Risk factors, coronary artery disease and mortality in giant cell arteritis: a population-based study
BOSTON UNIVERSITY
SCHOOL OF PUBLIC HEALTH

Dissertation

RISK FACTORS, CORONARY ARTERY DISEASE
AND MORTALITY IN GIANT CELL ARTERITIS:
A POPULATION-BASED STUDY

by

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MD, University of Iceland, 2000

Submitted in partial fulfillment of the
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I dedicate this work to my wife, Elfa, for all her support and patience

One morning in September 2014 about 6am, our bedroom:

Gunnar (enters the room): I've got some really good news

Elfa (half a sleep): Oh, what's that?

Gunnar: We will get a tax return this year, instead of having to pay back like we expected.

Elfa: That's nice, but I was hoping you were going to tell me that you made some progress with your analyses.
Acknowledgements

First, I want to express my gratitude towards Boston University and Boston Medical Center. It was a fortunate and defining step in my professional development to match into a clinical fellowship program in rheumatology with such strong emphasis on academia and clinical research. I had a lot of protected time to grow and nurture the nerd inside me and set the compass for the career path that I have chosen.

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of my thesis-related work and promoting its completion.
Giant Cell arteritis (GCA) is a systemic inflammatory disease that affects arteries of medium- and large size. Symptoms of GCA such as headache and fever usually promptly improve with treatment of glucocorticoids. Apart from advanced age, female sex and Northern-European descent, risk factors for GCA are unknown. Most studies have found that life expectancy for patients with GCA is not reduced compared with the general population and studies on cardiovascular disease in GCA have provided conflicting results.

Data for the studies of this thesis are drawn from the Reykjavik Study (RS) that is a general population-based cohort study with continuous surveillance for coronary heart disease and vital status. Subjects born in 1907–1934 and living in Reykjavik, Iceland or adjacent communities in 1966 were invited for study visit from 1967-1994. Information on cardiovascular risk factors were collected at study visit. Diagnosis of GCA for this study was based on re-examination of all temporal arteries biopsies (TAB) from members of the RS cohort; however, information was also obtained from the original pathology report.
Of 19,360 subjects included in the RS, 194 developed GCA during the follow-up period. Body mass index was inversely associated with the occurrence of GCA. Among men, but not women, hypertension was associated and smoking inversely associated with the occurrence of GCA. Among women, but not men, GCA was associated with coronary heart disease. Subjects with GCA had approximately 50% increase in mortality risk compared with the general population. Increase mortality was mainly observed among GCA patients based on the diagnosis of re-examination of TAB; however, no such an association was found if diagnosis of GCA was made based on the original pathology report. Those subjects were likely not clinically diagnosed with GCA, signaling that treatment for GCA might be beneficial with respect to mortality risk.
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<tbody>
<tr>
<td>AGES</td>
<td>Age Gene/Environment Study</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>cRR</td>
<td>Crude risk ratio</td>
</tr>
<tr>
<td>csHR</td>
<td>Cause-specific hazard ratio</td>
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<tr>
<td>DAG</td>
<td>Directed acyclic graph</td>
</tr>
<tr>
<td>dL</td>
<td>Deciliter</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>GC</td>
<td>Giant cell</td>
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<tr>
<td>GCA</td>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>IHA</td>
<td>Icelandic Heart Association</td>
</tr>
<tr>
<td>IR</td>
<td>Incidence rate</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence rate ratio</td>
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<tr>
<td>IPEW</td>
<td>Inverse probability of exposure weighting</td>
</tr>
<tr>
<td>IPCW</td>
<td>Inverse Probability of Censoring Weighting</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mm/hr</td>
<td>Millimeter per hour</td>
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<tr>
<td>mmol/L</td>
<td>Millimol per liter</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PMR</td>
<td>Polymyalgia rheumatica</td>
</tr>
<tr>
<td>PY</td>
<td>Person-year</td>
</tr>
<tr>
<td>RD</td>
<td>Risk difference</td>
</tr>
<tr>
<td>RS</td>
<td>Reykjavik Study</td>
</tr>
<tr>
<td>sdHR</td>
<td>subdistribution hazard ratio</td>
</tr>
<tr>
<td>SCORE</td>
<td>Systemic Coronary Risk Evaluation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form 36</td>
</tr>
<tr>
<td>stdIRR</td>
<td>Standardized incidence rate ratio</td>
</tr>
<tr>
<td>TAB</td>
<td>Temporal artery biopsy</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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General Introduction

Giant cell arteritis

Giant cell arteritis (GCA) is systemic inflammatory disease of older adults involving large- and medium-sized arteries (1, 2). The disease has a tropism towards extra-cranial vessels but involvement of large vessels is well known (3-6) and vasculitis in multiple organs has been described (7-9). GCA was first described as vasculitis in 1937 by Horton and the term “temporal arteritis” proposed for the disease (10). Other names suggested for this disease include Horton’s disease and cranial arteritis. It is not known whether GCA is a relatively new disease in humans or an ancient disease that was merely undescribed until few decades ago. Potential hints of representation of GCA in ancient artwork and articles has been reviewed (11, 12) but is not conclusive.

The incidence of GCA is highest in Northern European countries and populations of Northern-European descent with incidence rate (IR) over 20/100,000 person-years over the age of 50 (13-15), but much lower in Southern European countries and elsewhere (16-19). There is limited data on the cause of GCA. In a crude experiment (20), Horton injected samples of finely ground temporal artery into the scalp of 5 healthy volunteers who had no reaction to the foreign tissue. He also injected a similar specimen alongside a forearm vein in a patient with GCA who was in disease remission. The patient developed fever, anemia and elevated erythrocyte sedimentation rate (ESR). From this set of experiments, Horton concluded that GCA was an autoimmune disease. A few studies have reported a
cyclical pattern of the incidence of GCA with peaks in the incidence every 7 years (14, 18, 19). That has sparked speculations and the hypothesis that GCA might have an infectious or other environmental cause. Recently, preliminary reports have described identification of a species of the bacteria *Burkholderia* in the temporal arteries of patients with GCA and that vasculitis can be induced in mice by injecting them with the organism (21). At present, these findings remain to be fully described and replicated. Few studies have explored the association of cardiovascular risk factors with the occurrence of GCA (22-24).

Manifestations of GCA include constitutional symptoms resulting from systemic inflammation and ischemia in tissues served by an affected artery. GCA often has a fairly abrupt onset. Symptoms include headache, scalp tenderness, jaw claudication and visual disturbances that can include double vision, monocular- and even bilateral blindness (25-27). In addition pain and stiffness in shoulders, hips, buttocks and lower back with pronounced morning stiffness are common in GCA (27). Those musculoskeletal symptoms are identical to symptoms of polymyalgia rheumatica (PMR). PMR and GCA also share pathologic mechanisms and by some investigators and clinicians, PMR is considered an incomplete form of GCA where vascular inflammation is not present or difficult to detect (28). Inflammatory markers are usually elevated and ESR is often markedly raised (27). Prompt resolution of symptoms is usually observed with treatment; symptoms resistant to high dose glucocorticoids should lead to reevaluation of the diagnosis of GCA. Data are scarce as to how GCA affects
health related quality of life (HRQoL). One study found no association of scores on the short form 36 (SF-36) with disease manifestations of the vasculitis and sub-scores appear comparable with those from the general population (29), but another study identified that domains of HRQoL that are important to patients with GCA are poorly covered by generic HRQoL instruments (30).

Classification criteria for GCA have been developed (1) that are useful for discriminating between patients with GCA and patients with other systemic vasculitis. These criteria, however, are not useful for discriminating between GCA from various common diseases (for example sinusitis) and therefore, have very limited utility for clinical practice. While some clinical symptoms are specific for GCA, it is recommended to confirm the diagnosis with a temporal artery biopsy (TAB) as management requires committing patients to high doses of glucocorticoids for substantial period of time. However, obtaining a TAB should not delay starting treatment (31). The histologic findings on TAB that are compatible with GCA are heterogeneous and no defined subtypes that are of clinical importance have been reliably described (32–34). Giant cells (GC), from which the disease takes its name, are often seen. GC are formed by coalescence of inflammatory cells and are characteristic for the disease. Giant cells are not uniquely seen in GCA; they may occur in many other inflammatory diseases.

Glucocorticoids are the main treatment for GCA. Treatment with glucocorticoids is based on experience but not randomized controlled trials (RCT). Treatment is usually started at 40 to 60mg of prednisone or prednisolone daily. The
glucocorticoids are then tapered slowly, over a period of at least 4 to 5 months, and often much longer. Treatment with methotrexate (MTX) in addition to glucocorticoids has been shown to increase likelihood of successfully tapering glucocorticoids, reducing total dose of glucocorticoids and decreasing risk of disease relapse (35). Despite the available data on the utility of MTX for GCA, it is not universally accepted as a first-line treatment. It is possible that aspirin might prevent occurrence of visual complications (36, 37) and it is usually recommended (31). After disease remission has been induced, at least 50% of patients experience a disease relapse (38–40). Disease relapses most often manifest themselves as headache, constitutional symptoms and elevated inflammatory markers, but serious ischemic events such as vision loss can occur (38).

While GCA affects large vital arteries and being diagnosed with the disease is associated with prolonged exposure of high doses of glucocorticoids, most (41–44) but not all (45, 46) studies have found no shortened lifespan among patients with GCA compared with the general population. As the disease is always treated with glucocorticoids, data are unavailable as how treatment of disease affects mortality risk. Despite well-documented involvement of multiple vascular beds in GCA, data are conflicting as to how GCA is associated with important cardiovascular events (47–49).
The objectives of the projects included in this thesis are to study the association of cardiovascular risk factors with incident GCA and to measure the effect of GCA on risk for coronary heart disease and mortality in the general population.

**The Reykjavik Study**

*History*

The Reykjavik Study is a general population-based cohort study run by the Icelandic Heart Association (IHA) (50). The IHA was founded in 1964 with the mission to fight cardiovascular disease and study its occurrence and complications in the Icelandic population. In 1967, the Reykjavik Study was initiated in response to this stated objective of the IHA. Initial funding was obtained from successful fundraising among the Icelandic general public allowing IHA to build a research facility and support a young physician to study epidemiology at London School of Hygiene and Tropical Medicine. The World Health Organization (WHO) European regional office in Copenhagen, Denmark provided operational guidance for initiation of the study. The research facilities were equipped with the state-of-the-art devices of the time, including the nation’s first automatic chemical analyzer for blood test, x-ray machines, respiratory analyzer for pulmonary function tests, and devices for conducting exercise tolerance tests. Each day, the research facility could invite about 30 participants for a study visit.

The first research subject came to the RS in 1967 and the last study visit was in
1997. Over the 30-year period, data collection followed the same research protocol. Since 1981 IHA has participated in a multinational study (MONICA) under the oversight of WHO for standardized detection of myocardial infarctions among all Icelanders.

The IHA has collaborated extensively both internationally and with the community of physicians and epidemiology researchers in Iceland. In addition to data collected on behalf of RS, the IHA has invited investigators to collect additional data on research subjects from other sources (as is done in the projects of this thesis) and therefore, many data elements are available that are outside of the scope of cardiovascular disease. Several other population studies have been conducted that build on the RS, such as the RS offspring study and The Age-Gene Environment Study (AGES) (51). Data originating from the RS have been a major asset for epidemiological and clinical studies in Iceland. To date over 500 scientific papers and multiple PhD thesis have resulted from RS data.

Study population.
All men born between 1907 and 1934 and women born between 1908 and 1935 and living in Reykjavik, Iceland on December 1\textsuperscript{st}, 1967 (n=30,795) were invited for participation in RS. Of them, about 70\% enrolled in the study (N=\textbf{19,360}: 10,050 women and 9,310 men). The study participants were divided into six groups (A-F) based on their birth date within a month. Examination took place in six stages from 1967–1996 (stage I: 1967–1969, stage II: 1970–1972, stage III:
1974–1979, stage IV: 1979–1984, stage V: 1985–1991 and stage VI: 1991–1996). Groups were examined at one examination stage except one group (B), which was designed for longitudinal follow-up and was examined in all six stages. Men and women were examined in separate years for more efficient clinic operation. At the last stage of the study (stage VI), only subjects who had reached 70 years of age were invited. Timeline of events are depicted in Figure 1. Cardiovascular disease is the primary focus of the RS, and the effect of cardiovascular risk factors (hypertension, smoking, diabetes mellitus and serum cholesterol) on cardiovascular events have been found to be almost identical to data originating from 12 European cohorts compiled as part of the Systemic Coronary Risk Evaluation project (SCORE) (52). Loss to follow-up and vital status are only due to emigration, which during the study’s follow-up time has been low, with only 0.5% of the RS cohort having emigrated from Iceland (53).
The Dungal repository of histopathological specimens

The Dungal repository was initiated in 1934 by Niels Dungal, former professor of pathology and chancellor of University of Iceland. Under Dr. Dungal’s oversight all histopathological specimens obtained among Icelanders for clinical purposes were collected for permanent storage. To date the three pathology laboratories in Iceland continue to submit their specimens to repository, which currently has over 500,000 specimens. The specimens are stored in the original blocks of paraffin wax, but not on the glass slides, allowing for creation of new pathologic slides if quality of existing slides deteriorates or if new staining techniques emerge. This nationwide collection naturally includes all TABs obtained in
Iceland during the study period of the RS and allowed for re-staining of old TAB (where the original staining had fainted), for the purpose of studies included in this thesis.
References


Risk Factors, Coronary Heart Disease and Mortality in Giant Cell Arteritis – A Population-Based Study

Study A: Cardiovascular Risk Factors and Incident Giant Cell Arteritis

Gunnar Tómasson

Word count: 4,303 excluding abstract, tables, legends and references
Abstract

**Objective:** To assess the strength of the effect of cardiovascular risk factors on incidence of GCA within a longitudinal cohort study where detailed information on cardiovascular risk factors has been collected.

**Methods:** Data from the Reykjavik Study (RS), a population-based, prospective cohort study with a primary focus on cardiovascular disease, were used. All persons born in 1907–1935 who were living in Reykjavik, Iceland or in adjacent communities on December 1, 1967 were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors: smoking habits, blood pressure, diabetes, body mass index, and serum cholesterol was obtained. All temporal artery biopsies (TABs) obtained on members of the RS cohort were identified in all three pathology laboratories in Iceland during the period 1961–2009. All TABs were re-examined in a protocolled and blinded fashion by a single pathologist with expertise in vascular pathology. Incidence was calculated for exposed and unexposed subjects and incidence rate ratios (IRR) presented with 95% confidence intervals.

**Results:** For this analysis, data from 19,241 subjects who were followed for a median 23.1 (IQR: 17.6–29.4) years after the age of 50, were used. Over 444,126 person-years of follow-up, 194 subjects had developed GCA, corresponding to an incidence rate of 43.6 (95% CI: 37.8–50.2) per 100,000 person-years. Woman had increased incidence of GCA compared with men, IRR = 1.93 (95% CI: 1.42–2.62). Among cardiovascular risk factors, high BMI
was inversely associated with GCA, with those of BMI>25kg/m² having IRR=0.66 (95% CI: 0.50–0.88) and smoking was inversely associated with GCA among men, but not women,

Conclusion: This study shows a very high incidence of GCA in Iceland, greater than previously reported. A high BMI is protective for the occurrence of GCA and smoking may be protective for the occurrence of the disease among men.
Introduction
Apart from advanced age, female sex, and Northern European descent, risk factors for GCA are not well defined. There is limited information on the association between traditional cardiovascular risk factors and GCA. Twenty years ago, the question about the relationship between GCA and common vascular disease was raised by a description of an association of GCA with smoking, peripheral arterial disease, and angina (1). More recent studies have described an association between smoking (2, 3) and GCA and an inverse association of serum cholesterol (2) and body mass index (BMI) with GCA. Limitations of previous studies include retrospective designs with reliance on self-report of risk factors obtained after the outcome of interest (GCA) has occurred. Few studies have reported a cyclical pattern in the incidence of GCA with peaks occurring every 5–10 years (4–6), while others have not (7, 8).

The objective of this study was to assess the strength of the effect of cardiovascular risk factors on incidence GCA within a longitudinal cohort study where detailed information on cardiovascular risk factors was obtained, and to explore if incidence follows a cyclical pattern similar to what has been described in other cohort studies.
Methods

Study Design
To examine the effect of cardiovascular risk factors on incident GCA, a cohort study design was used. Ethical approvals were obtained from Boston Medical Center Institutional Review Board and the National Bioethics Committee in Iceland.

Study population
The Reykjavik Study (RS) has been described in a detail previously (see page 4). Briefly, persons, who were born in 1907–1935 and living in Reykjavik or in adjacent communities, Iceland on December 1, 1967, were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors was obtained. Individuals who died before the age of 50 (at which age, follow-up for this study started) and subjects with GCA at baseline were excluded from this analysis.

Baseline assessment
Baseline data was obtained from all members of the RS cohort in a standardized fashion during the whole study period. The examination was carried out during two separate visits scheduled approximately 1 week apart. The former visit included a blood draw after an overnight fasting and anthropometric measures including height and weight. During the second visit, a physical examination was performed. The following baseline data used in studies of this thesis is listed
below:

1. **Hypertension**

   Blood pressure was measured at both visits, in a supine position after 5 minutes of rest and was recorded to the nearest 2mmHg; a mercury sphygmomanometer (Erka-meter wall model; Richard Kallmeyer Nachforschung, Badtölz, Germany) was used. A mean value of two blood pressure measurements was used for analysis. Hypertension was defined as systolic blood pressure $\geq 140$ mmHg or medication use to lower blood pressure.

