes of death were cardiovascular diseases, cancer, and respiratory diseases.

Our study has limitations, but also strengths. Retrospective data retrieval is the main limitation of the study. In addition, patients with large vessel involvement are less frequently TAB-positive (49,50), therefore the inclusion of only TAB-positive patients has probably underestimated the incidence of GCA and the risk of mortality linked to aortic aneurysm/dissection. It is also possible that some cases may have been diagnosed by general practitioners, and not referred for biopsy. Strengths of the study were the population-based design, the inclusion of patients with fully established diagnosis using TAB as the gold standard, and the inclusion of a referral cohort from the same population for comparison.

REFERENCES

1. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant cell arteritis. *N Engl J Med*. 2002; 347: 261-71.
2. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Fillooy JA, Gonzalez-Juanatey C, Martin J, Llorca J. Epidemiology of giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheum*. 2009; 61: 1454-61.
3. Baldursson O, Steinsson K, Björnsson J, Lie JT. Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. *Arthritis Rheum*. 1994; 37: 1007-12.
4. Rajala SA, Ahvenainen JE, Mattila KJ, Saarni MI. Incidence and survival rate in cases of biopsy-proven temporal arteritis. *Scand J Rheumatol*. 1993; 22: 289-91.
5. Gran JT, Myklebust G. The incidence of polymyalgia rheumatica and temporal arteritis in the county of Aust Agder, south Norway: a prospective study 1987-94. *J Rheumatol*. 1997; 24: 1739-43.
6. Haugeberg G, Paulsen PQ, Bie RB. Temporal arteritis in Vest Agder County in southern Norway: incidence and clinical findings. *J Rheumatol*. 2000; 27: 2624-7.
7. Petursdottir V, Johansson H, Nordborg E, Nordborg C. The epidemiology of biopsy-positive giant cell arteritis: special reference to cyclic fluctuations. *Rheumatology (Oxford)*. 1999; 38: 1208-12.
8. Nordborg C, Johansson H, Petursdottir V, Nordborg E. The epidemiology of biopsy-positive giant cell arteritis: special reference to changes in the age of the population. (Sweden) *Rheumatology (Oxford)*. 2003; 42: 549-52.
9. Mohammad AJ, Nilsson JA, Jacobsson L, Merkel PA, Turesson C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. *Ann Rheum Dis*. 2015; 74: 993-7.
10. Boesen P, Sørensen SF. Giant cell arteritis, temporal arteritis, and polymyalgia rheumatica in a Danish county. A prospective investigation, 1982-1985. *Arthritis Rheum*. 1987; 30: 294-9.
11. Elling P, Olsson AT, Elling H. Synchronous variations of the incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark; association with epidemics of *Mycoplasma pneumoniae* infection. *J Rheumatol*. 1996; 23: 112-9.
12. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. *Ann Rheum Dis*. 2006; 65:1093-8. Epub 2006 Jan 13.
13. Barrier J, Pion P, Massari R, Peltier P, Rojouan J, Grolleau JY. Epidemiologic approach to Horton's disease in the department of Loire-Atlantique. 110 cases in 10 years (1970-1979)]. *Rev Med Interne*. 1982;3:13-20.
14. Gonzalez-Gay MA, Miranda-Fillooy JA, Lopez-Diaz MJ, Perez-Alvarez R, Gonzalez-

Juanatey C, Sanchez-Andrade A et al. Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. *Medicine (Baltimore)*. 2007; 86: 61-8.

15. Salvarani C, Macchioni PL, Tartoni PL, Rossi F, Baricchi R, Castri C et al. Polymyalgia rheumatica and giant cell arteritis: a 5-year epidemiologic and clinical study in Reggio Emilia, Italy. *Clin Exp Rheumatol*. 1987; 5: 205-15.

