RHEUMATOLOGY

Rheumatology 2018;57:1047–1055
doi:10.1093/rheumatology/key028
Advance Access publication 14 March 2018

Original article

Mortality causes and trends associated with giant cell arteritis: analysis of the French national death certificate database (1980–2011)

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Abstract

Objectives. Comprehensive analyses of cause-specific death patterns in GCA are sparse. We studied the patterns and time trends in GCA-related mortality using a large death certificate database.

Methods. We obtained multiple-cause-of-death data from the French national death certificate database for 1980–2011. GCA-associated deaths were defined as decedents $\geqslant$55 years old with GCA listed as an underlying or non-underlying cause of death. Time trends of death rates were analysed and the mean age at death with GCA and in the general population $\geqslant$55 years old were calculated. Standardized mortality odds ratios (SMORs) were calculated for 17 selected causes of death (based on 2000–11 data).

Results. The analyses pertained to approximately 15 000 death certificates listing GCA (including approximately 6300 for 2000–11). Annual standardized death rates for GCA increased to a peak in 1997 and then decreased (Spearman's correlation test, both $P < 0.0001$). Mean age at death was higher for GCA than for general population decedents (Student's *t*-test, $P < 0.0001$). GCA deaths were frequently or strongly associated with aortic aneurysm and dissection (1.85% of death certificates, SMOR: 3.09, 95% CI: 2.48, 3.82), hypertensive disease (20.78%, SMOR: 2.22, 95% CI: 1.97, 2.50), diabetes mellitus (11.27%, SMOR: 1.96, 95% CI: 1.72, 2.23), certain infectious and parasitic diseases (12.12%, SMOR: 1.76, 95% CI: 1.55, 2.00) and ischaemic heart disease (16.54%, SMOR: 1.45, 95% CI: 1.35, 1.64).

Conclusion. GCA is associated with increased risk of dying from large-vessel disease, other cardiovascular diseases and potentially treatment-related co-morbidities. These findings help provide better insights into the outcomes of GCA.

Key words: giant cell arteritis, mortality, multiple-cause-of-death analysis, cardiovascular disease, cancer

Rheumatology key messages

- Deaths from cardiovascular and potentially treatment-related causes are overrepresented in decedents with GCA.
- Conversely, GCA is associated with decreased risk of death caused by malignant neoplasms.
- For reasons that are unclear, the mortality rates for GCA have declined since 1995–2000.

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Submitted 21 October 2017; revised version accepted 25 January 2018

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Introduction

GCA is a rare vasculitis of the aorta and its branches that affects individuals $\geqslant$50 years old, and more commonly females and people of northern European background. The aetiology of GCA is unknown. First-line treatment relies on glucocorticoids for 18–24 months, although the frequently relapsing disease course often requires maintaining glucocorticoid therapy for longer periods and sometimes the addition of cytotoxic or biologic agents. The most feared complications are blindness due to

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optic ischaemic neuropathy and aortic aneurysms [1, 2], but also side effects of long-term immunosuppressive therapy [3].

Questions remain on the impact of a GCA diagnosis on survival. Current data suggest that a GCA diagnosis only marginally increases the overall mortality as compared with the general population [4]. However, these data do not preclude that risk of cause-specific deaths with GCA may differ from that in the general population. Results of several studies indicate that GCA is associated with increased mortality due to cardiovascular disease [5, 6] or infections [7, 8]. Cohort studies, which are generally small because of the rarity of GCA, do not allow for comprehensive analysis of the cause-specific mortality risks in GCA. In contrast, death certificate databases provide the opportunity to generate quantitative and qualitative data on the mortality of given illnesses in large populations and for long time periods. In particular, multiple-cause-of-death analysis, which takes into account both underlying and non-underlying causes of death (UCD and NUCD, respectively) reported in death certificates, enables powerful analysis of death patterns of diseases [9].

We performed a multiple-cause-of-death analysis of the French national death certificate database to describe the temporal and demographic characteristics of mortality in GCA and to study the cause-specific mortality patterns associated with GCA.

Methods

Data sources

The French Epidemiological Center for the Medical Causes of Death (CépiDc) has compiled nationwide information on causes of death since 1968. For each death occurring on French territory, a physician mandatorily completes a two-part death certificate. The certificate gathers a ranked list of 'diseases directly related to the morbid process leading to death' (part 1) and 'other significant conditions contributing to the death, but not related to the diseases or conditions reported in part 1' (part 2). Among the conditions listed in part 1, the CépiDC assigns a single UCD to each death according to internationally adopted rules; all other conditions listed in either part are considered NUCDs. The UCD and NUCDs are coded according to the 9th and, since 2000, the 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10, respectively). The process of coding the causes of death and selecting the UCD was performed manually by experienced coders until 2000 and thereafter automatically with the coding software Styx [10]. Data on the number of decedents with a specific UCD or NUCD code, aggregated by calendar year, sex and age, have been stored in a computerized database since 1979. In addition to the aggregate data, since 2000, the CépiDc database has stored detailed information on UCDs and NUCDs of decedents at the individual level.

For the period 1980–2011, we retrieved data on GCA-associated deaths defined as death certificates that contained the ICD-9 code 446.5 or the ICD-10 codes M31.5 or M31.6 as UCD or NUCDs. Data were obtained as number of decedents aggregated by calendar year, sex, 10-year age groups (55–64, 65–74, 75–84, 85–94, $\geqslant$95 years) and GCA code position as UCD or NUCD. For all death certificates from 2000 onward, we additionally extracted the multiple-cause-of-death data with individual-level information on each GCA-associated death. The same information for the general population was obtained from the CépiDc website [11] or specifically extracted from the CépiDc database.