2. **Smoking**

   Information on smoking was obtained through questionnaire and smoking status defined as never, former or current smoker.

3. **Diabetes Mellitus (DM)**

   DM was defined as fasting serum glucose $\geq 110$ mg/dL or use of medications to treat diabetes mellitus.

4. **Total cholesterol**

   Total cholesterol was measured in serum after overnight fasting. To explore potential non-linear association of total cholesterol with GCA, associations of serum cholesterol quartiles with GCA were examined in tabular analysis but in regression analyses total cholesterol was entered as a continuous variable.
5. Body mass index (BMI)
BMI calculated as weight in kg/(height in meters)$^2$ was used to define undeweight (BMI<18.5), normal weight (18.5≤BMI<25) overweight (25≤BMI<30) and obese (BMI>30).

6. Inflammation
The effect of systemic inflammatory response as measured by erythrocyte sedimentation rate (ESR), obtained from all members of RS cohort during a study visit. It was studied after grouping into three categories: 0 to 10, 11 to 20, and 21 and higher; it was also included as a continuous linear predictor in a regression analysis.

Follow-up and outcome assessment
All subjects were followed from the time of study visit or the age of 50, whichever occurred later until the time of death, December 31$^{st}$ 2008, or the outcome of GCA, whichever occurred first. The outcome of GCA was defined as a diagnostic temporal artery biopsy at $i)$ Department of Pathology, University of Iceland; $ii)$ a private pathology laboratory in Reykjavik; or $iii)$ the Pathology Laboratory at Akureyri Hospital. Together, these laboratories have computerized records back to 1960 and serve the whole Icelandic population. Information was linked to the RS through the Social Security Number. All temporal artery biopsies obtained from members of the RS cohort for clinical purpose were re-
examined according to a predefined protocol by a single pathologist with expertise in pathology of the vasculitides. In this analysis, we defined a subject to have diagnosis of GCA if his/her biopsy showed infiltration of inflammatory cells to the vessel wall with the exception of very scant inflammatory cells in the outermost layer (tunica adventitia) of the vessel wall in an otherwise normal vessel.

**Statistical Analysis**

Secular incidence of GCA and TAB was calculated as number of events each calendar year divided by person-years contributed by members of the RS cohort that year. RS is a fixed cohort with all its members born in a 28 year period, between 1907 and 1935 but some subjects contributed longer follow-up time, up to 41 years (from 1967–2008) In this situation there is not enough age-overlap between early and later calendar times to fully assess any secular incidence trend that is standardized according to age; at the beginning of the study period (1967), the oldest subjects are younger than the youngest subjects in 2008. Therefore, age standardization was done in three periods to evaluate for secular changes in occurrence of temporal artery biopsies.

To assess for if secular incidence of GCA in the RS cohort followed a cyclical pattern with peaks, a sine curve of cycle-length 7 years was fit and the seasonal intensity estimator calculated as previously described (9): The total period during which incident GCA occurred among member of the cohort (1980–2008) was divided to four 7 year cycles (1980–1986, 1987–1993, 1994–2000 and 2001–
2007) (subjects with GCA in 2008 were omitted from this analysis). Then total number of subjects with GCA in the first sector of the cycle, $N_1$ was the sum of subjects with GCA in the years 1980, 1987, 1994 and 2001, the number of subjects for the second sector, $N_2$, was the number of subjects with GCA in the years 1981, 1988, 1995 and 2002 etc. The seasonal estimator, $R$ which is the ratio between the peaks and troughs in the incidence of the fitted sine curve, was calculated as

$$R = \frac{1+\alpha}{1-\alpha}.$$ 

Where $\alpha$ is the hemi amplitude of the fitted sine curve calculated as

$$\alpha = 2 \sqrt{\frac{D^2 k^2 - N}{N(N-1)}}.$$ 

Where $k$ is set to 7 and $N$ is the total number of subjects with GCA during the period under study and $D$ calculated as

$$D = \sqrt{\left(\frac{1}{k} \sum_{i=1}^{k} N_i \sin(\theta_i)\right)^2 + \left(\frac{1}{k} \sum_{i=1}^{k} N_i \cos(\theta_i)\right)^2}.$$ 

Where $\theta_i = 2\pi i / k$. The measure of cyclical occurrence with peak every 7 years is expressed as the seasonal estimator $R$ with 95% CI. The CIs for this estimate are calculated in usual fashion where the standard error for $\ln(R)$ is:
\[
\frac{2\sqrt{\text{VAR}(\alpha)}}{(1+\alpha)(1-\alpha)}
\]

Where \text{VAR}(\alpha) is \(2/N\)

For evaluation of the effect of cardiovascular risk factors on the occurrence of GCA, the incidence rate (IR) for subjects was calculated using the number of incident GCA during the person-time contributed by the exposed with each cardiovascular risk factor. The IR was calculated among the exposed and unexposed subjects and effect of each exposure is expressed as an incidence rate ratio (IRR) with 95% confidence intervals (CI). The effect of each cardiovascular risk factor was explored in the strata of sex and age categorized as younger (50 to 70 years) and older than 70 years. To adjust for potential confounding, standardized IRR were calculated using person-time contributed by the exposed group as weights. In the light of scarce previous data and therefore limited insight to the potential causal pathways from cardiovascular risk factors to GCA, standardized effect estimates were calculated across strata of all the other cardiovascular risk factors. To explore the magnitude of confounding, relative risk due to confounding was calculated as \(\frac{\text{IRR}_{\text{STD}}}{\text{IRR}_{\text{CRUDE}}}\). As we found substantial effect measure modification by sex, effects of all cardiovascular risk factors on incident GCA are reported separately for men and women.

In addition, a Cox proportional hazards regression was used to examine the association between each risk factor and risk of GCA. As age is very strong risk
factor for GCA, we chose subjects’ age as the time-scale for the regression analysis; age was also included as an independent variable (10). For risk factors that appeared to be of particular interest (smoking), survival curves adjusted for other risk factors with inverse probability weights were constructed (11).

As cardiovascular risk factors were obtained at a single time-point, often many years before GCA, cardiovascular risk factors might have changed over time. To evaluate for the effect for changing risk factors in this cohort with respect to GCA risk, analysis with time-varying predictors was done on the subset that came in for repeated study visits and compared with those that only came for one visit. Effects of cardiovascular risk factors were also calculated stratified for the period of their study visit (1970 and earlier, 1971–1980 and after 1980). As we found that TABs were exceedingly rarely performed on members of the RS cohort before 1980, in a supplemental analysis we explored the effect of cardiovascular risk factors on incident GCA using only person-time contributed after January 1st 1980.

In the survival analysis there are two types of censoring events: i) censoring at the time of death and ii) administrative censoring at the end of study follow-up. The assumption of uninformative censoring has to be made for the analyses of time to GCA. If this assumption is not met, for example if cardiovascular risk factors are truly risk factors for mortality but not GCA, that will adversely affect the estimate on the cause-specific hazard ratio (csHR) of cardiovascular risk factors on GCA by preferentially removing exposed individuals from the risk set.
Therefore, the true risk from cardiovascular risk factors on GCA is both a function of csHR for the event of interest and the competing event (death)(12). In an attempt to measure the effect of cardiovascular risk factors on GCA accounting for the competing event (death), the subdistribution hazard ratio (sdHR) was calculated according to the Fine and Gray method (6). Using that method, both subjects that remain at risk for GCA and those that have died at time T are retained in the risk set (every subject fulfilling the criteria \( Y \neq \text{GCA} \) or \( Y = \text{death} \mid \text{time}<T \)). For calculations of the values for the covariates in the model, \( \beta \), that best fit the data (maximal likelihood calculations (score equations)), a weighted score function is used. Weights for all subjects in the risk set at each failure time, T, are calculated from inverse probability of censoring weighting (IPCW) using the Kaplan-Meier estimate at that time.

SAS 9.2 (SAS institute Cary, NC) was used for all calculations, a SAS macro (appendix A) was developed for calculations of standardized rate ratios. The macro was developed based on (and tested for errors against) Episheet (13) for calculations of standardized rate ratios. A SAS macro (11) for graphically depicting adjusted survival curves inverse probability weights was used with minor modifications. A SAS macro was developed for calculating the seasonality estimator (appendix B) The statistical package cmprsk in R was used for calculations subdistribution hazards ratios according to the Fine and Gray method (12).
Results

Study population
There were 19,360 subjects that participated in the Reykjavik Study and came for a study visit from October 26th 1967 to April 23rd 1996, about 70% of those originally invited. Twelve subjects had a temporal artery biopsy diagnostic of GCA before their RS study visit and are excluded from the analysis. One hundred and seven subjects died before the age of 50 and therefore contributed no person-time to this analysis. Therefore, 19,241 subjects are included in this analysis.

Baseline characteristics
Of the 19,241 subjects included, there were 10,006 women and 9,235 men. The baseline characteristics at the first visit to the RS (or last visit before the age of 50 when subjects started to contribute follow-up time) are shown in Table A.1. There was very high prevalence of tobacco smoking in this cohort. Only 21% of the men and 44% of the women were never smokers. Less than 5% study subjects had diabetes mellitus at baseline. There were considerable secular changes in smoking habits during the study visit period: 62% of men and 47% of women who came for their first study visit between 1967–1970 were current smokers, whereas 41% of men and 34% of women who came for their first study visit after 1980 were current smokers. There was clear trend for increase in BMI and prevalence of diabetes mellitus. However, as very few subjects had DM, no
meaningful estimates of the association of DM with incident GCA could be obtained. Other risk factors were more stable during follow-up.

**Temporal artery biopsies**

Of the 19,241 subjects, 703 underwent TAB. TABs were rarely performed on members of this cohort until about 1980, but then there was an abrupt increase. Although maximal numbers of biopsies were not obtained from members of this cohort until 1990 that was probably appropriate given the age distribution of the cohort. Crude incidence of temporal artery biopsies in the RS cohort is shown in the Figure A.1 and age-standardized incidence in Figure A.2.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Women (N=10,006 PY=238,128)</th>
<th>Men (N=9,235 PY=205,999)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 to 60 years</td>
<td>56,267 (24%)</td>
<td>56,036 (27%)</td>
</tr>
<tr>
<td>60 to 70 years</td>
<td>81,095 (34%)</td>
<td>72,552 (35%)</td>
</tr>
<tr>
<td>70 to 80 years</td>
<td>69,807 (29%)</td>
<td>57,157 (28%)</td>
</tr>
<tr>
<td>after 80 years</td>
<td>30,958 (13%)</td>
<td>20,254 (10%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>86,280 (36%)</td>
<td>82,439 (40%)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>110,609 (46%)</td>
<td>48,078 (23%)</td>
</tr>
<tr>
<td>former</td>
<td>37,712 (16%)</td>
<td>50,868 (25%)</td>
</tr>
<tr>
<td>current smoking</td>
<td>89,807 (38%)</td>
<td>107,024 (52%)</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.7</td>
<td>51,849 (22%)</td>
<td>51,849 (22%)</td>
</tr>
<tr>
<td>5.7–6.3</td>
<td>54,791 (23%)</td>
<td>54,791 (23%)</td>
</tr>
<tr>
<td>6.4–7.1</td>
<td>62,345 (26%)</td>
<td>62,345 (26%)</td>
</tr>
<tr>
<td>&gt;7.2</td>
<td>68,857 (29%)</td>
<td>68,857 (29%)</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td>6,261 (3%)</td>
<td>6,951 (3%)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>underweight (&lt;18.5)</td>
<td>4,494 (2%)</td>
<td>1,379 (1%)</td>
</tr>
<tr>
<td>normal weight (18.5–24.9)</td>
<td>124,511 (53%)</td>
<td>86,237 (42%)</td>
</tr>
<tr>
<td>overweight (25.0–24.9)</td>
<td>81,240 (34%)</td>
<td>97,885 (48%)</td>
</tr>
<tr>
<td>obese (≥30)</td>
<td>26,481 (11%)</td>
<td>19,903 (10%)</td>
</tr>
<tr>
<td><strong>ESR (mm/hr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>135,895 (57%)</td>
<td>168,653 (82%)</td>
</tr>
<tr>
<td>11–20</td>
<td>66,659 (28%)</td>
<td>28,146 (14%)</td>
</tr>
<tr>
<td>&gt;21</td>
<td>34,037 (14%)</td>
<td>8,514 (4%)</td>
</tr>
</tbody>
</table>

Table A.1. Baseline characteristics of the study subjects. Variables expressed as number of person-years (percentage) in each strata (N=number of subjects, PY=person-years, L=liter, DM=diabetes mellitus, BMI=body mass index, ESR=erythrocyte sedimentation rate, mm=millimeter, hr=hour).
Figure A.1. Crude incidence rate of temporal artery biopsies and GCA for people age 50 or greater. The figure shows the secular crude incidence of GCA and first temporal artery biopsy among members of the RS cohort. On the x-axis is calendar time in years and on the y-axis the incidence per 100,000 person-years above the age of 50. The numbers below the x-axis is number of subjects at the age 65-80 (the age period at which 75% of patients with GCA were, when diagnosed with GCA) that are contributing person-time (TAB= temporal artery biopsy, GCA= Giant cell arteritis, RS= Reykjavik Study).
Figure A.2. Age-standardized incidence of temporal artery biopsies for different age groups at three secular periods:  
B. Incidence of biopsies among 60–75 year old subjects of RS in 1980 to 1995, age-standardized to the 1988 population, and  
C. Incidence of temporal artery biopsies in 1993 to 2008 standardized to the 2000 population.

Elevated ESR was associated with having a TAB performed both among men and women (Table A.2). Among women, ever smoking was modestly associated with TAB and in men, HTN was associated with TAB.

Incidence of GCA

The 19,241 study subjects were followed for a mean 24.3 years after they achieved the age of 50 (IQR: 17.6–29.8). During 444,126 person-years of the follow-up period, 194 subjects had developed GCA, representing an incidence rate of 43.6 (95% CI: 37.8–50.2) per 100,000 person-years after the age of 50.
<table>
<thead>
<tr>
<th></th>
<th>Women IRR</th>
<th>Men IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.10(0.92-1.32)</td>
<td>1.52(1.16-2.01)</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>1.27(1.06-1.51)</td>
<td>0.89(0.65-1.21)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.7</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>5.7-6.3</td>
<td>0.96(0.73-1.27)</td>
<td>1.28(0.86-1.91)</td>
</tr>
<tr>
<td>6.4-7.1</td>
<td>1.19(0.92-1.55)</td>
<td>1.39(0.94-2.06)</td>
</tr>
<tr>
<td>&gt;7.2</td>
<td>1.04(0.81-1.35)</td>
<td>1.23(0.80-1.88)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>underweight (&lt;18.5)</td>
<td>0.51(0.21-1.24)</td>
<td>0.96(0.13-6.91)</td>
</tr>
<tr>
<td>normal weight (18.5-24.9)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>overweight (25.0-24.9)</td>
<td>0.94(0.78-1.14)</td>
<td>0.99(0.74-1.32)</td>
</tr>
<tr>
<td>obese (≥30)</td>
<td>0.76(0.56-1.04)</td>
<td>0.85(0.50-1.42)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 10</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>11 to 20</td>
<td>1.46(1.18-1.79)</td>
<td>2.21(1.60-3.06)</td>
</tr>
<tr>
<td>21 and higher</td>
<td>2.41(1.94-3.00)</td>
<td>3.03(1.89-4.85)</td>
</tr>
</tbody>
</table>

Table A.2. Age standardized analysis of cardiovascular risk factors with having temporal artery biopsy done. (IRR=incidence rate ratio, L=liter, BMI=body mass index, IRR=incidence rate ratio, ESR=Erythrocyte sedimentation rate, mm=millimeter, hr=hour)

The IR fluctuated somewhat between calendar years (Figure A.2) and analysis was consistent with that cyclical occurrence in GCA following a sine curve with seasonality estimator of R=2.07 (95% CI 1.31–3.26). The mean age of diagnosis of GCA was 73.4 years (range: 56.1–90.0 years) and 71% subjects were between 65 and 80 years of age when they had a TAB diagnostic of GCA. Women had higher risk of GCA than men, especially among those less than 80 years (Table A.3).
### Table A.3. Age- and sex-specific incidence rate of GCA