16. Salvarani C, Macchioni P, Zizzi , Mantovani W, Rossi F, Castri C et al. Epidemiologic and immunogenetic aspects of polymyalgia rheumatica and giant cell arteritis in northern Italy. *Arthritis Rheum*. 1991; 34: 351-6.

17. Friedman G, Friedman B, Benbassat J. Epidemiology of temporal arteritis in Israel. *Isr J Med Sci*. 1982; 18: 241-4.

18. Sonnenblick M, Neshar G, Friedlander Y, Rubinow A.. Giant cell arteritis in Jerusalem: a 12-year epidemiological study. *Br J Rheumatol*. 1994; 33: 938-41.

19. Bas-Lando M, Breuer GS, Berkun Y, Mates M, Sonnenblick M, Neshar G. The incidence of giant cell arteritis in Jerusalem over a 25-year period: annual and seasonal fluctuations. *Clin Exp Rheumatol*. 2007; 25,S44:S15-7.

20. Pamuk ON, Dönmez S, Karahan B, Pamuk GE, Cakir N. Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: Clinical features and epidemiological data. *Clin Exp Rheumatol*. 2009; 27: 830-3.

21. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG.. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med*. 1995; 123: 192-4.

22. Salvarani C, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE.. Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. *Arthritis Rheum*. 2004; 51: 264-8.

23. Abdul-Rahman AM, Molteno AC, Bevin TH. The epidemiology of giant cell arteritis in Otago, New Zealand: a 9-year analysis. *N Z Med J*. 2011; 124: 44-52.

24. Dunstan E, Lester SL, Rischmueller M, Dodd T, Black R, Ahern M et al. Epidemiology of biopsy-proven giant cell arteritis in South Australia. *Intern Med J*. 2014;44:32-9.

25. Carmona FD,Gonzalez-Gay MA,Martin J. Genetic component of giant cell arteritis. *Rheumatology (Oxford)* 2014;53 :6-18

26.Salvarani C, Pipitone N, Versari A, Hunder GG. Clinical features of polymialgia rheumatica and giant cell arteritis. *Nat Rev Rheumatol*. 2012; 8: 509-21.

27. Ninan J, Nguyen AM, Cole A, Rischmueller M, Dodd T, Roberts-Thomson P et al. Mortality in patients with biopsy-proven giant cell arteritis: a south australian population-based study. *J Rheumatol* 2011; 38: 2215–7.

28. González-Gay MA, Blanco R, Abaira V, García-Porrúa C, Ibáñez D, García-Pais MJ, Rigueiro MT et al. Giant cell arteritis in Lugo, Spain, is associated with low longterm

mortality. *J Rheumatol*. 1997; 24: 2171-6. Erratum in: *J Rheumatol* 1998; 25: 193.

29. Gran JT, Myklebust G, Wilsgaard T, Jacobsen BK.. Survival in polymyalgia rheumatica and temporal arteritis: a study of 398 cases and matched population controls. *Rheumatology* 2001; 40: 1238-42.

30. Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. *Am J Med*. 1996; 100:193–6.

31. Nordborg E, Bengtsson BA. Death rates and causes of death in 284 consecutive patients with giant cell arteritis confirmed by biopsy. *Br Med J*. 1989; 299: 549–50.

32. Baslund B, Helleberg M, Faurschou M, Obel N. Mortality in patients with giant cell arteritis. *Rheumatology (Oxford)*. 2015; 54: 139-43.

33. Crow RW1, Katz BJ, Warner JE, Alder SC, Zhang K, Schulman S et al. Giant cell arteritis and mortality. *J Gerontol A Biol Sci Med Sci*. 2009; 64: 365–9.

34. Uddhammar A, Eriksson AL, Nyström L, Stenling R, Rantapää-Dahlqvist S. Increased mortality due to cardiovascular disease in patients with giant cell arteritis in northern Sweden. *J Rheumatol* 2002; 29: 737-42.

35. Bisgård C, Sloth H, Keiding N, Juel K. Excess mortality in giant cell arteritis. *J Intern Med*. 1991; 230: 119–23.

36. Neshar G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. *J Rheumatol*. 1994; 21: 1283-6.

37. Graham E, Holland A, Avery A, Russell RW. Prognosis in giant-cell arteritis. *Br Med J (Clin Res Ed)* 1981; 282: 269–71.

38. Restuccia G, Cavazza A, Boiardi L, Pipitone N, Macchioni P, Bajocchi G et al. Small-vessel vasculitis surrounding an uninflamed temporal artery and isolated vasa vasorum vasculitis of the temporal artery: two subsets of giant cell arteritis. *Arthritis Rheum*. 2012; 64: 549-56.

39. Cavazza A, Muratore F, Boiardi L, Restuccia G, Pipitone N, Pazzola G et al. Inflamed temporal artery: histologic findings in 354 biopsies with clinical correlations. *Am J Surg Pathol* 2014; 38: 1360-70.

40. Ermes. Emilia-Romagna: the region in figures. URL: <http://www.regione.emilia-romagna.it/statistica>.

41. 14° Censimento delle popolazioni e delle abitazioni 2001./sistema statistico nazionale istituto nazionale di statistica. Roma. URL: <http://www.istat.it/it/censimento-popolazione/censimento-popolazione-2001>.

42. <http://surveillance.cancer.gov/joinpoint/>

43. Kim HJ, Fay MP, Feuer EJ, Midthune DN, Permutation Tests for Joinpoint Regression with Applications to Cancer Rates. *Stat Med* 2000; 19: 335-351. (correction: 2001;20:655).
44. Kermani TA, Schäfer VS, Crowson CS, Hunder GG, Gabriel SE, Matteson EL, et al. Increase in age at onset of giant cell arteritis: a population-based study. *Ann Rheum Dis*. 2010; 69: 780-1.
45. Kobayashi S, Yano T, Matsumoto Y, Numano F, Nakajima N, Yasuda K et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. *Arthritis Rheum*. 2003; 49: 594-8.
46. Chaudhry IA, Shamsi FA, Elzaridi E, Arat YO, Bosley TM, Riley FC. Epidemiology of giant-cell arteritis in an Arab population: a 22-year study. *Br J Ophthalmol*. 2007;91:715-8.
47. Gonzalez-Gay MA, Boiardi L, Garcia-Porrúa C, Macchioni P, Amor-Dorado JC, Salvarani C. Geographical and genetic factors do not account for significant differences in the clinical spectrum of giant cell arteritis in southern Europe. *J Rheumatol*. 2004; 31: 520-3.
48. Gonzalez-Gay MA, Rubiera G, Piñeiro A, Garcia-Porrúa C, Pego-Reigosa R, Gonzalez-Juanatey C, et al. Ischemic heart disease in patients from Northwest Spain with biopsy proven giant cell arteritis. A population based study. *J Rheumatol*. 2005; 32: 502-6.
49. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum*. 1999; 42: 311-7.
50. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology (Oxford)*. 2015; 54: 463-70. doi: 10.1093/rheumatology/keu329. Epub 2014 Sep 5.

Table 1. Annual incidence of biopsy-proven GCA among residents of Reggio Emilia area (provincia) 1986-2012, age 50 years or older, by sex and time period