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>GCA</th>
<th>PY</th>
<th>IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>0.5</td>
<td>4</td>
<td>56,267</td>
</tr>
<tr>
<td>50 to 60</td>
<td>0.6</td>
<td>39</td>
<td>81,095</td>
<td>48.1</td>
</tr>
<tr>
<td>60 to 70</td>
<td>0.6</td>
<td>74</td>
<td>69,807</td>
<td>106</td>
</tr>
<tr>
<td>70 to 80</td>
<td>0.6</td>
<td>19</td>
<td>30,958</td>
<td>61.4</td>
</tr>
<tr>
<td>over 80</td>
<td>0.6</td>
<td>1</td>
<td>56,036</td>
<td>1.8</td>
</tr>
<tr>
<td>50 to 60</td>
<td>0.6</td>
<td>15</td>
<td>72,552</td>
<td>20.7</td>
</tr>
<tr>
<td>60 to 70</td>
<td>0.6</td>
<td>25</td>
<td>57,157</td>
<td>43.7</td>
</tr>
<tr>
<td>70 to 80</td>
<td>0.6</td>
<td>17</td>
<td>20,254</td>
<td>83.9</td>
</tr>
<tr>
<td>over 80</td>
<td>0.6</td>
<td>5</td>
<td>112304</td>
<td>4.5</td>
</tr>
<tr>
<td>50 to 60</td>
<td>0.6</td>
<td>54</td>
<td>153646</td>
<td>35.1</td>
</tr>
<tr>
<td>60 to 70</td>
<td>0.6</td>
<td>99</td>
<td>126963</td>
<td>78.0</td>
</tr>
<tr>
<td>70 to 80</td>
<td>0.6</td>
<td>36</td>
<td>51213</td>
<td>70.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Both sexes</th>
<th>GCA</th>
<th>PY</th>
<th>IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 to 60</td>
<td>0.5</td>
<td>5</td>
<td>112304</td>
<td>4.5</td>
</tr>
<tr>
<td>60 to 70</td>
<td>0.5</td>
<td>54</td>
<td>153646</td>
<td>35.1</td>
</tr>
<tr>
<td>70 to 80</td>
<td>0.5</td>
<td>99</td>
<td>126963</td>
<td>78.0</td>
</tr>
<tr>
<td>over 80</td>
<td>0.5</td>
<td>36</td>
<td>51213</td>
<td>70.3</td>
</tr>
</tbody>
</table>

**Association of cardiovascular risk factors with incident GCA**

Several cardiovascular risk factors were associated with incident GCA. The effect of cardiovascular risk factors stratified according to age and sex is presented in **Table A.4** and standardized effect estimates in **Table A.5**. There was an inverse association between tobacco smoking and GCA among men. Compared with never smokers, IRR for GCA for ever smokers was 0.51 (95% CI: 0.30–0.87). However, such an association was not observed among women. The corresponding IRR was 1.12 (95% CI: 0.80–1.57). BMI was inversely associated with GCA, especially among women. Hypertension was strongly associated with risk of GCA among men over 70 years of age (IRR= 3.04, 95% CI: 2.00–4.40).
CI: 1.58–5.86), but such an effect was not observed in the other strata of age and sex. Almost identical results were obtained in a Cox proportional hazards regression analysis (Table A.6). Cumulative incidence plots for of smoking among men and women adjusted for other risk factors are shown in Figure A.3.

As there were secular changes in smoking habits during the conductance of the RS, we examined the effect of smoking in strata of calendar-period of study visit. The association of smoking on incident GCA was modified by the decade of study visit, especially among women. Among women that came for their study visit before 1970, smoking was inversely associated with GCA, but among those that came after 1980, smoking was positively associated with GCA (Table A.7). There was less effect-measure modification observed with smoking in men by time of study visit.

Figure A.3. Cumulative incidence of GCA. Cumulative GCA-incidence curves for ever-smokers vs. never smokers among women and men in the RS cohort adjusted for HTN, BMI and cholesterol
Table A.4. Incident GCA stratified according to age, sex and cardiovascular risk factors. Pearson-years are expressed in thousands of years (L=liter, BMI=body mass index, PY=Pearson-years IR=incidence rate, IRR=incidence rate ratio, ESR=Erythrocyte sedimentation rate)

<table>
<thead>
<tr>
<th></th>
<th>Age 50 to 70</th>
<th></th>
<th></th>
<th></th>
<th>After age 70</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GCA</td>
<td>PY</td>
<td>IR</td>
<td>IRR</td>
<td>GCA</td>
<td>PY</td>
<td>IR</td>
<td>IRR</td>
</tr>
<tr>
<td><strong>WOMEN</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>93.3</td>
<td>32.2</td>
<td>1 (ref)</td>
<td>58</td>
<td>58.5</td>
<td>99.1</td>
<td>1 (ref)</td>
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<tr>
<td>Yes</td>
<td>13</td>
<td>44.0</td>
<td>29.5</td>
<td>0.92 (0.48-1.76)</td>
<td>35</td>
<td>42.2</td>
<td>82.9</td>
<td>0.84 (0.55-1.27)</td>
</tr>
<tr>
<td>Smoking</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>17</td>
<td>60.5</td>
<td>28.1</td>
<td>1 (ref)</td>
<td>44</td>
<td>50.0</td>
<td>87.9</td>
<td>1 (ref)</td>
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<tr>
<td>Ever</td>
<td>26</td>
<td>76.7</td>
<td>33.9</td>
<td>1.21 (0.65-2.22)</td>
<td>49</td>
<td>50.7</td>
<td>96.6</td>
<td>1.1 (0.73-1.65)</td>
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<tr>
<td>Cholesterol</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.3 mmol/L</td>
<td>19</td>
<td>66.4</td>
<td>28.6</td>
<td>1 (ref)</td>
<td>39</td>
<td>40.2</td>
<td>96.9</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>≥6.3 mmol/L</td>
<td>24</td>
<td>70.8</td>
<td>33.9</td>
<td>1.19 (0.65-2.16)</td>
<td>54</td>
<td>60.4</td>
<td>89.4</td>
<td>0.92 (0.61-1.39)</td>
</tr>
<tr>
<td>BMI*</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>24</td>
<td>77.0</td>
<td>31.2</td>
<td>1 (ref)</td>
<td>61</td>
<td>52.0</td>
<td>117</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>≥25</td>
<td>17</td>
<td>59.7</td>
<td>28.5</td>
<td>0.91 (0.49-1.7)</td>
<td>30</td>
<td>48.0</td>
<td>62.5</td>
<td>0.53 (0.34-0.82)</td>
</tr>
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<td>ESR**</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≤20 mm/hour</td>
<td>34</td>
<td>117</td>
<td>29</td>
<td>1 (ref)</td>
<td>72</td>
<td>85.3</td>
<td>84.5</td>
<td>1 (ref)</td>
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<tr>
<td>&gt;20 mm/hour</td>
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<td>19.3</td>
<td>46.7</td>
<td>1.61 (0.77-3.36)</td>
<td>20</td>
<td>14.8</td>
<td>135</td>
<td>1.60 (0.98-2.63)</td>
</tr>
<tr>
<td><strong>MEN</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>No</td>
<td>11</td>
<td>78.9</td>
<td>13.9</td>
<td>1 (ref)</td>
<td>13</td>
<td>44.7</td>
<td>29.1</td>
<td>1 (ref)</td>
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<td>10.1</td>
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<td>29</td>
<td>32.7</td>
<td>88.6</td>
<td>3.04 (1.58-5.86)</td>
</tr>
<tr>
<td>Smoking</td>
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<td>7</td>
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<td>9</td>
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<td>26</td>
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<td>45.2</td>
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<tr>
<td>&lt;6.3 mmol/L</td>
<td>9</td>
<td>66.7</td>
<td>13.5</td>
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<td>20</td>
<td>40.5</td>
<td>49.4</td>
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<td>61.6</td>
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<td>0.84 (0.31-2.27)</td>
<td>22</td>
<td>36.7</td>
<td>59.9</td>
<td>1.21 (0.66-2.22)</td>
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<tr>
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<td>54.8</td>
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<td>18</td>
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<tr>
<td>≥25</td>
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<td>10.9</td>
<td>0.75 (0.28-1.99)</td>
<td>24</td>
<td>44.4</td>
<td>54</td>
<td>0.98 (0.53-1.81)</td>
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<td>15</td>
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<td>42</td>
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</tr>
<tr>
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<td>18.2</td>
<td>1.49 (0.2-11.29)</td>
<td>0</td>
<td>3.00</td>
<td>0</td>
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Table A.5. Age-standardized- and CVD risk factor standardized- estimates of effects of cardiovascular risk factors on GCA. Standardized incidence rate ratios are expressed with 95% confidence intervals. Relative risk due to confounding by cardiovascular risk factors is expressed with cRR (IRR/stdIRR). (IRR=incidence rate ratio, CVD = cardiovascular disease, cRR=Relative risk due to confounding, BMI=body mass index, ESR=erythrocyte sedimentation rate)

*Age standardization was done in 4 strata i) 50 to 60 year, ii) 61 to 70 years, iii) 71 to 80 years and iv) after 80 years.

**CVD Risk factor standardization was performed by calculating stratum specific incidence rate according to Hypertension, ever smoking, cholesterol (quartiles), BMI in 4 categories (listed in table) and ESR in 3 categories (listed in table)

***No outcome events occurred in the strata.

<table>
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<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
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<td>Age</td>
<td>CVD risk</td>
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<td>cRR</td>
<td>IRR</td>
<td>cRR</td>
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<tr>
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<td>0.99(0.69-1.41)</td>
<td>1.13</td>
<td>0.51(0.30-0.87)</td>
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<td>Cholesterol (mmol/L)</td>
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<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>5.7-6.3</td>
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<td>0.97(0.57-1.66)</td>
<td>0.99</td>
<td>0.89(0.43-1.84)</td>
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<td>6.4-7.1</td>
<td>1.06(0.65-1.72)</td>
<td>0.99(0.59-1.66)</td>
<td>1.07</td>
<td>1.14(0.58-2.27)</td>
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<td>&gt;7.2</td>
<td>0.89(0.54-1.45)</td>
<td>0.82(0.47-1.43)</td>
<td>1.09</td>
<td>0.88(0.40-1.92)</td>
</tr>
<tr>
<td>BMI &lt;18.5</td>
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<tr>
<td>18.5-24.9</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>25.0-24.9</td>
<td>0.70(0.48-1.02)</td>
<td>0.75(0.51-1.12)</td>
<td>0.93</td>
<td>0.90(0.52-1.54)</td>
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<tr>
<td>≥30</td>
<td>0.31(0.14-0.71)</td>
<td>0.31(0.13-0.74)</td>
<td>1.00</td>
<td>0.85(0.33-2.22)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
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<tr>
<td>0-10</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>11-20</td>
<td>0.99(0.66-1.48)</td>
<td>0.99(0.64-1.53)</td>
<td>1.00</td>
<td>1.44(0.76-2.73)</td>
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<tr>
<td>&gt;20</td>
<td>1.61(1.04-2.48)</td>
<td>1.75(1.04-2.96)</td>
<td>0.92</td>
<td>0.42(0.06-3.03)</td>
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<td></td>
<td>Women</td>
<td>Men</td>
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<td>SubHR</td>
<td>HR</td>
<td>SubHR</td>
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<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td>Ever smoking</td>
<td>1.12 (0.80-1.57)</td>
<td>0.98 (0.70-1.38)</td>
<td>0.51 (0.30-0.86)</td>
<td>0.43 (0.25-0.73)</td>
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<tr>
<td>Cholesterol (mmol/L)</td>
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<td></td>
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<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>5.7-6.3</td>
<td>0.96 (0.57-1.61)</td>
<td>1.03 (0.61-1.72)</td>
<td>0.90 (0.43-1.85)</td>
<td>0.92 (0.44-1.91)</td>
</tr>
<tr>
<td>6.4-7.1</td>
<td>1.07 (0.65-1.74)</td>
<td>1.16 (0.71-1.89)</td>
<td>1.16 (0.58-2.30)</td>
<td>1.18 (0.58-2.36)</td>
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<tr>
<td>&gt;7.2</td>
<td>0.93 (0.57-1.52)</td>
<td>1.03 (0.63-1.68)</td>
<td>0.90 (0.41-1.96)</td>
<td>0.89 (0.41-1.93)</td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>&lt;18.5</td>
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<tr>
<td>18.5-24.9</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>25.0-24.9</td>
<td>0.72 (0.49-1.04)</td>
<td>0.74 (0.51-1.07)</td>
<td>0.89 (0.52-1.53)</td>
<td>0.90 (0.53-1.55)</td>
</tr>
<tr>
<td>≥30</td>
<td>0.32 (0.14-0.74)</td>
<td>0.32 (0.14-0.72)</td>
<td>0.84 (0.33-2.21)</td>
<td>0.75 (0.29-1.97)</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
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<tr>
<td>0-10</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>11-20</td>
<td>0.99 (0.66-1.48)</td>
<td>0.98 (0.65-1.47)</td>
<td>1.50 (0.79-2.84)</td>
<td>1.34 (0.72-2.50)</td>
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<tr>
<td>&gt;20</td>
<td>1.62 (1.05-2.49)</td>
<td>1.47 (0.95-2.26)</td>
<td>0.44 (0.06-3.17)</td>
<td>0.30 (0.04-2.23)</td>
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</tbody>
</table>

Table A.6. Effect of cardiovascular risk factors on GCA. Estimates of effects are expressed with hazards ratios with 95% confidence intervals from Cox proportional hazards regression and subdistribution hazards ratio accounting for the competing event of mortality adjusted for hypertension, ever smoking, cholesterol and BMI (BMI=body mass index, ESR=erythrocyte sedimentsations rate).
Table A.7. The association of smoking status with incident GCA stratified for decade of study visit to the RS. Estimates of effects are presented as standardized* IRR with 95% confidence intervals.

* standardization was for age (done in 4 strata i) 50 to 60 year, ii) 61 to 70 years, iii) 71 to 80 years and iv) after 80 years) hypertension, cholesterol (in quartiles), BMI (in 4 categories: underweight, normal weight, overweight and obese) and ESR (in three categories: 0–10, 11–20 and 21 and greater)
Supplemental Analysis 2- Survival analysis accounting for the competing risk of death

During follow-up, 11,285 (58.7%) of the 19,241 subjects died and the remaining 7,956 subjects were censored on December 31\textsuperscript{st} 2008. Cardiovascular risk factors were associated with death in this cohort (data not shown).

Subdistribution hazards ratios (sdHR) based on the Fine and Gray method are shown in Table A.6. As expected, positive associations are somewhat attenuated compared with the cause-specific hazard ratios. Analysis accounting for the competing risk of death suggested even stronger inverse association between smoking and GCA among men.

Supplemental analysis - Cardiovascular risk factors as time-varying predictors

Of the 19,241 subjects, 6,154 came for a total of 19,413 study visit, median 2 (range 2–6). The incidence of GCA was similar among those that came for one vs. more study visits (Table A.7). The association of cardiovascular risk factors stratified according to whether subjects came for one or more study visits is shown in Table A.8. Among women, the effect of smoking was different between those that came for one study visit vs. those that came for more study visits although confidence intervals are wide.
Table A.8. Age- and sex stratified incidence rate of GCA among those that came for a single study visit and those that came for repeated visits in the Reykjavik study. Incidence rate is presented as events/100,000 person-years (GCA= Giant cell arteritis, PY=Person-years, IR=incidence rate).
Table A.9. Association of risk factors with GCA according to those who came for a single vs. multiple study visits. All effect estimates (hazard ratios) are adjusted for age and the other risk factors included in the table.

Supplemental analysis 3- Restricted Analysis to person-time contributed after January 1\textsuperscript{st} 1980.

Temporal artery biopsies were exceedingly rarely obtained on members of the Reykjavik study before 1980 despite substantial portion of the RS cohort having achieved the age at which the incidence of GCA in Iceland is high. There were 18,632 subjects that contributed person-time after 1980: Almost identical effect estimates of cardiovascular risk factors were obtained in the analysis restricted to the person-time contributed after January 1\textsuperscript{st}, 1980 in comparison to the whole person-time contributed are shown in Table A.10.
Table A.10: Effect of cardiovascular risk factors on incidence GCA during the total follow-up time and after January 1st, 1980 only. The effect of cardiovascular risk factors is expressed with age standardized* incidence rate ratios and 95% confidence intervals. (N=number of subjects, PY=person-years, BMI=body mass index, ESR=erythrocyte sedimentation rate)

<table>
<thead>
<tr>
<th></th>
<th>Women Entire follow-up (N=10,006 PY=238,128)</th>
<th>Women Person-time contributed after 1980 (N=9,825 PY=207,603)</th>
<th>Men Entire follow-up (N=9,235 PY=205,999)</th>
<th>Men Person-time contributed after 1980 (N=8,807 PY=170,831)</th>
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<td>Hypertension</td>
<td>0.88(0.61-1.25)</td>
<td>0.92(0.64-1.31)</td>
<td>2.00(1.18-3.37)</td>
<td>2.03(1.20-3.45)</td>
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<td>Ever smoking</td>
<td>1.12(0.80-1.57)</td>
<td>1.12(0.80-1.57)</td>
<td>0.51(0.30-0.87)</td>
<td>0.50(0.29-0.84)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
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<td></td>
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</tr>
<tr>
<td>&lt;5.7</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>5.7-6.3</td>
<td>0.96(0.58-1.61)</td>
<td>0.99(0.59-1.66)</td>
<td>0.89(0.43-1.84)</td>
<td>0.83(0.39-1.74)</td>
</tr>
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<td>6.4-7.1</td>
<td>1.06(0.65-1.72)</td>
<td>1.10(0.67-1.80)</td>
<td>1.14(0.58-2.27)</td>
<td>1.15(0.58-2.29)</td>
</tr>
<tr>
<td>&gt;7.2</td>
<td>0.89(0.54-1.45)</td>
<td>0.96(0.58-1.57)</td>
<td>0.88(0.40-1.92)</td>
<td>0.90(0.41-1.96)</td>
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<td>***</td>
<td>***</td>
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<td>1 (ref)</td>
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<tr>
<td>-overweight (25.0-24.9)</td>
<td>0.70(0.48-1.02)</td>
<td>0.71(0.49-1.03)</td>
<td>0.90(0.52-1.54)</td>
<td>0.94(0.54-1.62)</td>
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<td>-obese (≥30)</td>
<td>0.31(0.14-0.71)</td>
<td>0.31(0.14-0.72)</td>
<td>0.85(0.33-2.22)</td>
<td>0.89(0.34-2.33)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0-10</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>11-20</td>
<td>0.99(0.66-1.48)</td>
<td>1.01(0.67-1.52)</td>
<td>1.44(0.76-2.73)</td>
<td>1.50(0.79-2.84)</td>
</tr>
<tr>
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<td>1.61(1.04-2.48)</td>
<td>1.74(1.12-2.69)</td>
<td>0.42(0.06-3.03)</td>
<td>0.52(0.07-3.76)</td>
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</table>
Discussion

This study confirms a very high incidence of GCA in Iceland, 43.6/100,000 person-years after the age of 50, even higher than previously reported (27/100,000 person-years after the age of 50, (14)). Women have overall about twice the incidence of GCA compared with men, but after the age of 70, the incidence is similar in men and women. We found that high BMI is protective for the occurrence of GCA and smoking appears to be protective for the occurrence of the disease among men but not women.