Time period	Men				Women				Total			
	n	Rate*	95% CI		n	Rate*	95% CI		n	Rate&	95%CI	
1986/1988	3	1.5	-0.2	3.1	4	1.5	0.03	2.9	7	1.5	0.4	2.6
1989/1991	6	2.9	0.5	5.3	8	2.9	0.9	5.0	14	2.9	1.4	4.4
1992/1994	4	1.7	0.02	3.4	13	4.9	2.2	7.6	17	3.5	1.8	5.1
1995/1997	7	2.9	0.7	5.2	28	9,6	6.0	13.3	35	6.6	4.4	8.8
1998/2000	19	7.7	4.2	11.2	38	12,8	8.7	16.8	57	10.5	7.7	13.2
2001/2003	7	2.7	0.7	4.6	33	10.8	7.1	14.5	40	7.1	4.9	9.3
2004/2006	10	3.3	1.1	5.6	34	10.5	6.9	14.1	44	7.2	5.0	9.4
2007/2009	9	3.2	1.1	5.3	26	7.3	4.3	10.3	35	5.4	3.5	7.2
2010/2012	10	3.8	1.4	6.1	26	8.2	5.0	11.4	36	6.1	4.1	8.1
Total	75	3.3	2.6	4.1	210	7.8	6.7	8.9	285	5.8	5.1	6.5

*Incidence per 100,000 person-years population per year, age-adjusted to 2001 Italian population 50 years of age or older (Istat national census).

&Incidence per 100,000 person-years population per year, age- and sex-adjusted to 2001 Italian population 50 years of age or older (Istat national census). 95%CI = 95% confidence interval.

Table 2. Causes of death among biopsy-GCA cases and controls

Causes of death	Male				Female			
	GCA		Controls		GCA		Controls	
	n	%	n	%	n	%	n	%
Diseases of circulatory system	16	45.7	16	40.0	42	49.4	44	50.0
Neoplasms	8	22.9	9	22.5	12	14.1	19	21.6
Diseases of respiratory system	5	14.3	7	17.5	9	10.6	10	11.4
Diseases of digestive system	2	5.7	1	2.5	7	8.2	4	4.5
Endocrine diseases*	2	5.7	1	2.5	3	3.5	1	1.1
Injury, poisoning and other consequences of external causes	-	-	2	5.0	3	3.5	4	4.5
Infectious and parasitic diseases	-	-	-	-	2	2.4	-	0.0
Other diseases	2	5.7	4	10	7	8.2	6	6.8
Total	35	100	40	100	85	100	88	100

*Including diabetes mellitus. GCA = giant cell arteritis.

Figures

Figure 1. (A) Total age- and sex-adjusted and (B and C) gender-specific age-adjusted to 2001 Italian census population giant cell arteritis incidence rates (joinpoint regression analysis). Note: lines represent joinpoint regression lines. PC = Percentage change. * The PC is statistically significant ($p < 0.05$).

Figure 2. Annual incidence of giant cell arteritis among residents of Reggio Emilia area (provincia), 1986-2012 by sex and age group, per 100,000 population. Total incidence per 100,000 person-years population per year, age- and sex-adjusted to 2001 Italian population 50 years of age or older. Male and females incidence per 100,000 person-years population per year, age-adjusted to 2001 Italian population 50 years of age or older.

Figure 3. Total age- and sex-adjusted (to 2001 Italian census population) and males and females age-adjusted annual incidence rates for biopsy-proven GCA in Reggio Emilia area (provincia), 1986-2012, per 100,000 persons age ≥ 50 years.

Figure 4. Survival curve for patients with giant cell arteritis compared with survival in controls. No difference in survival was observed.

Supplementary Figure S1. Number of positive and negative temporal artery biopsies (TABs) and the proportion of patients with a positive TAB during the study period.

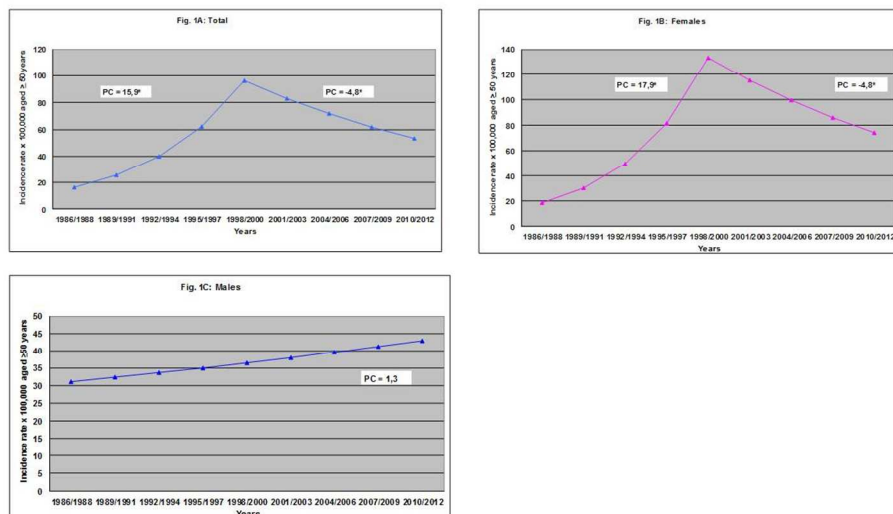


Figure 1. (A) Total age- and sex-adjusted and (B and C) gender-specific age-adjusted to 2001 Italian census population giant cell arteritis incidence rates (joinpoint regression analysis). Note: lines represent joinpoint regression lines. PC = Percentage change. * The PC is statistically significant ($p < 0.05$).
338x190mm (96 x 96 DPI)

Accepted

Figure 2

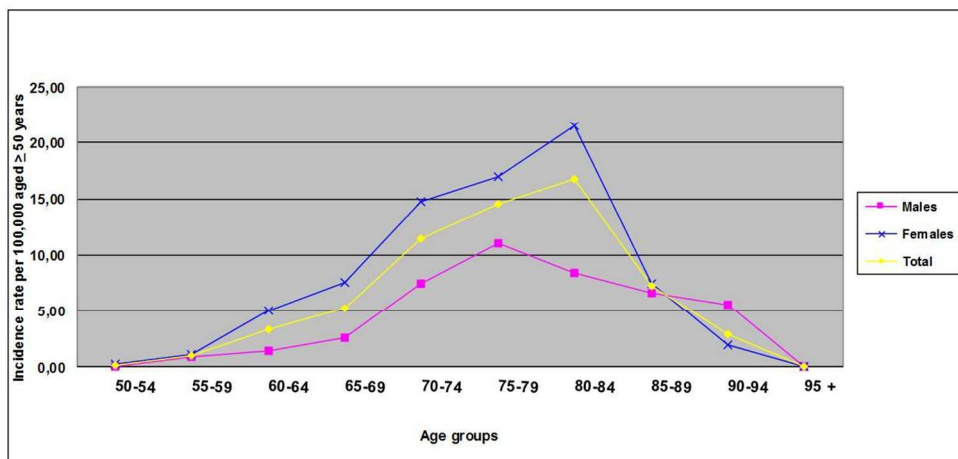


Figure 2. Annual incidence of giant cell arteritis among residents of Reggio Emilia area (provincia), 1986-2012 by sex and age group, per 100,000 population. Total incidence per 100,000 person-years population per year, age- and sex-adjusted to 2001 Italian population 50 years of age or older. Male and females incidence per 100,000 person-years population per year, age-adjusted to 2001 Italian population 50 years of age or older.
338x190mm (96 x 96 DPI)