Findings from this study add to the knowledge on the occurrence of GCA. It is well established that women are at increased risk of GCA compared with men(4, 15) Previous studies that have reported age- and sex- specific incidence of GCA have found women at increased risk compared with men in all age categories and that peak incidence occurs at 70–74 years of age and then declines both in men and women (4, 16, 17). In contrast, this study finds that the peak incidence of GCA occurs after the age of 80 among men. We found that secular incidence of GCA fluctuated with peaks in 1983, 1990, 1998 and 2005.

The finding of an inverse association between higher BMI and GCA has been previously reported (3) and contrasts with findings for some other inflammatory diseases such as rheumatoid arthritis and psoriatic arthritis where obesity appears to increase the risk of disease (18–20). The finding of an inverse association between smoking and incident GCA among men was unexpected although sex has been reported as an effect-measure modifier for the association.
of interest. However, several potential biases may threat the validity of this finding and thus prevent from making a valid conclusion on this relation (see below).

This study has important strengths. The RS cohort is population-based cohort and information on cardiovascular risk factors was obtained from all members of the cohort in a standardized fashion during a study visit to the RS. The follow-up is long and complete The GCA outcome was based on review of all temporal artery biopsies performed in the country on members of the RS cohort. A single pathologist with expertise in vascular pathology examined the biopsies in a protocolled fashion. The pathologist was blinded to both exposure information and original biopsy conclusion (that is whether the biopsy was reported to be diagnostic of GCA).

This study also has some important limitations. The study visits occurred over a period of 30 years and information on cardiovascular risk factors and ESR was usually obtained many years (often decades) before incident GCA. During the follow-up time, considerable changes occurred in smoking habits, resulting in inherent misclassification in this study with respect to smoking: A hypothetical example to illustrate this would be 2 men, A and B, both born in 1920 who both started smoking in 1945, quit smoking in 1970 and both developed GCA in 1995. Man A comes for a RS study visit in 1969 and is classified as a current smoker. Man B comes for a study visit in 1985, and is classified as a former smoker.
Therefore, dichotomizing smoking to ever vs. never is probably appropriate in this longitudinal cohort. In our analysis male smokers appear to have about half the risk of GCA compared with nonsmokers and findings from the analysis in which death is treated as a competing risk suggested even more protected effect of smoking. One possibility of this finding would be that clinicians caring for a patient who smokes would be less likely to obtain a temporal artery biopsy for male who smokes and might be inclined to perform diagnostic procedures pertaining to diseases with known relationship with smoking. Male smokers were less likely to undergo temporal artery biopsy, but only marginally so. However, there are several other possible sources of bias with respect to the smoking-GCA association in men that could exist in the RS cohort. The strong effect modification by calendar time on this relationship among women is of particular concern: smoking was inversely associated with GCA among women that came for study visit before 1970, but positively associated with GCA among those that came for study visit after 1980. This is not biologically plausible and we do not have an explanation for this finding; in the subset of patients that came for multiple visits, no attenuation of the smoking-GCA association is found. It is possible that effect-measure modification by decade of study examination is not seen in men because they get GCA at older age compared with the women in this cohort, and almost always a very long time after their RS study visit. It should be pointed out that in calculation of the effects of covariates for each subject with the outcome of GCA, only data from those alive at that age and at
risk for the event are used. Therefore, this smoking-GCA association among men cannot be explained by the competing event of mortality as those who smoke are more likely to die at younger age and not contribute data when they achieve the age where the risk of GCA is high. This was confirmed in a supplemental analysis with methods aiming to adjust for this modification of the risk set by the competing event, where even stronger inverse relationship between smoking and incident GCA among men was found.

The effect of cardiovascular risk factors on risk of cardiovascular disease in this population has been found very consistent with estimates obtained in other population cohorts(21). Thus, it is possible that smoking is truly protective for the occurrence of GCA among men. It could potentially be viewed as a limitation of our study that not all subjects with GCA have positive temporal artery biopsy confirmative of the disease. In an Icelandic study, 5% of those with GCA did not have biopsy-confirmed disease(14). Other studies have also found high sensitivity of temporal artery biopsy(22). Nonetheless, it is likely we missed some with GCA. However, given lack of diagnostic criteria for GCA (current ACR criteria are classification criteria designed to classify subjects with GCA from a reference population where all members have been diagnosed with some kind of vasculitis(23)), it is probably a greater risk for misclassification if the biopsy criteria was relaxed. We believe this view is shared by many investigators in the field as many studies rely on biopsy-proven GCA as their exposure or outcome.
definition. In this analysis, the effect of each cardiovascular risk factor is presented after age-standardization and after standardization across strata of the cardiovascular risk factors. It has been advised against to provide the effect of each risk factor on the outcome adjusted for all other potential risk factors. If some of the risk factors are on the causal pathway of each other the effect estimates for the risk factors from a single model requires different interpretation(24). Figure A4 shows a directed acyclic graph (DAG) of a hypothetical causal structure between age, hypertension and BMI on GCA. In a Cox regression model (or by any other method of multiple adjustments), the estimate for HTN should be interpreted as the effect of hypertension adjusted for the effect of age and BMI. The estimate for BMI should be interpreted as the proportion of the effect of BMI that is not mediated by HTN and the estimate for age should be interpreted as the proportion of the effect of age that neither mediated by BMI nor HTN.

![Diagram of causal structure between risk factors of GCA]

**Figure A4. Hypothetical causal structure between risk factors of GCA.**

(HTN=Hypertension, BMI=Body mass index, GCA=Giant cell arteritis)
For studying cardiovascular risk factors and cardiovascular events, similar causal structure between variables has been proposed.(25). In this analysis of risk factors for incident GCA, there exists extremely limited, if any, prior data to base on candidate causal diagrams including cardiovascular risk factors and ESR. Furthermore, findings from crude analysis in which BMI is protective and the substantial effect modification by sex with respect to the effect of smoking and hypertension, argues against the basing analytic process on the approach that would be taken if cardiovascular disease was the outcome.

In summary, this study confirms the high incidence of GCA in Iceland and reveals that men get GCA at older age compared with women. This study validates an inverse association of BMI with GCA and reveals an unexpected inverse association between smoking and incident GCA in men but not women.
References


Risk Factors, Coronary Heart Disease and Mortality in Giant Cell Arteritis – A Population-Based Study

Study B: Giant Cell Arteritis and Incident Coronary Heart Disease

Gunnar Tómasson

Word count: 2,990 excluding abstract, tables, legends and references.
Abstract

Objective: To measure the effect of GCA on incident coronary heart disease within a longitudinal cohort study where detailed information on cardiovascular risk factors has been collected.

Methods: Data from the Reykjavik Study (RS), a population-based, prospective cohort study with a primary focus on cardiovascular disease, were used. Exposure status with GCA was defined as a temporal artery biopsy consistent of GCA. Subjects contributed person-time as unexposed until they met exposure criteria. The association of GCA with incident CHD is expressed as incidence rate ratios (IRR) with 95% confidence intervals, standardized across strata of age, sex and cardiovascular risk factors.

Results: One hundred seventy six subjects contributed person time as exposed with GCA in this analysis. Subjects were followed for a median of 6.2 (IQR: 2.7–11.5) years after being diagnosed with GCA; the referent subjects were followed for mean of 22.5 (IQR: 14.7–28.2) years. During follow-up approximately 25% of study subjects had incident CHD. Compared with those without GCA, risk of CHD was increased by 77% (IRR= 1.77: 95% CI: 1.17-2.67) among women; such an association was not observed among men (IRR 1.08:95% CI: 0.60–1.95). Standardization over strata of cardiovascular risk factors and inflammation modestly attenuated the effect estimates among women.

Conclusion: GCA is associated with incident CHD among women but estimates for men are too imprecise to draw definite conclusions.
Introduction

Large-artery stenoses and aneurysms are well described complications of GCA (1, 2), but studies exploring the association of GCA with clinically important cardiovascular events have provided conflicting results (3-5): Large population-based studies from Canada and the UK that relied on diagnostic codes for GCA in the medical records found risk of cardiovascular events increased 2-fold (3, 4). In contrast, a preliminary report from Olmsted County, Minnesota, found no increased risk of acute coronary events among patients with biopsy confirmed GCA compared with those without GCA (5). In addition, previous studies have also shown that traditional cardiovascular risk factors are associated with occurrence and complications of GCA (6-9). Using data collected from Reykjavik Study we found an inverse association of body mass index (BMI) with incident GCA among both men and women as well as inverse association between smoking and risk of GCA among men. Therefore, collection of information on cardiovascular risk factors and appropriate adjustment for these factors are important when investigators examine the effect of GCA on the risk of cardiovascular disease. Study A of this thesis found that among those with a temporal artery biopsy consistent with GCA, the diagnosis was not made according the original biopsy report in a proportion of these subjects. That provides an opportunity to assess how GCA that is not reported at the time of biopsy (and therefore possibly untreated) affects cardiovascular risk compared to the risk of incident CHD among those with early biopsy confirmation of GCA. The
objective of this study was to determine the association between GCA and incident coronary heart disease (CHD) in a population cohort with information on risk factors for cardiovascular disease and to explore how early biopsy confirmation of GCA affects risk of CHD.
Methods

Study Design
We conducted a cohort study to examine the effect of GCA on incident CHD among participants in the Reykjavik Study.

Study population
The Reykjavik Study (RS) has been described in detail (see page 5). Briefly, persons, who were born in 1907–1935 and living in Reykjavik or in adjacent communities, Iceland on December 1, 1967, were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors was obtained. Individuals with GCA or CHD at baseline were excluded from this analysis.

For a supplemental analysis accounting for the competing risk of non-cardiovascular mortality, a cohort design with a matched reference group was used. For each subject with GCA we randomly selected 25 subjects alive and free of GCA, matched on sex and birth year.

Exposure Assessment
The exposure of GCA was defined as diagnostic temporal biopsy in the three pathologic laboratories in Iceland. All temporal artery biopsies obtained from members of the RS cohort were re-examined by a single pathologist as previously described (see page 22). For a temporal artery biopsy to be
considered diagnostic for GCA, for the purpose of this study, it must have infiltration of inflammatory cells to the vessel wall. To explore if temporal artery biopsies were thought to be consistent with GCA at the time they were obtained, the original pathology reports were reviewed. An *early biopsy confirmed GCA* was defined as when at least one of the following features were described in the original biopsy report: *i*) vasculitis, *ii*) presence of inflammatory infiltrate in the vessel wall, or *iii*) giant cells.

**Covariate assessment**

Information on hypertension, smoking, diabetes mellitus (DM), cholesterol, BMI and erythrocyte sedimentation rate (ESR) was obtained as previously described (see page 20) at baseline RS study visit before incident GCA.

**Follow-up and outcome assessment**

All subjects were followed from the time of RS study visit or from the time they reached 50 years of age, whichever occurred later, until the time of death, December 31st, 2007 or the occurrence of CHD, whichever occurred first. A CHD event was defined as a myocardial infarction (MI), revascularization procedure, or sudden cardiac death. Diagnostic criteria for MI included clinical symptoms, typical changes on an ECG, enzyme activity and signs of possible or definite MI on autopsy. The quality of the registry of MI in the RS Study has been subject to external oversight and its accuracy has been excellent (10).

Revascularization procedures included percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG). On behalf of the Icelandic
Heart Association, there is surveillance for those procedures performed at Landspitali University Hospital and earlier at Brompton Hospital London, UK where Icelanders in need of CABG were referred to in the 1970’s and early 1980’s. These two hospitals were the sole providers of coronary artery revascularization procedures for the Icelandic population. Information on sudden cardiac death was obtained from death certificates.

**Statistical analysis**

We excluded follow-up before age 50 because GCA rarely occurs before age 50. Specifically, for subjects with GCA the follow-up time started from the date of TAB that was consistent with GCA by our examination for the purpose of this study. For subjects who did not develop GCA during the follow-up their follow-up time started from the date of entry if subjects’ age at entry was older than 50 years old; otherwise their follow-up time started as soon as subjects reached 50 years of age. In addition, subjects with GCA contributed person-time to the non-GCA cohort before diagnosis of GCA. All subjects were followed up until time of CHD diagnosis, or death, or end of follow-up, whichever occurred first. The incidence rate (IR) was calculated as the number of incident CHD divided by the person-years of follow-up for GCA cohort and non-GCA cohort separately.

The effect of GCA on the risk of CHD was expressed as incidence rate ratio (IRR) with 95% confidence intervals (CIs). To adjust for potential confounding, standardized IRRs were calculated, standardizing to the distribution of person-time among subjects with GCA. Standardized effect estimates were calculated
across strata of age and cardiovascular risk factors. Age was divided into four strata: 50 to <60, 60 to <70, 70 to <80 and ≥ 80 years old. Smoking was divided into two categories: never smokers and ever-smokers. BMI was divided into four categories according to the WHO classification: underweight (<18.5 kg/m²), normal weight (18.5–<25 kg/m²), overweight (25–<30 kg/m²) and obese (≥30 kg/m²). Total cholesterol was divided to strata according to quartiles and ESR was stratified as ≤10, 11–20 and >20 mm/hour. As there was substantial effect-measure modification by sex, the effect of GCA on incident CHD was calculated separately for women and men. Standardized effect estimates were calculated across strata of i) age; ii) age and cardiovascular risk factors; and iii) age, cardiovascular risk factors and ESR. To explore the magnitude of confounding, we calculated the rate ratio due to confounding (RRc), which is equal to IRR/IRRSTD. Stratified analysis was also performed with GCA status stratified according to whether the diagnosis was supported by the original pathology report (early biopsy confirmed GCA vs. not originally reported GCA), using the same standardization weights as in the other analyses.

In a supplemental analysis using matched cohort design, a Cox proportional hazards regression with age of CHD as the outcome variable and GCA status as a time-varying predictor. We chose subjects’ age as the time-scale for the regression analysis; age was also included as an independent variable. To allow for better comparison with analysis accounting for the competing event of mortality Cox proportional regression was also performed with time on study as
the time-scale for the regression analysis. In an attempt to measure the effect of GCA on CHD accounting for the effect of GCA on the competing event (death from other causes than “sudden cardiac death” that is embedded in the CHD definition), for reasons previously outlined (see page 26), the subdistribution hazard ratio (sdHR) was calculated according to the Fine and Gray method (11).

SAS 9.2 (SAS institute Cary, NC) was used for calculations, a SAS macro (appendix A) was developed for calculations of standardized rate ratios. The macro was developed based on (and tested for errors against Episheet (12) for calculations of standardized rate ratios and their confidence interval. The statistical package cmprsk in R was used for calculations subdistribution hazards ratios according to the Fine and Gray method (11).
Results

Approximately 70% (19,360) of participants who were originally invited to participate in the Reykjavik Study came for a study visit from October 26th, 1967 to April 23rd, 1996. Of them 12 subjects had a temporal artery biopsy diagnostic of GCA before their RS study visit, 107 subjects died before the age of 50, and 461 subjects had CHD at baseline. Therefore, 18,780 subjects are included in this analysis.

Baseline characteristics

During the follow-up period 189 subjects developed incident GCA. Of them, 14 subjects (8 women and 6 men) had incident CHD before their GCA diagnosis and contributed person-time only to non-GCA cohort. Thus, 175 subjects had incident GCA for the purpose of this analysis. The baseline characteristics of GCA and comparison subjects are shown in Table B.1. The mean age at diagnosis of subjects with GCA was 73.0 (sd=6.6) and most were women, 125 (71.4%). At baseline there was minimal missing data with respect to serum cholesterol (n=40, 0.21%), BMI (n=142, 0.76%) and ESR (n=125, 0.67%), Distribution of cardiovascular risk factors was similar among CGA and comparison subjects.