Accepte

Figure 3

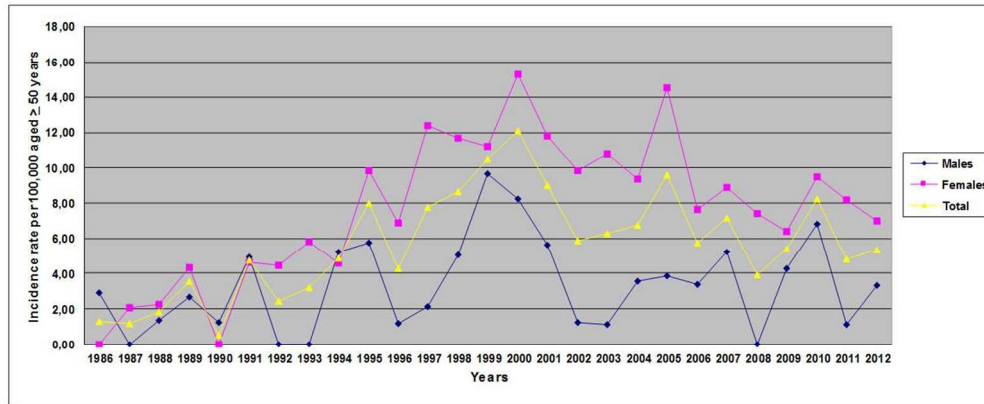


Figure 3. Total age- and sex-adjusted (to 2001 Italian census population) and males and females age-adjusted annual incidence rates for biopsy-proven GCA in Reggio Emilia area (provincia), 1986-2012, per 100,000 persons age > 50 years.
338x190mm (96 x 96 DPI)

Accepted

Figure 4

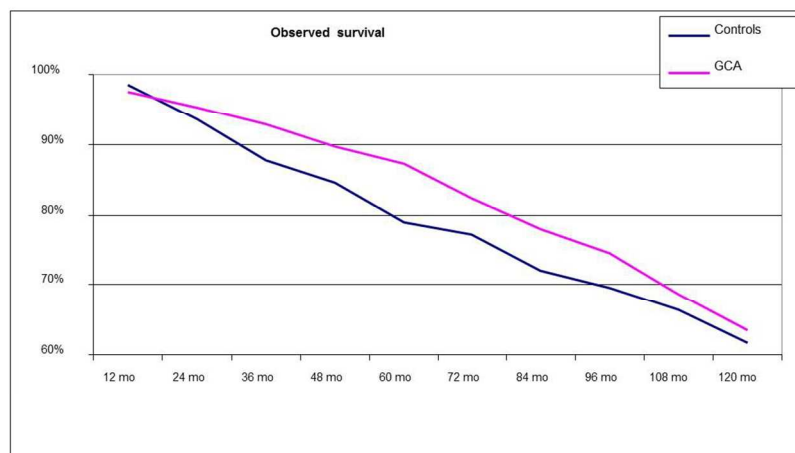
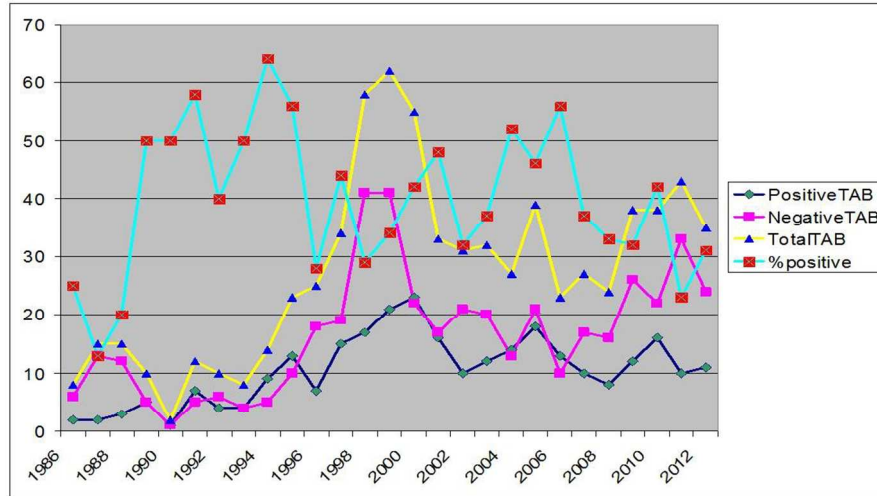


Figure 4. Survival curve for patients with giant cell arteritis compared with survival in controls. No difference in survival was observed.
338x190mm (96 x 96 DPI)

Accepted

Figure S1



338x190mm (96 x 96 DPI)

Accepted