Incident coronary heart disease

Subjects (n=175) with GCA were followed for 1,399 person-years, of which 1,151 person-years (83%) were contributed by study subjects after achieving the age of
Median follow-up time for subjects with GCA after the diagnosis of GCA was 6.2 years (IQR: 2.7–11.5 years). Comparison subjects (n=18,605) were followed for 399,456 person-years, of which 147,474 (37%) were contributed by study subjects after achieving the age of 70. The median follow-up time for the comparison subjects was 22.5 (IQR: 14.7–28.2) years. During follow-up 5,027 subjects (34 among GCA cohort and 4,993 in comparison cohort) developed incident CHD. The crude IR of CHD was 24.3/1000 person-years among GCA cohort and 12.5/1000 person-years among non-GCA cohort, respectively.
Table B.1. Baseline characteristics According to Status of GCA

Variables are expressed as number of person-years (percentage) in each stratum

(GCA=Giant cell arteritis, DM=diabetes mellitus, BMI=body mass index,
ESR=erythrocyte sedimentation rate).

**Association of GCA with incident CHD**

Among subjects with GCA, incident CHD was almost exclusively observed
among the two highest age strata (70–80 years and over 80 years). Incidence of CHD was higher among subjects with GCA than those without GCA, age- and sex standardized IRR=1.32 (95% CI: 0.94–1.84). Age- and sex-specific IRs and IRRs are shown in Table B.2. There was considerable effect-measure modification by sex. The age-standardized IRR of CHD according to GCA was 1.77 (95% CI: 1.17–2.67) among women and 1.08 (95% CI: 0.60-1.95) among men. This different effect between men and women was more prominent for non-fatal CHD, with IRR for non-fatal CHD of 2.33 (95% CI: 1.46–3.71) among women and 0.74 (95% CI: 0.31–1.78) among men. There was positive association of GCA with sudden cardiac death in both men and women. Age- and sex stratified IRs and IRRs of GCA with non-fatal CHD and sudden cardiac death and are shown in Table B.3.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>GCA</th>
<th>CHD</th>
<th>PY</th>
<th>IR</th>
<th>CHD</th>
<th>PY</th>
<th>IR</th>
<th>RD</th>
<th>IRR</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 to 60</td>
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<td>0</td>
<td>114</td>
<td>55,817</td>
<td>2</td>
<td></td>
<td>-2</td>
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<tr>
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<td>0</td>
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<td>78,924</td>
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<td>4.7</td>
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<td></td>
</tr>
<tr>
<td>70 to 80</td>
<td>13</td>
<td>540.15</td>
<td>24.1</td>
<td>670</td>
<td>62,937</td>
<td>10.6</td>
<td>13.5</td>
<td>2.27 (1.31-3.94)</td>
<td></td>
</tr>
<tr>
<td>over 80</td>
<td>10</td>
<td>316.52</td>
<td>31.6</td>
<td>534</td>
<td>25,866</td>
<td>20.6</td>
<td>11</td>
<td>1.53 (0.82-2.87)</td>
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<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>50 to 60</td>
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<td>0.66</td>
<td>0</td>
<td>511</td>
<td>53,490</td>
<td>9.6</td>
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<tr>
<td>60 to 70</td>
<td>1</td>
<td>88.85</td>
<td>11.3</td>
<td>1187</td>
<td>63,750</td>
<td>18.6</td>
<td>-7.3</td>
<td>0.61 (0.09-4.32)</td>
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</tr>
<tr>
<td>70 to 80</td>
<td>3</td>
<td>183.37</td>
<td>16.4</td>
<td>1066</td>
<td>44,127</td>
<td>24.2</td>
<td>-7.8</td>
<td>0.68 (0.22-2.1)</td>
<td></td>
</tr>
<tr>
<td>over 80</td>
<td>7</td>
<td>110.7</td>
<td>63.2</td>
<td>537</td>
<td>14,543</td>
<td>36.9</td>
<td>26.3</td>
<td>1.71 (0.81-3.61)</td>
<td></td>
</tr>
<tr>
<td>Both sexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>9.15</td>
<td>0</td>
<td>625</td>
<td>109,307</td>
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<td>-5.7</td>
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<tr>
<td>60 to 70</td>
<td>1</td>
<td>239.28</td>
<td>4.2</td>
<td>1561</td>
<td>142,675</td>
<td>10.9</td>
<td>-6.7</td>
<td>0.39 (0.05-2.74)</td>
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</tr>
<tr>
<td>70 to 80</td>
<td>16</td>
<td>723.52</td>
<td>22.1</td>
<td>1736</td>
<td>107,064</td>
<td>16.2</td>
<td>5.9</td>
<td>1.36 (0.83-2.23)</td>
<td></td>
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<tr>
<td>over 80</td>
<td>17</td>
<td>427.22</td>
<td>39.8</td>
<td>1071</td>
<td>40,410</td>
<td>26.5</td>
<td>13.3</td>
<td>1.5 (0.93-2.43)</td>
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</tr>
</tbody>
</table>

Table B.2. Age- and sex-specific incidence of CHD. Age- and sex- stratified number of deaths, person-years, Incidence rate of death expressed as number of CHD
events/1,000 person-years and the association of GCA with death expressed as IRR with 95% confidence intervals in strata of age and sex (GCA=Giant cell arteritis, CHD=Coronary heart disease, PY= Person-years, IR=incidence rate, RD=risk difference, IRR=incidence rate ratio).
<table>
<thead>
<tr>
<th>Age Group</th>
<th>GCA IR</th>
<th>No GCA IR</th>
<th>IRR (95% CI)</th>
<th>GCA IR</th>
<th>No GCA IR</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
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<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>50–60</td>
<td>0</td>
<td>1.8</td>
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<td>0</td>
<td>0.3</td>
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<tr>
<td>61–70</td>
<td>0</td>
<td>4.6</td>
<td></td>
<td>0</td>
<td>0.2</td>
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<tr>
<td>71–80</td>
<td>24.1</td>
<td>8.5</td>
<td>2.84 (1.64–4.92)</td>
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<td>2.2</td>
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</tr>
<tr>
<td>&gt;80</td>
<td>15.8</td>
<td>7.8</td>
<td>2.03 (0.83–4.92)</td>
<td>15.8</td>
<td>12.8</td>
<td>1.23 (0.51–2.99)</td>
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<td><strong>Men</strong></td>
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<td></td>
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<td></td>
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<td>0</td>
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<td>17.3</td>
<td>0.65 (0.09–4.64)</td>
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<td>1.3</td>
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<tr>
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<td>16.4</td>
<td>20</td>
<td>0.82 (0.26–2.55)</td>
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<td>4.2</td>
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<td>&gt;80</td>
<td>9</td>
<td>14.1</td>
<td>0.64 (0.09–4.55)</td>
<td>54.2</td>
<td>22.8</td>
<td>2.38 (1.06–5.33)</td>
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<tr>
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<td>0</td>
<td>0.7</td>
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</tr>
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</tr>
<tr>
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</tr>
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<td>&gt;80</td>
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<td>10.1</td>
<td>1.39 (0.62–3.1)</td>
<td>25.7</td>
<td>16.4</td>
<td>1.57 (0.86–2.84)</td>
</tr>
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</table>

**Table B.3. Incidence rate of non-fatal coronary heart disease (MI, PCI and CABG) and sudden cardiac death.** Measures of associations are expressed as the number of events/100,000 person years and association of GCA with incident coronary heart disease expressed as IRR with 95% confidence intervals in strata of age and sex (GCA=Giant cell arteritis, IR=incidence rate, IRR=incidence rate ratio, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting)

**Stratified and standardized association of cardiovascular risk factors and inflammation**

Stratified analysis across different strata of cardiovascular risk factors did not reveal great effect measure modification (**Table B.4**), except that among women GCA appeared to have stronger association with CHD among those with low vs. high serum cholesterol with age standardized IRR = 2.77 (95% CI: 1.48–5.19)
and 1.38 (95% CI: 0.80–2.39) respectively.

<table>
<thead>
<tr>
<th></th>
<th>GCA</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>PY</td>
</tr>
<tr>
<td><strong>WOMEN</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>HTN</strong></td>
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<td></td>
</tr>
<tr>
<td>yes</td>
<td>12</td>
<td>0.36</td>
</tr>
<tr>
<td>no</td>
<td>11</td>
<td>0.65</td>
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<tr>
<td><strong>Smoking</strong></td>
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</tr>
<tr>
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<td>0.52</td>
</tr>
<tr>
<td>never</td>
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</tr>
<tr>
<td>&lt;6.3 mmol/L</td>
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<tr>
<td>≥6.3 mmol/L</td>
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<td>11*</td>
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</tr>
<tr>
<td>≥25</td>
<td>8*</td>
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<td>&gt;20 mm/hour</td>
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</tr>
<tr>
<td><strong>MEN</strong></td>
<td></td>
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</tr>
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<td><strong>HTN</strong></td>
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<td></td>
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<tr>
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<td>0.16</td>
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<td>high</td>
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<tr>
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</tr>
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</tr>
<tr>
<td><strong>ESR</strong></td>
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<td></td>
</tr>
<tr>
<td>≤20 mm/hour</td>
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<td>0.37</td>
</tr>
<tr>
<td>&gt;20 mm/hour</td>
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<td>0.01</td>
</tr>
</tbody>
</table>

Table B.4. Incidence of CHD stratified according to cardiovascular risk factors.

Person-years are expressed in thousands. Incidence rates expressed as number of event/100,000 person-years and association of giant cell arteritis with incident coronary heart disease across strata of sex, cardiovascular risk factors and inflammation expressed as crude IRR and standardized IRR across four age-strata (50–60, 60–70,
70–80 and older than 80) (GCA=Giant cell arteritis, CHD=Coronary Heart disease
HTN=hypertension, BMI=body mass index, ESR=erythrocyte sedimentation rate,
IR=incidence rate, IRR=incidence rate ratio Std IRR= age standardized incidence rate
ratio).

*Among women with GCA who had incident CHD, 4 out of 23 had missing data on BMI.

A standardization across strata of cardiovascular risk factors (hypertension,
smoking, and cholesterol) did not materially attenuate the effect estimate:
IRR=1.80 (95% CI: 1.19–2.73) among women and IRR=1.13 (0.62–2.04) among
men. Further standardization for inflammation at baseline (as measured by the
ESR) also resulted in minimal changes of the effect estimate in either women
(IRR=1.66, 95% CI: 1.09–2.55) or men (IRR=1.12, 95% CI: 0.62–2.04).

Standardization across strata of cardiovascular risk factors and inflammation also
had minimal effect on the individual CHD-defining events (Table B.5). Although
missing data for covariates was minimal in the whole study cohort, there was
substantial missing data for BMI among women with GCA who sustained incident
CHD, among whom 4 out of 23 (17.3%) had missing data on BMI. In a sensitivity
analysis imputing data for BMI, additionally adjusting for BMI did not change the
estimates between GCA and CHD very much (Table B.6).
Table B.5. Association of giant cell arteritis with incident CHD with three different methods for standardization. Measures of associations are expressed as incidence rate ratios with 95% confidence intervals standardized across four age-strata (50-60, 60-70, 70-80 and older than 80), cardiovascular risk factors and ESR.

Standardization 1 is across strata of age

Standardization 2 is across strata of age, ever smoking, hypertension and cholesterol.

Standardization 3 is across strata of age, ever smoking, hypertension, cholesterol and erythrocyte sedimentation rate.

(MI=myocardial infarction, CHD=coronary heart disease, ESR=Erythrocyte sedimentation rate)

*Only 22 out of 23 CHD events (12 out of 13 MIs) included in the analysis as one woman with GCA had missing data for ESR.

For the analysis on association of GCA with CHD based on statistical modeling with and without accounting for the competing event of mortality, we compared a cohort of 175 patients with GCA and 4,375 matched comparison subjects.

Results were almost identical to the tabular analysis.
<table>
<thead>
<tr>
<th></th>
<th>Standardization/Model 1</th>
<th>Standardization/Model 2</th>
<th>Standardization/Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR</td>
<td>1.66 (1.09-2.53)</td>
<td>1.50 (0.94-2.40)</td>
<td>1.22 (0.73-2.04)*</td>
<td></td>
</tr>
<tr>
<td>HR#</td>
<td>1.72 (1.13-2.6)</td>
<td>1.57 (0.99-2.49)</td>
<td>1.45 (0.90-2.33)*</td>
<td>1.42 (0.88-2.78)*</td>
</tr>
<tr>
<td>HR$</td>
<td>1.68 (1.10-2.56)</td>
<td>1.51 (0.95-2.40)</td>
<td>1.39 (0.87-2.24)*</td>
<td>1.36 (0.85-2.18)*</td>
</tr>
<tr>
<td>HR†</td>
<td>1.54 (1.00-2.36)</td>
<td>1.57 (1.02-2.42)</td>
<td>1.41 (0.89-2.22)*</td>
<td>1.40 (0.89-2.19)*</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR</td>
<td>0.96 (0.53-1.76)</td>
<td>0.94 (0.51-1.75)</td>
<td>0.89 (0.47-1.70)</td>
<td></td>
</tr>
<tr>
<td>HR#</td>
<td>1.00 (0.55-1.93)</td>
<td>0.99 (0.54-1.80)</td>
<td>0.99 (0.54-1.80)</td>
<td>0.98 (0.53-1.78)</td>
</tr>
<tr>
<td>HR$</td>
<td>1.01 (0.55-1.84)</td>
<td>0.99 (0.54-1.80)</td>
<td>0.99 (0.54-1.80)</td>
<td>0.97 (0.53-1.77)</td>
</tr>
<tr>
<td>HR†</td>
<td>0.78 (0.42-1.44)</td>
<td>0.75 (0.41-1.39)</td>
<td>0.75 (0.41-1.40)</td>
<td>0.76 (0.41-1.38)</td>
</tr>
</tbody>
</table>

Table B.6. Association of GCA with incident CHD with IRR and HR from different survival models in a matched cohort analysis.

Standardization/model 1 is across strata or adjusted for of age (in four strata in the tabular analysis and as continuous linear predictor in the regression models)

Standardization/model 2 is across strata/adjusted for age, ever smoking, hypertension and cholesterol.

Standardization/model 3 is across strata/adjusted for of age, ever smoking, hypertension, cholesterol and erythrocyte sedimentation rate.

Model 4 is adjusted for of age, ever smoking, hypertension, cholesterol and erythrocyte sedimentation rate with all continuous variables entered as linear predictors.

#HR with subjects’ age as the time-scale for analysis

$HR with follow-up time as the time-scale for analysis

†HR accounting for the competing event of mortality with follow-up time as the time-scale for analysis.

*Only 22 out of 23 CHD events included in the analysis as one woman with GCA and CHD had missing data for ESR.

(GCA=Giant cell arteritis, CHD=Coronary heart disease, IRR=Incidence rate ratio, HR=hazards ratios)
Effect of early biopsy confirmed vs. not biopsy-reported GCA with incident CHD.

Among the 176 subjects with GCA (women: 126) 118 subjects' diagnosis of GCA (women: 92) was made based on either the original biopsy report or description of inflammatory infiltrate on temporal artery. For the remaining 58 subjects (women: 34), there was discordance between the examination of the temporal arteries for the purpose of this study and the original pathology report. Biopsies from all those subjects met exposure criteria for GCA in this study, but the original biopsy report mentioned neither GCA nor inflammatory infiltrate of the temporal artery; thus the temporal artery was normal or with intimal hyperplasia only according to the original report. For both men and women the association between GCA and risk of CHD varied according to how GCA was defined in the original pathology report. As shown in Table B.7, subjects with GCA confirmed by early biopsy had lower risk of incident CHD than those whose GCA was not confirmed by biopsy report.
<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized IRR</td>
<td>Standardized IRR</td>
</tr>
<tr>
<td>No GCA</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>GCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Early biopsy confirmed GCA</td>
<td>1.57 (0.94-2.60)</td>
<td>0.70 (0.29-1.69)</td>
</tr>
<tr>
<td>-No GCA according to original biopsy report</td>
<td>2.46 (1.21-4.99)</td>
<td>1.38 (0.62-3.08)</td>
</tr>
</tbody>
</table>

Table B.7. Association of GCA with incident CHD stratified according to results of original biopsy report. Measures of association are expressed as IRR with 95% confidence intervals in strata of sex and whether features of GCA were described on the original biopsy report. Estimates are standardized across four age-strata (50–60, 60–70, 70–80 and older than 80). (GCA=giant cell arteritis, IRR=incidence rate ratio).
Discussion

This study found an association between GCA and incident CHD among women. The effect estimate for risk of GCA on CHD among men was close to 1. The effect estimates are modest but adjustment for cardiovascular risk factors, inflammation and supplemental analysis accounting for the competing risk of mortality did not result in attenuation of the risk estimates. In addition to different effect estimates for women and men, there also was substantial effect-measure modification according to whether features of GCA were described in the original pathology report, signaling that there might be benefits of early detection and treatment of GCA with respect to cardiovascular risk.

This study has important strengths. Information on cardiovascular risk factors was obtained from nearly all members of the cohort in standardized fashion regardless of exposure status. Treatment with high dose glucocorticoids is the standard of care for newly diagnosed patients with GCA. Finding a substantial number of subjects with GCA, for which the diagnosis was not originally reported provides a rare opportunity for insight in to the natural history of probably-untreated GCA in the context of developing cardiovascular disease.

This study also has several limitations. This study is small; of 176 GCA patients (men: 50) with incident GCA only 34 (men: 11) had developed CHD events. No data on clinical presentation and treatment are available to us and we have no information on the clinical diagnosis by the treating physician, which might have
set the diagnosis based on clinical findings. However, a nationwide study on the occurrence of GCA in Iceland 1983–1990, for which some overlap exists to this study (of the 118 with early biopsy confirmed GCA in our cohort, 35 occurred during 1984–1990), found that 95% of subjects with GCA in Iceland during that period had biopsy confirmed disease (13). Therefore, we deduce that for a substantial number of subjects with GCA in our study for whom the diagnosis was not found on the original biopsy report the diagnosis was in fact not made by the clinician. Although missing data were rare, missing BMI information was associated with GCA status among women. We do not have an explanation for this differential missing data between subjects with GCA and comparison subjects. Several sensitivity analyses with imputed data for BMI did not suggest that the association between GCA and CHD is confounded by BMI.

The substantial effect-measure modification according to sex is not readily explained. Some of this effect is driven by the fact that women represent a higher proportion of those for whom the diagnosis was not made according to original biopsy report compared with those with early biopsy confirmed disease. This study also indicates that the effect of GCA might be associated with different types of CHD defining events in women and men. Women have increased risk of non-fatal presentation of CHD (MI, and revascularization procedure) whereas among men the effect estimates demonstrated an increased risk of sudden cardiac death. However, all effect estimates for different types of CHD-defining events have wide confidence intervals.
This study provides information as to whether risk of GCA on CHD is confounded by cardiovascular risk factors. It finds that the association of GCA on CHD in women is not driven by different distribution cardiovascular risk factors between the subjects with GCA and referent subjects. The lack of confounding by inflammation as measured by the ESR should not be interpreted as the effect of GCA on incident CHD is being mediated by systemic inflammation. The ESR measurements were obtained at the RS study visit, in most cases many years before the onset of GCA, and subject who developed GCA within our cohort almost certainly sustained much greater systemic inflammatory response at the time of onset of GCA.

Glucocorticoids have well-documented pro-atherosclerotic effects such as elevation in blood lipids, blood glucose and can cause hypertension (14). Treatment with glucocorticoids is often considered as potential cause for increased cardiovascular disease observed among patient with chronic inflammatory diseases. Our findings, however, indicate the opposite, that treatment with glucocorticoids might be of value for reducing the risk of CHD as observed among those with early biopsy confirmed GCA, and therefore those who are more likely to have received early treatment with systemic glucocorticoids have less risk of CHD, providing a suggestion that untreated inflammation may be detrimental for CHD risk.
In summary, GCA is associated with modestly increased risk of CHD among women but there is inadequate information to draw a conclusion for men. Early disease detection might be of benefit with respect to cardiovascular risk.
References


Risk Factors, Coronary Heart Disease and Mortality in Giant Cell Arteritis – A Population-Based Study

Study C: The Association of Giant cell arteritis and Its Histopathology with All-Cause and Cardiovascular Mortality

Gunnar Tómasson

Word count: 3,083 excluding abstract, tables, legends and references.
Abstract

Objective: To measure the effect of giant cell arteritis (GCA) and its histopathology on all-cause and cardiovascular mortality within a population cohort with detailed information on temporal artery biopsies (TAB).

Methods: Data from the Reykjavik Study were used. GCA status was defined from examination of TABs by a single expert pathologist. Original histological diagnosis was obtained from the original pathology report. Cardiovascular mortality was assessed from death certificates. Subjects contributed person-time as unexposed until they met exposure criteria. Effect of GCA, compared with those without GCA, is expressed as incidence rate ratios (IRR) (95% confidence intervals (CI)) standardized for age and sex. Effects of TAB findings were compared with those who did not undergo TAB.

Results: Of 19,241 included subjects, 692 underwent TAB and 196 had GCA. Subjects were followed for a median of 7.1 (IQR: 3.5–12.4) years after exposure of GCA, but referent subjects for 24.3 (IQR: 17.6–29.8) years. GCA was associated with all-cause and cardiovascular mortality, with IRRs=1.45 (1.20–1.75) and IRR=1.50 (1.13–1.99) respectively. For 71 subjects with GCA but a negative pathology report, there was substantially increased mortality risk with IRR=2.18 (1.65–2.90) compared with IRR=1.10(0.85–1.42) for those (n=125) with an original histological diagnosis of GCA. There was an inverse association between TAB inflammation and mortality risks with IRRs of 2.15 (1.60–2.88),
1.26 (0.85–1.85) and 1.13 (0.81–1.57), for mild, moderate and severe inflammatory intensity, respectively.

**Conclusion:** GCA is associated with modestly increased mortality risks that are driven by GCA patients without original histological diagnosis of GCA.
Introduction

Most (1-6), but not all (7, 8) studies have found decreased or minimally increased mortality among patients with giant cell arteritis (GCA) compared with the general population. In a multi-center study from North-America (3), a population-based study from Minnesota (6) and a single center from Northern Spain (1), no increase in mortality was found. Three studies have found increased mortality risks only in the first year after diagnosis (4, 5, 8).

The histopathology of GCA is characterized by inflammation to a varying degree of an affected vessel and hyperplasia of the intima layer of the vessel. Sometimes the inflammatory infiltrate contains multinucleated giant cells, from which the disease takes its name (9), but are of undetermined significance with respect to disease occurrence, clinical presentation and prognosis. There is scant information on how histopathology findings are associated with complications and outcomes of patients with GCA (10, 11) and we are not aware of studies that have examined how histopathological features seen with temporal artery biopsy (TAB) are associated with mortality risks in GCA.

The objective of this study is to determine the association between GCA and cardiovascular- and all-cause mortality. In study B of this thesis, a substantial discordance was observed between our classification of GCA-status and the original pathology report. Furthermore, those with GCA that did not have histological diagnosis of GCA according to the original pathology report had substantially higher risk of incident CHD. Such association could be confounded
by histologic features of biopsies that are associated with both diagnostic
discordance and risk of CHD. Therefore, an added objective to this study was to
explore how early histological diagnosis, inflammatory intensity and other
histologic features on TABs affect mortality risks.
Methods

Study Design
To examine the effect of GCA on mortality, a cohort study design was used, where incident mortality of subjects with GCA was compared with all other members of the Reykjavik Study cohort.

Study population
Data from Reykjavik Study were used. The Reykjavik Study has been described (see page 5). Briefly, persons, who were born in 1907–1935 and living in Reykjavik, Iceland or in adjacent communities on December 1, 1967, were invited to participate. Subjects came for a study visit in 1967–1996, during which information on cardiovascular risk factors was obtained. Those with GCA at baseline were excluded.

For the analysis on the association of GCA with mortality risk at different periods after the occurrence of GCA and for an analysis accounting for the competing risk of non-cardiovascular mortality, a cohort design with a matched comparison group was used. For each subject with GCA we selected 10 subjects alive and free of GCA were selected matched on sex and birth year.

The analysis of histopathology findings of TABs, was done in the cohort after excluding those who had underwent TAB at baseline Overview of the sub-cohorts of the total RS study cohorts used for the analyses of the association between GCA and mortality is provided in Table C.1.
### Table C1. Three sub-cohorts generated from the parent RS study cohort used for assessing mortality risks

<table>
<thead>
<tr>
<th>Inclusion/exclusion</th>
<th>Primary cohort</th>
<th>Matched Cohort</th>
<th>Biopsy cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=19,241</td>
<td>N=2,156</td>
<td>N=19,196</td>
<td></td>
</tr>
<tr>
<td>107 subjects who died before the age of fifty and 12 subjects with GCA before RS study visit excluded</td>
<td>196 subjects with GCA and 1960 matched reference subjects included</td>
<td>107 subjects who died before the age of fifty and 57 subjects who underwent TAB before an RS study visit excluded</td>
<td></td>
</tr>
<tr>
<td>Analyses: Baseline data and main effects of GCA on study outcomes</td>
<td>The effect of GCA on study outcomes early and late after incident GCA.</td>
<td>The effect of findings on TAB on study outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The effect of GCA on cardiovascular mortality accounting for the competing event of non-cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exposure Assessment and pathologic review of temporal arteries**

GCA was defined as diagnostic TAB in any of the three pathologic laboratories in Iceland. All TABs obtained from members of the RS cohort were re-examined by a single pathologist as previously described (see page 22). For a TAB to be considered diagnostic for GCA in the current study, it must have infiltration of inflammatory cells to the vessel wall.

Intima hyperplasia was graded as absent (when almost no tissue was present between the lumen and the internal elastic membrane (IEM)), mild, moderate and
severe (when the intima layer obliterated the vessel lumen on the pathology 
slide). Calcifications were scored as present if found in at least one section at 
any site of the biopsy. For biopsies considered diagnostic for GCA the 
inflammatory intensity was scored as mild, moderate or severe. For each vessel 
layer (adventitia, media and intima) inflammation was scored as present or 
absent. Extent of inflammation was graded as present in 1, 2 or all 3 layers of the 
temporal artery. Giant cells were scored as present if at least one giant cell was 
found on any section in any vessel layer. The presence of fibrinoid deposition 
was scored as present or absent. To explore whether TABs were thought to be 
consistent with GCA at the time they were obtained, the original pathology 
reports were reviewed. An early histologic diagnosis of GCA was defined as 
when at least one of the following features were described in the original biopsy 
report: i)vasculitis, ii)presence of inflammatory infiltrate in the vessel wall, or iii) 
giant cells. Those with a positive TAB (by our “gold standard” review) were 
further classified as having an original report that was positive vs. an original 
report that was negative.

Covariate assessment

Information on smoking, BMI, cholesterol, ESR, hypertension and DM was 
obtained as previously described (see pages 21–22) during the baseline RS 
study visit before incident GCA.
Follow-up and outcome assessment

All subjects were followed from the time of RS study visit or from the time they became 50 years of age, whichever occurred later, until the earlier of the time of death or December 31\textsuperscript{st}, 2008. Cardiovascular mortality was assessed from death certificates and non-cardiovascular mortality was mortality from all other causes. For the analysis of mortality risks early and later after incident GCA, follow-up started at the time when TAB was obtained for each GCA patient and its matched reference subjects.

Statistical analysis

Since no subject developed GCA before the age of 50 years, person-time of follow-up before age 50 was not included in this study. Specifically, for subjects with GCA the follow-up started from the date of GCA diagnosis. For subjects who did not develop GCA during the follow-up, their follow-up started from the date of entry if subjects’ age at entry was older than 50 years old; otherwise their follow-up time started when they became 50 years old. In addition, subjects with GCA contributed person-time to the non-GCA cohort before diagnosis of GCA. All subjects were followed until time of death, or December 31\textsuperscript{st}, 2008, whichever occurred first. The incidence rate (IR) was calculated as the number of deaths divided by the person-years of follow-up for GCA cohort and non-GCA cohort separately. The effect of GCA on study outcomes was expressed as incidence rate ratio (IRR) with 95% confidence intervals (CIs). The effect of TAB feature was expressed as the IRR with 95% CI, with those subjects that did not undergo
TAB as the reference group. To adjust for potential confounding, standardized IRRs were calculated using person-time contributed by GCA patients as weights in all analyses. Standardized effect estimates were calculated across strata of age and sex. For analysis of cardiovascular mortality additional standardization across cardiovascular risk factors was done as previously described (see page 25). In addition, for the outcome of cardiovascular mortality a Cox proportional hazards regression and survival analysis accounting for the competing event of mortality according to the Fine and Gray method (12), with death from CVD as the outcome variable. As GCA could not be modeled as time-varying predictors in the competing risk analysis this was done in the matched cohort analysis.

SAS 9.2 (SAS institute Cary, NC) was used for calculations. A SAS macro was developed for calculations of standardized rate ratios. The macro was developed based on (and tested for errors against Episheet (13) for calculations of standardized rate ratios and their confidence interval. The statistical package cmprsk in R was used for calculations subdistribution ratios according to the Fine and Gray method (12).
Results

Approximately 70% (19,360) of participants who were originally invited to participate in the RS came for a study visit from October 26th, 1967 to April 23rd, 1996. Of these, 12 subjects had a TAB diagnostic of GCA before their RS study visit, and 107 subjects died before age 50. Therefore, 19,241 subjects were included in this analysis.

Baseline characteristics

During follow-up, 196 subjects developed incident GCA. The baseline characteristics of subjects with GCA and their matched comparison cohort are shown in Table C.2. The mean age at diagnosis of GCA was 73.0 (sd=6.6) and 138 (70.4%) were women. Distribution of cardiovascular risk factors was similar among those with GCA and the comparison subjects.
<table>
<thead>
<tr>
<th>Variable</th>
<th>GCA (1,664 PY)</th>
<th>No GCA (444,237 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1,201 (72%)</td>
<td>238,177 (54%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-50 to 60 years</td>
<td>10 (1%)</td>
<td>112,307 (25%)</td>
</tr>
<tr>
<td>-60 to 70 years</td>
<td>260 (15%)</td>
<td>153,651 (35%)</td>
</tr>
<tr>
<td>-70 to 80 years</td>
<td>825 (50%)</td>
<td>126,988 (29%)</td>
</tr>
<tr>
<td>-after 80 years</td>
<td>567 (34%)</td>
<td>51,289 (11%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>661 (40%)</td>
<td>168,549 (38%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-never</td>
<td>742 (45%)</td>
<td>158,510 (36%)</td>
</tr>
<tr>
<td>-former</td>
<td>384 (23%)</td>
<td>88,404 (20%)</td>
</tr>
<tr>
<td>-current smoking</td>
<td>538 (32%)</td>
<td>197,295 (44%)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>6.5 (1.2)</td>
<td>6.5 (1.2)</td>
</tr>
<tr>
<td>&lt;5.6</td>
<td>377 (23%)</td>
<td>104,126 (23%)</td>
</tr>
<tr>
<td>5.7-6.3</td>
<td>360 (22%)</td>
<td>109,848 (25%)</td>
</tr>
<tr>
<td>6.4-7.1</td>
<td>438 (26%)</td>
<td>116,799 (26%)</td>
</tr>
<tr>
<td>7.2-19</td>
<td>489 (29%)</td>
<td>112,750 (25%)</td>
</tr>
<tr>
<td>DM</td>
<td>56 (3%)</td>
<td>13,235 (3%)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>0</td>
<td>5,963 (1%)</td>
</tr>
<tr>
<td>18.5 – 24.9</td>
<td>971 (58%)</td>
<td>210,941 (47%)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>530 (32%)</td>
<td>178,902 (40%)</td>
</tr>
<tr>
<td>≥30</td>
<td>115 (7%)</td>
<td>46,433 (10%)</td>
</tr>
<tr>
<td>ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 10</td>
<td>1,055 (60%)</td>
<td>304,247 (68%)</td>
</tr>
<tr>
<td>11-20</td>
<td>384 (23%)</td>
<td>94,962 (21%)</td>
</tr>
<tr>
<td>&gt;21</td>
<td>271 (16%)</td>
<td>42,732 (10%)</td>
</tr>
</tbody>
</table>

Table C.2. Baseline characteristics of the GGA and non-GCA subjects Variables expressed with number of person-years (percentage) in each strata (GCA=Giant cell arteritis, DM=diabetes mellitus, BMI=body mass index, ESR=erythrocyte sedimentation rate).

Follow-up and mortality

Subjects with GCA (n=196) accumulated 1,664 person-years of follow-up and comparison subjects (n=19,048) accumulated 444,237 person-years. Person-
time of follow-up comprised older years of life for GCA patients; 84% were older than age 70, compared with only 40% among the comparison cohort (Table C.3). The median follow-up time for GCA cohort and non-GCA cohort was 7.1 (IQR: 3.5–12.5) and 24.3 (IQR: 17.6-29.8) years respectively. During follow-up, 11,396 (58.6%) subjects died, 111 deaths occurred among GCA subjects and 11,285 in the comparison cohort.

| Age Group | GCA Deaths | GCA PY | GCA IR | No GCA Deaths | No GCA PY | No GCA IR | RD | IRR  
|-----------|-------------|--------|--------|---------------|-----------|-----------|-----|------ 
| Women     |             |        |        |               |           |           |     |      
| 50-60     | 0           | 8.7    | 0.0    | 240           | 56,269.3  | 4.3       | -4.3|      
| 61-70     | 4           | 163.5  | 24.5   | 730           | 81,095.2  | 9.0       | 15.5| 2.72 (1.02-7.26) 
| 71-80     | 26          | 616.2  | 42.2   | 1653          | 69,816.4  | 23.7      | 18.5| 1.78 (1.21-2.63) 
| >80       | 40          | 412.2  | 97.0   | 2549          | 30,996.6  | 82.2      | 14.8| 1.18 (0.86-1.61) 
| Men       |             |        |        |               |           |           |     |      
| 50-60     | 0           | 3.8    | 0.0    | 450           | 56,038.0  | 8.0       | -8.0|-- 
| 61-70     | 1           | 8.1    | 10.3   | 1247          | 72,556.4  | 17.2      | -6.9| 0.60 (0.08-4.26) 
| 71-80     | 12          | 17.1   | 57.2   | 2229          | 57,172.3  | 39.0      | 18.2| 1.47 (0.83-2.59) 
| >80       | 28          | 51.9   | 180.5  | 2187          | 20,293.0  | 107.8     | 72.7| 1.67 (1.15-2.43) 
| Both sexes|             |        |        |               |           |           |    |      
| 50-60     | 0           | 2.3    | 0.0    | 690           | 112,307.3 | 6.1       | -6.1|-- 
| 61-70     | 5           | 4.9    | 19.2   | 1977          | 153,651.7 | 12.9      | 6.3 | 1.49 (0.62-3.59) 
| 71-80     | 38          | 12.1   | 46.0   | 3882          | 126,988.8 | 30.6      | 15.4| 1.51 (1.09-2.07) 
| >80       | 68          | 43.7   | 119.9  | 4736          | 512,89.7  | 92.3      | 27.5| 1.3 (1.02-1.65) 

Table C.3. Age- and sex-specific incidence of mortality Age- and sex stratified number of deaths, person-years, Incidence rate of death expressed as number of events/1,000 person-years and the association of GCA with death expressed as IRR with 95% confidence intervals in strata of age and sex (GCA=Giant cell arteritis, PY=Person-years, IR=incidence rate, RD=risk difference, IRR=incidence rate ratio)
Association of GCA with all-cause and cardiovascular mortality

Table C.3 shows age- and sex-specific incidence rates for mortality among GCA and non-GCA cohorts. Subjects with GCA had modestly increased risk for all-cause mortality; the IRR= 1.45 (95% CI: 1.20–1.75) for all-cause mortality standardized across age and sex. Sex-specific IRRs were 1.40 (95% CI: 1.11–1.77) for women and 1.54 (95% CI 1.13–2.10) for men, respectively.

GCA was associated with increased cardiovascular mortality (IRR=1.50, 95% CI: 1.13–1.99); the IRR was lower among women (IRR= 1.19, 95% CI: 0.79–1.78) than that among men (IRR=2.01, 95% CI: 1.36–2.98). Age-sex stratified IRs and IRRs for cardiovascular mortality among GCA and non-GCA subjects are shown in Table C.4. Standardization across strata of cardiovascular risk factors did not change the overall estimate much: IRR=1.46 (95% CI: 1.09–1.96) and further standardization across strata of ESR attenuated this effect estimate very slightly, with IRR=1.39 (95% CI: 1.03–1.88).

Effect of GCA on cardiovascular death from Cox proportional hazards regression was HR=1.50 (95% CI 1.07–2.10), adjusting for cardiovascular risk factors but not ESR.

In an analysis for cardiovascular mortality, accounting for the competing event of non-cardiovascular mortality, risk ratio of GCA for cardiovascular mortality was 1.17 (95% CI: 0.85 –1.59) adjusting for cardiovascular risk factors but not ESR.
### Table C.4. Age- and sex specific incidence of cardiovascular mortality and non-cardiovascular mortality

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular Mortality</th>
<th>Non-cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GCA</td>
<td>No GCA</td>
</tr>
<tr>
<td></td>
<td>IR</td>
<td>GCA</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>0.0</td>
<td>0.9</td>
</tr>
<tr>
<td>61-70</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>71-80</td>
<td>11.4</td>
<td>7.8</td>
</tr>
<tr>
<td>&gt;80</td>
<td>41.2</td>
<td>36.4</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>0.0</td>
<td>3.8</td>
</tr>
<tr>
<td>61-70</td>
<td>0.0</td>
<td>8.1</td>
</tr>
<tr>
<td>71-80</td>
<td>47.7</td>
<td>17.1</td>
</tr>
<tr>
<td>&gt;80</td>
<td>96.7</td>
<td>51.9</td>
</tr>
<tr>
<td><strong>Both sexes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>0.0</td>
<td>2.3</td>
</tr>
<tr>
<td>61-70</td>
<td>0.0</td>
<td>4.9</td>
</tr>
<tr>
<td>71-80</td>
<td>20.6</td>
<td>12.0</td>
</tr>
<tr>
<td>&gt;80</td>
<td>56.4</td>
<td>42.5</td>
</tr>
</tbody>
</table>

**Cardiovascular Mortality** and **Non-cardiovascular Mortality**. IR, absolute RDs and IRRs of cardiovascular and non-cardiovascular mortality among subjects with GCA and non-GCA in the RS cohort.

(GCA=Giant cell arteritis, IR=incidence rate, IRR=incidence rate ratio)

**Association of GCA with mortality risks early and late after diagnosis.**

For the analysis on association of GCA with mortality within strata of early and late periods after the diagnosis of GCA, 193 subjects with GCA and 1,875 matched reference subjects were included. Of the 193 subjects with GCA, only 9 died in the first year after TAB with IRR= 1.19 (95% CI: 0.58–2.45) during the first year after incident GCA (Table C.5).
Table C.5. Mortality risks early and late after diagnosis of GCA. Associations of GCA with all-cause mortality, cardiovascular mortality and non-cardiovascular mortality in the first year-, first 5 years after incident GCA and during the total follow-up period.

Associations are expressed as sex and age-standardized IRRs with 95% CIs (GCA=Giant cell arteritis)

<table>
<thead>
<tr>
<th></th>
<th>1 year after GCA</th>
<th>5 years after GCA</th>
<th>Total follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td>1.25 (0.66-2.36)</td>
<td>1.49 (1.08-2.05)</td>
<td>1.39 (1.11-1.66)</td>
</tr>
<tr>
<td><strong>Cardiovascular Mortality</strong></td>
<td>0.75 (0.23-2.49)</td>
<td>1.51 (0.93-2.45)</td>
<td>1.56 (1.16-2.09)</td>
</tr>
<tr>
<td><strong>Non-cardiovascular Mortality</strong></td>
<td>1.68 (0.78-3.59)</td>
<td>1.49 (0.98-2.28)</td>
<td>1.28 (0.99-1.67)</td>
</tr>
</tbody>
</table>

**TABs and mortality risks**

Of the 19,253 subjects that contributed person-time to the RS study after the age of 50, 57 underwent a TAB before their study visit and are excluded from the analysis. Therefore, 19,196 subjects were included in the analysis on histopathology features of TABs. Six hundred and ninety two subjects underwent TAB during the follow-up time. Of them, 496 had negative TAB and the remaining 196 had GCA. For 69 (35.7%) of those with GCA, the biopsy was described as negative according to the original pathology report. Baseline characteristics and primary histologic features of subjects with negative and positive TAB are shown in Table C.6. Compared with those who never underwent TAB, subjects with either negative or positive TAB had increased mortality risks, with IRR being 1.83 (95% CI: 1.64–2.05) and 1.38 (95% CI: 1.15–1.67) respectively. For those with positive TAB, this increased risk was driven by the subjects with original pathology report negative for GCA (IRR= 2.02, 95% CI: 1.52–2.69); but those
with positive TAB and early histologic diagnosis of GCA had little increased mortality (IRR= 1.09, 95% CI: 0.84–1.41). Similar results were also observed for cardiovascular mortality (Table C.7).

<table>
<thead>
<tr>
<th></th>
<th>No TAB (n=18,498)</th>
<th>Negative TAB (n=501)</th>
<th>Positive TAB (GCA) (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>234,659 (53%)</td>
<td>3,225 (75%)</td>
<td>322 (71%)</td>
</tr>
<tr>
<td></td>
<td>322 (71%)</td>
<td></td>
<td>878 (73%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>112,129 (26%)</td>
<td>143 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>143 (3%)</td>
<td>0 (0%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>61-70</td>
<td>152,725 (35%)</td>
<td>840 (20%)</td>
<td>44 (10%)</td>
</tr>
<tr>
<td></td>
<td>840 (20%)</td>
<td>44 (10%)</td>
<td>217 (18%)</td>
</tr>
<tr>
<td>71-80</td>
<td>124,792 (28%)</td>
<td>2,034 (47%)</td>
<td>210 (46%)</td>
</tr>
<tr>
<td></td>
<td>2,034 (47%)</td>
<td>210 (46%)</td>
<td>616 (51%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>49,825 (11%)</td>
<td>1,267 (30%)</td>
<td>202 (44%)</td>
</tr>
<tr>
<td></td>
<td>1,267 (30%)</td>
<td>202 (44%)</td>
<td>366 (30%)</td>
</tr>
<tr>
<td>Intima thickening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-none</td>
<td>519 (12%)</td>
<td>0 (0%)</td>
<td>18 (2%)</td>
</tr>
<tr>
<td>-mild</td>
<td>2,421 (57%)</td>
<td>33 (8%)</td>
<td>16 (1%)</td>
</tr>
<tr>
<td>-moderate</td>
<td>1,220 (29%)</td>
<td>275 (63%)</td>
<td>408 (34%)</td>
</tr>
<tr>
<td>-severe</td>
<td>73 (2%)</td>
<td>132 (30%)</td>
<td>759 (63%)</td>
</tr>
<tr>
<td>Calcification</td>
<td>237 (6%)</td>
<td>46 (10%)</td>
<td>148 (13%)</td>
</tr>
<tr>
<td>Inflammatory intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-mild</td>
<td>311 (68%)</td>
<td>123 (10%)</td>
<td></td>
</tr>
<tr>
<td>-moderate</td>
<td>97 (21%)</td>
<td>486 (40%)</td>
<td></td>
</tr>
<tr>
<td>-severe</td>
<td>47 (10%)</td>
<td>600 (50%)</td>
<td></td>
</tr>
<tr>
<td>Giant Cells</td>
<td>166 (37%)</td>
<td>984 (81%)</td>
<td></td>
</tr>
</tbody>
</table>

Table C.6. Baseline characteristics and primary histologic findings among subjects who did not undergo TAB, subjects with negative TABs, and subjects with positive TABs further stratified according to whether TAB was originally reported negative or positive. Characteristics expressed as number of person-years (percentage) in each stratum (TAB=Temporal artery biopsy, GCA=Giant cell arteritis, BMI=body mass index, ESR=erythrocyte sedimentation rate, IQR=interquartile range)
<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>CVD Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Temporal artery biopsy</strong></td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>Biopsy results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.83(1.64-2.05)</td>
<td>2.02(1.72-2.38)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- originally reported negative</td>
<td>2.18(1.65-2.90)</td>
<td>2.34(1.57-3.49)</td>
</tr>
<tr>
<td>-- originally reported positive</td>
<td>1.10(0.85-1.42)</td>
<td>1.06(0.71-1.58)</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2.15(1.60-2.88)</td>
<td>2.13(1.36-3.32)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.26(0.85-1.85)</td>
<td>1.38(0.78-2.43)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.13(0.81-1.57)</td>
<td>1.07(0.65-1.78)</td>
</tr>
<tr>
<td>Adventitia Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>1.94(1.14-3.32)</td>
<td>1.94(1.14-3.32)</td>
</tr>
<tr>
<td>present</td>
<td>1.33(0.95-1.86)</td>
<td>1.33(0.95-1.86)</td>
</tr>
<tr>
<td>Media Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>2.30(1.57-3.37)</td>
<td>2.43(1.37-4.29)</td>
</tr>
<tr>
<td>present</td>
<td>1.25(1.01-1.56)</td>
<td>1.26(0.91-1.76)</td>
</tr>
<tr>
<td>Intima Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>2.53(0.62-10.29)</td>
<td>1.88(0.47-7.53)</td>
</tr>
<tr>
<td>present</td>
<td>1.39(1.15-1.68)</td>
<td>1.40(1.05-1.86)</td>
</tr>
<tr>
<td><strong>Extent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 layer</td>
<td>2.49(1.66-3.72)</td>
<td>2.11(1.08-4.15)</td>
</tr>
<tr>
<td>2 layers</td>
<td>1.74(0.93-3.27)</td>
<td>1.66(0.81-3.39)</td>
</tr>
<tr>
<td>3 layers</td>
<td>1.24(0.98-1.56)</td>
<td>1.24(0.87-1.77)</td>
</tr>
<tr>
<td><strong>Intima hyperplasia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative biopsies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- none</td>
<td>1.23(0.73-2.07)</td>
<td>1.22(0.53-2.82)</td>
</tr>
<tr>
<td>-- mild</td>
<td>1.71(1.47-1.98)</td>
<td>1.89(1.53-2.35)</td>
</tr>
<tr>
<td>-- moderate</td>
<td>2.24(1.86-2.69)</td>
<td>2.61(2.00-3.40)</td>
</tr>
<tr>
<td>-- severe</td>
<td>2.00(0.85-4.72)</td>
<td>1.13(0.16-8.06)</td>
</tr>
<tr>
<td>Positive biopsies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- none</td>
<td>1.72(0.24-12.18)</td>
<td>-</td>
</tr>
<tr>
<td>-- mild</td>
<td>0.54(0.17-1.69)</td>
<td>0.64(0.13-3.09)</td>
</tr>
<tr>
<td>-- moderate</td>
<td>1.57(1.20-2.06)</td>
<td>1.60(1.07-2.40)</td>
</tr>
<tr>
<td>-- severe</td>
<td>1.32(1.00-1.74)</td>
<td>1.34(0.88-2.05)</td>
</tr>
<tr>
<td><strong>Giant cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>1.93(1.45-2.58)</td>
<td>1.89(1.24-2.89)</td>
</tr>
<tr>
<td>present</td>
<td>1.19(0.92-1.54)</td>
<td>1.23(0.83-1.80)</td>
</tr>
<tr>
<td><strong>Fibrinoid deposition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>1.48(1.20-1.82)</td>
<td>1.45(1.05-2.00)</td>
</tr>
<tr>
<td>present</td>
<td>1.16(0.73-1.84)</td>
<td>1.24(0.63-2.45)</td>
</tr>
<tr>
<td><strong>Eosinophils</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>1.41(1.15-1.72)</td>
<td>1.41(1.03-1.91)</td>
</tr>
<tr>
<td>present</td>
<td>1.07(0.31-3.68)</td>
<td>-</td>
</tr>
</tbody>
</table>
Mortality | CVD Mortality
--- | ---
**Calcification**
Negative biopsies 
-- absent | 1.74 (1.55-1.96) | 1.91 (1.61-2.26)
-- present | 3.64 (2.45-5.41) | 5.45 (3.14-9.45)
Positive biopsies 
-- absent | 1.38 (1.12-1.69) | 1.48 (1.09-2.02)
-- present | 2.06 (1.20-3.53) | 1.35 (0.54-3.38)

Table C.7. The association of temporal artery biopsies and histologic features with all-cause mortality and cardiovascular mortality. The association of each level of biopsy finding/histologic feature with study outcomes is expressed as IRR with 95% CI with those that never underwent TAB as the referent group (CHD=Coronary heart disease, CVD=cardiovascular disease, IRR=incidence rate ratio, CI=confidence interval). * Only assessed on positive temporal artery biopsies

**Histopathology and mortality risks**

TABs that were originally reported positive for GCA where characterized by more severe intima hyperplasia (thickening), more intense infiltration of inflammatory cells and more frequently observed giant cells than those TABs that were originally reported negative but found positive for the purpose of this study (Table C.6).

Among those with negative TABs, intima hyperplasia and calcifications were markedly associated with mortality (Table C.7). Among subjects with GCA, mild inflammatory intensity was associated with higher mortality risks than those with moderate and severe inflammatory intensity, IRR=2.15 (95% CI: 1.60–2.88),
An inverse association between inflammatory intensity was also observed with cardiovascular mortality. These inverse associations were not driven by those with GCA who originally had TAB reported as negative, as analysis restricted to those with early histologic diagnosis of GCA, showed inverse associations between inflammatory intensity and mortality risks (Table C.8).

In the analysis of association of histopathology features with mortality no substantial effect measure modification between men and women was observed (results not shown).

<table>
<thead>
<tr>
<th>No Temporal artery biopsy</th>
<th>Mortality</th>
<th>CVD Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsies originally reported negative</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Inflammatory intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-mild</td>
<td>2.65(1.81-3.87)</td>
<td>2.34(1.39-3.95)</td>
</tr>
<tr>
<td>-moderate</td>
<td>1.46(0.58-3.68)</td>
<td>2.60(0.85-8.01)</td>
</tr>
<tr>
<td>-severe</td>
<td>2.06(0.87-4.90)</td>
<td>3.69(1.30-10.48)</td>
</tr>
<tr>
<td>Biopsies originally reported positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(early histologic diagnosis of GCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-mild</td>
<td>1.43(0.74-2.77)</td>
<td>1.86(0.76-4.51)</td>
</tr>
<tr>
<td>-moderate</td>
<td>1.23(0.80-1.90)</td>
<td>1.19(0.60-2.34)</td>
</tr>
<tr>
<td>-severe</td>
<td>0.98(0.68-1.43)</td>
<td>0.80(0.43-1.49)</td>
</tr>
</tbody>
</table>

Table C.8. The association of levels of inflammatory intensity on mortality and cardiovascular mortality among subjects with GCA stratified according to whether the diagnosis of GCA was made by the original biopsy report. The association of each level of inflammatory intensity with study outcomes is expressed as age- and sex standardized IRRs with 95% CI (CVD=cardiovascular disease, CHD=Coronary heart disease)
Discussion

This study finds a modest association between GCA and all-cause mortality. This finding is mainly driven by subjects who had biopsies were classified as having GCA for the purpose of this study but were not diagnosed with GCA on the basis of the original pathology report. On the other hand, subjects with an early histologic diagnosis of GCA have mortality risks similar to those of the general population. This study suggests an inverse relationship between inflammatory changes on TABs and mortality risks.

This study has important strengths. Detailed pathologic examination was done according to a predefined protocol on all TABs obtained in a well-defined population-based cohort. Identifying a group of patients with GCA, who was not diagnosed with GCA at the time of TAB, could provide a valuable insight to the natural history of GCA pertaining to mortality risks.

This study also has several limitations. No data on clinical presentation and treatment are available; thus we have no information of the clinical diagnosis by the treating physician who might have made the diagnosis of GCA based on clinical findings. However, that practice appears to be rare in Iceland (14). Data on ESR and cardiovascular risk factors were obtained long before TABs were performed.

In contrast to some other studies (4, 5, 8), we did not find an increased mortality risks in the first year after incident GCA, but the IRRs are too imprecise to draw
firm conclusions. It is not surprising that a negative TAB is associated with increased mortality risks as those who undergo TAB are often patients with some undefined illness requiring hospitalization. Our study is consistent with most previous studies reporting no or minimal increased mortality risks among subject diagnosed with GCA (1-7) compared with the general population. The finding of substantial effect-measure modification based on whether diagnosis of GCA was made on the original pathology report is intriguing. There are at least four scenarios that could explain this finding: First, it is likely that several of the patients classified as having GCA for the purpose of this study with no mention of GCA on the original pathology report and never were clinically diagnosed with GCA later; thus, these subjects may have never received treatment with high dose glucocorticoids. It is possible that anti-inflammatory treatment for GCA that is mainly targeted towards symptoms and to prevent ocular complications also has benefits with respect to mortality risks. Second, it is possible that our findings are driven by misclassification of GCA status, that most of the 71 subjects that we classify as having GCA but were not diagnosed with GCA according to the original pathology report, are indeed free of GCA; thus they could have experienced the same elevated risk for the study outcomes as those with truly negative biopsies. Third, our data suggest that those with less inflammatory intensity on TAB are at higher all-cause mortality- and cardiovascular mortality risks. This counterintuitive finding (see below) could partially explain why those with GCA but without early histologic diagnosis have higher mortality risks.
Fourth, it is possible that our findings are driven by chance. While an inverse association between inflammatory intensity and several study outcomes are consistently found, our estimates are driven by few events among those with GCA and are surrounded by wide confidence intervals.

The finding of an inverse association between inflammatory intensity on TAB and study outcomes was unexpected. We are not aware of any published studies describing the association between histologic findings and CHD and/or mortality. There was a paucity of data on the association between histologic features of TABs, clinical symptoms and outcomes in GCA (10, 15-17). One study has reported that inflammatory intensity is not associated with visual loss among patients with GCA (10). Two studies have found that intima hyperplasia was associated with cranial ischemic complications (10, 11). In this study, no clear association was found between intima hyperplasia and study outcomes among subjects with GCA, although there was a clear association of intima hyperplasia with CHD and mortality among those with truly negative biopsies. It is evident that the inverse relationship between inflammatory intensity and mortality risks observed in this study must be produced by a strong confounder. One such confounder could be duration of disease: specifically, subjects with low level of inflammation have had longer disease duration that had gone undetected for longer periods of time than those with intensive inflammatory infiltration.

Susceptibility to treatment is another potential confounder of this association that is, patients with less intense inflammation might be more resistant to treatment
than those with intense vascular inflammation.

Sub-distribution risk ratio for the association of GCA with cardiovascular mortality accounting for the competing event of other causes of mortality obtained from the Fine and Gray model was substantially lower than the IRR and cause-specific hazards ratio obtained from the traditional Cox proportional hazards model. The underlying distribution for Fine and Gray model is the cumulative incidence function but the underlying distribution for the Cox model is the hazard function. In this older age population with long follow-up time over 50% of subjects experienced the competing event (mortality). With long follow-up times, cumulative incidence of mortality approaches 1. Those modeling differences may be the explanation for the discrepant results between the two modeling approaches. In an analysis of the association of GCA with cardiovascular mortality restricted to the first five years, cause specific hazards ratio and sub-distribution risk ratio gave similar numerical estimates (HR=1.81 and sub-distribution risk ratio 1.76). A recent study originating from the RS cohort on cumulative incidence of bony fractures found that estimates adjusted for competing event of death only deviated from unadjusted estimates after long periods of follow-up (18).

In summary, patients diagnosed with GCA have similar cardiovascular- and all-cause mortality risks as those observed for the general population. However, subjects without early histologic diagnosis of GCA and those with very mild inflammatory changes on TAB have substantially increased mortality risks.
References


Appendix A: SAS macro for calculations of standardized incidence ratios

/*

The levelstrat macro provides standardized incidence rate ratios
with 95% CI. across age and across level of variables
specified by the user.
the data set must contain the following variables

1. py50to60: number of person-years contributed by the
subject from
the age of 50 to 60.
2. py60to70: number of person-years contributed by the
subject from
the age of 60 to 70.
3. py70to80: number of person-years contributed by the
subject from
the age of 70 to 80.
4. pypost80: number of person-years contributed by the
subject from
after the age of 80.

The following variables need to be specified when the macro
is executed

DATA= name of data set
OUTCOME=outcome variable that takes the level of 0 if
outcome did not occur,
takes the level of 1 if outcome occurred between the age of
50 to 60, 2 if
the outcome occurred between the age of 60 to 70, 3 if the
outcome occurred
between the age of 70 to 80 and 4 if the outcome occurred
after the age of 80.
MAIN=Exposure variable of primary interest.
LEVEL=The number of possible values for the MAIN variable
(2 for dichotomous)
weight will be based on person-type contributed by sum of
person-years with
main=1 in each strata.
STRATLIST=Up to 10 variables across which estimates will be
standardized.
RESTRICTVAR and RESTRICTVAL. for calculation of subset of the data for example if in a restricted analysis to man, RESTRICTVAR is specified as man and then RESTRICTVAL=1. RESTRICTVAR and RESTRICTVAL should be left blank if all observations are to be used.

*/

%macro
levelstrat(data,outcome,main,level,stratlist,restrictvar,restrictval);
data limdata;
set &data;
if &restrictvar=&restrictval;
run;

%let agelist=py50to60 py60to70 py70to80 pypost80;
%let a=%length(&stratlist);
%put &a;
%do j=1 %to 4;
    %let agef = %qscan(&agelist, &j);
    %let age&j=%upcase(&agef);
%if &a^=0 %then %do;
    %do count=1 %to 10;
        %let stratf = %qscan(&stratlist, &count);
        %let strat&count=%upcase(&stratf);
        %if (&stratf ne) %then %let numstrat=&count;
    %end;
%end;

%let freqset= macrotrikk;
%let sortset= macrotrikk;
%let type=111;
%let commaset=marcrotrikk,agegroup;
%if &a^=0 %then %do;
    %do i = 1 %to &numstrat;
        %let curstrat = &&strat&i;
        %let freqset= &freqset * &curstrat;
    %end;
%end;
ods output summary=sjit;
proc means data=limdata sum;
*where bxstatus3 ne 4;
class macrotrikk &stratlist &main;
var &&age&j;
run;
ods output close;
ods output summary=sjit2;
proc means data=limdata sum;
class macrotrikk &stratlist &main;
var &&age&j;
run;
ods output close;
proc sort data=sjit;
by &stratlist &main;
run;
proc sort data=sjit2;
by &stratlist &main;
run;
ods output CrossTabFreqs=prestuff;
proc freq data=limdata;
*where bxstatus3 ne 4;
tables &freqset * &main * &outcome/nocol norow
nopercent;
run;
ods output close;
data stuff;
set prestuff;
if &outcome=&j and _type_="&type";
run;
proc sort data=stuff;
by &stratlist macrotrikk;
run;

data mix&j;
merge sjit stuff;
by &stratlist macrotrikk;
agegroup=&j;
fyyears=&&age&j.._Sum;
run;

data wprep&j;
set sjit2;
agegroup=&j;
weightyears=&&age&j.._Sum;
run;
%end;

data catprep;
set mix1 mix2 mix3 mix4;
run;

data weightprep;
set wprep1 wprep2 wprep3 wprep4;
if &main=1;
run;

proc sort data=catprep;
by agegroup &stratlist &main;
run;

proc sort data=weightprep;
by agegroup &stratlist &main;
run;

data combined;
merge weightprep catprep;
by agegroup &stratlist;
run;

proc sort data=combined;
by macrotrikk agegroup &main ;
run;
ods rtf file="C:\Users\Gunnar\Documents\GCA\study 2\augustremake\data\&main.Stratified.rtf";
proc print data=combined;
var macrotrikk agegroup &stratlist &main frequency fuyears weightyears;
run;
ods rtf close;

data combined2;
set combined;
strats=cats(&commaset);
exposed=&main;
keep strats macrotrikk agegroup &main frequency fuyears weightyears;
run;

proc sort data=combined2;
by strats descending &main;
run;

data combined3;
set combined2;
by strats descending &main;
retain fu_exposed1-fu_exposed&level freq_exposed1-
freq_exposed&level;

%do k=1 %to &level;
    if &level=2 then do;
        if &main=2 then do;
            fu_exposed2=fuyears;
            freq_exposed2=frequency;
        end;
        if &main=1 then do;
            fu_exposed1=fuyears;
            freq_exposed1=frequency;
        end;
    end;
else if &main=&k then do;
    fu_exposed&k=fuyears;
    freq_exposed&k=frequency;
end;
%end;
weight=weight*years;
keep macrotrikk &main fu_exposed1-fu_exposed&level
freq_exposed1-freq_exposed&level fuyears weight;
if last.strats then output;
run;

data combined4;
set combined3;
%do m=1 %to &level;
  if fu_exposed&m ne 0 then
  rate_exposed&m=freq_exposed&m/fu_exposed&m; else
  rate_exposed&m=0;
  wR_exposed&m=rate_exposed&m*weight;
  if fu_exposed&m ne 0 then
  WWvar_exposed&m=weight**2*rate_exposed&m/fu_exposed&m; else
  WWvar_exposed&m=0;
%end;
run;

ods output summary=sumstoff;
proc means data=combined4 sum;
class macrotrikk;
var
rate_exposed1-rate_exposed&level
wR_exposed1-wR_exposed&level
WWvar_exposed1-WWvar_exposed&level
weight;
run;
ods output close;

data sumstoff2;
set sumstoff;
keep macrotrikk
%do n=1 %to &level;
  rate_exposed&n._sum  wR_exposed&n._sum
  WWvar_exposed&n._sum
%end;
weight_sum
;
run;

data sumstoff3;
set sumstoff2;
%do x=1 %to &level;
\[ \text{stdrate\_exposed}\_x = \frac{wR\_exposed\_x\_\sum/\text{weight}\_\sum}{\text{stdrate}\_\sum/\text{weight}\_\sum}; \]

\%end;
\%do y = 2 %to &level;
  stdIRR\_y = \text{stdrate}\_\text{exposed}\_y/\text{stdrate}\_\text{exposed}\_1;
  \log\text{stdERR}\_y = \sqrt{(\text{WWvar}\_\text{exposed}\_1\_\sum/wR\_\text{exposed}\_1\_\sum^2) + (\text{WWvar}\_\text{exposed}\_y\_\sum/wR\_\text{exposed}\_y\_\sum^2)});
  \text{stdIRR}\_y\_\text{up} = \exp(\log(\text{stdIRR}\_y) + 1.96*\log\text{stdERR}\_y);
  \text{stdIRR}\_y\_\text{lo} = \exp(\log(\text{stdIRR}\_y) - 1.96*\log\text{stdERR}\_y);
\%end;
run;

data sumstoff4;
set sumstoff3;
\%do z = 2 %to &level;
  keep macrotrikk stdIRR\_z stdIRR\_z\_\text{lo} stdIRR\_z\_\text{up};
\%end;
run;

proc print data = sumstoff4;
run;

data sumstoff5;
set sumstoff4;
\%do z = 2 %to &level;
  \text{IRR}\_z = \text{round}(\text{stdIRR}\_z, .01);
  \text{LCL}\_z = \text{round}(\text{stdIRR}\_z\_\text{lo}, .01);
  \text{UCL}\_z = \text{round}(\text{stdIRR}\_z\_\text{up}, .01);
  \text{charIRR}\_z = \text{put}(\text{IRR}\_z, 7.2);
  \text{charLCL}\_z = \text{put}(\text{LCL}\_z, 7.2);
  \text{charUCL}\_z = \text{put}(\text{UCL}\_z, 7.2);
  \text{estimate}\_z = \text{cats}(\text{charIRR}\_z, " (", \text{charLCL}\_z,"-\text{charUCL}\_z, ")");
\%end;
run;

proc print data = sumstoff5;
run;

data sumstoff6;
set sumstoff5;
\%do z = 2 %to &level;
  keep macrotrikk \text{estimate}\_z;
\%end;
run;
proc print data=sumstoff6;
run;

data sumstoff7;
set sumstoff6;
estimate1=" 1 (ref)";
array estimates[&level] estimate1-estimate&level;
if macrotrikk=0 then do i=1 to &level;
   sex="women";
   level=i;
   estimate=estimates[i];
   output;
end;
if macrotrikk=1 then do j=1 to &level;
   sex="macrotrikk";
   level=j;
   estimate=estimates[j];
   output;
end;
keep sex level estimate;
run;

ods rtf file="C:\Users\Gunnar\Documents\GCA\study 2\augustremake\data\&outcome.&main..rtf";
proc print data=sumstoff7;
title "Effect of &main standardized according to age &stratlist";
run;
ods rtf close;

%mend levelstrat;
Appendix B: SAS macro for evaluation for cyclical incidence

```sas
%macro circular(inclist);
%do count=1 %to 100;
  %let incf= %qscan(&inclist, &count);
  %let incf&count=%upcase(&incf);
  %if (&incf ne) %then %let numincidence=&count;
%end;

data one;
  array counts [&numincidence] inc1-inc&numincidence (&inclist);
  N=sum(of counts[*]);
  k=&numincidence;
  pi=3.14156592;
  do i=1 to k;
    theta=(2*pi*i)/k;
    par1=1/k*counts[i]*sin(theta);
    par2=1/k*counts[i]*cos(theta);
    output;
  end;
  keep N k par1 par2;
run;

proc sort data=one;by k;run;

data two;
  set one;
  by k;
  retain sumpar1;
  if first.k then sumpar1=par1;
  else sumpar1=par1+sumpar1;
  retain sumpar2;
  if first.k then sumpar2=par2;
  else sumpar2=par2+sumpar2;
  if last.k then output;
  keep sumpar1 sumpar2 k N;
run;

data three;
  set two;
  D=sqrt(sumpar1**2 + sumpar2**2);
```
alpha=2*k*D/N;
R=(1+alpha)/(1-alpha);
VARalpha=2/N;
SElnR=(2*sqrt(VARalpha)/((1+alpha)*(1-alpha)));
Rlower=exp(log(R)-1.96*SElnR);
Rupper=exp(log(R)+1.96*SElnR);
run;

proc print data=three;
run;
%mend circular;

%circular(18 21 36 37 32 25 22)
/*
18 is the total number of subjects with gca in 1980, 1987, 1994 and 2001
21 is the total number of subjects with gca in 1981, 1988, 1995 and 2002
36 is the total number of subjects with gca in 1982, 1989, 1996 and 2003
37 is the total number of subjects with gca in 1983, 1990, 1997 and 2004
32 is the total number of subjects with gca in 1984, 1991, 1998 and 2005
25 is the total number of subjects with gca in 1985, 1992, 1999 and 2006
22 is the total number of subjects with gca in 1986, 1993, 2000 and 2007
*/
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Education:
2009-present: Boston University School of Public Health (Doctorate program in epidemiology)

Postgraduate Training and Fellowship Appointments
2008-2010: Research and vasculitis fellow. Boston University Medical Center, Boston MA.
2006-2008: Rheumatology fellow. Boston University Medical Center, Boston MA.
2003-2006: Internal Medicine Resident. University of Wisconsin Hospital and Clinics, Madison WI.
2000-2002: Internship and informal residency program. Landspitali University Hospital, Reykjavik Iceland.

Appointments
2010-present: Practicing rheumatologist, Reykjavik Iceland (30% effort)
2012-present: Research associate University of Iceland
2015-present: Independent contractor working for University of Pennsylvania (20% effort)
2012-2014: Independent contractor working for University of Pennsylvania (40% effort).
2010-2011: Research Associate Boston University (60% position).

Specialty Certification
2006: American Board of Internal Medicine: Internal Medicine
2009: American Board of Internal Medicine: Rheumatology.

Current Medical Licensure
Iceland
Memberships in Professional & Scientific Societies
2006-present: American College of Rheumatology
2000-present: The Icelandic Medical Society

Editorial Positions:
2015-present: Journal of Rheumatology: Editorial Board member.
2012-present: Arthritis and Rheumatology (formerly Arthritis and Rheumatism):
Advisory editor
2009-present: Reviewer: Annals of Internal Medicine, Arthritis Care and
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Competent computer programmer in the PHP programming language
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