Data extraction concerned exclusively mainland France, because complete data from overseas France was available only since 2000. For all analyses, we used only the data from decedents $\geqslant$55 years old; the 55-year cut-off (rather than 50 years) was chosen to comply with the age-group categorization for aggregated data in the CépiDc database. In accordance with the French policy, no specific ethical approval was required for our study, which used aggregated or anonymized data.

Descriptive analyses

Annual death rates for GCA were computed for 1980–2011 by using as a denominator the size of the mainland French population [12]. Rates were sex- and age-standardized by the direct method, with the European population as a reference [13]. Death rates were computed for all GCA decedents combined and by sex, age groups and GCA as UCD or NUCD.

Mean age at death was calculated for each calendar year and across the entire 32-year period for GCA and for all-cause deaths in the general population and separately by sex. Because the original data were aggregated by age groups, we used the midpoint of each class interval as the values for age at death. To calculate mean age at death in the general population, we used the data restricted to deaths occurring with age $\geqslant$55 years. We used Spearman's correlation analysis to assess the trends of death rates and mean age of death over time.

Causes of death analyses

To investigate cause-specific death patterns in GCA, we computed standardized mortality odds ratios (SMORs) with 95% CIs for 17 selected medical conditions chosen by their frequent occurrence in the general population or because they were previously linked with GCA morbidity or mortality [5–8]. Because such analyses require information on the detailed UCDs and NUCDs listed on individual death certificates, this analysis was feasible for only CépiDc data stored from 2000 onward. SMORs are calculated by using a simulated case–control study design in which the underlying disease (here: GCA) represents the exposure, and cases and controls represent the number of occurrences of deaths related to the cause under study and to an exposure-unrelated cause, respectively. In the context of our analyses, we chose external causes of morbidity and mortality (ICD-10 codes: V01–Y98) as controls because they were deemed aetiologically unrelated to GCA. For both cases and controls, the non-exposed group was the number of deaths related to these causes

in the general population. SMORs, which represent the ratio of odds of case and control death occurrences in the exposed (here: GCA) to the non-exposed (here: general population) groups, were derived by logistic regression analysis and were internally standardized by adding sex, age group and calendar year as covariates to the models [9].

For the causes of death found in the primary analysis as highly common in GCA decedents or strongly associated with GCA, SMORs were calculated by age at death (<75 *vs* ⩾75 years), sex and calendar period (2000–02, 2003–05, 2006–08 and 2009–11). Interaction terms were added to the logistic regression models to test whether SMORs significantly varied between subgroups. In addition to the multiple-cause-of-death analysis, we performed a sensitivity analysis by calculating SMORs for the 17 selected causes of death by considering only the death causes listed as UCD for people with GCA and from the general population.

Statistical principles and software

Categorical variables are presented as number (%) and were compared by Chi-square test. Continuous variables are presented as mean (S.D.) and were compared by Student's *t*-test or Mann–Whitney *U* test depending on the normality of the variables assessed by the Shapiro-Wilk test. The significance threshold for *P*-values was set at 0.05. SMORs were considered statistically significant if the 95% CI did not include 1. Statistical analyses involved use of R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Death rates and age at death (period 1980–2011)

Among 14 927 440 deaths recorded, 15 020 death certificates listed GCA as a cause of death. In all, 24 death certificates referred to decedents <55 years old; therefore, the analyses pertained to 14 996 death certificates for decedents ⩾55 years old: 13 540 (90.29%), 10 174 (67.84%) and 9418 (62.80%) were for decedents ⩾75 years old, females and GCA listed as NUCD, respectively.

Fig. 1 plots the annual GCA death rates for the 32-year period for all people with GCA and by age group, sex and GCA listed as UCD or NUCD. The plots indicated a biphasic time course with an initial increase in death rate (per 100 000 inhabitants ⩾55 years old) from 2.01 (year 1980) to 4.04–4.37 (period 1995–2000) and a subsequent decline to 2.11 (year 2011). With the peak rate of 4.37 for 1997 used as a break point, Spearman's rank correlation indicated a significant increase during 1980–97 (Spearman's ρ: 0.967; $P < 0.0001$) and a significant decrease during 1998–2011 (Spearman's ρ: −0.916; $P < 0.0001$). Closely similar bell-shaped patterns were seen in subgroups. The annual death rate across the entire 32 years was 3.16 (95% CI: 3.11, 3.21).

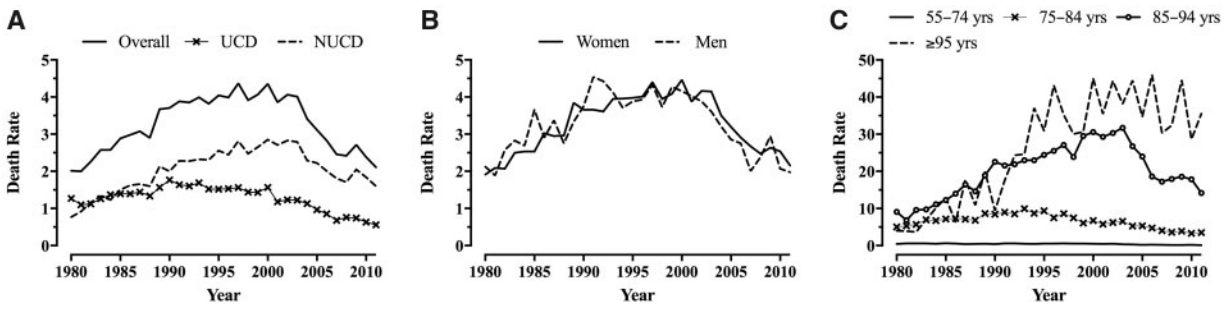
For decedents with GCA, the mean age at death was 83.2 (2.3) years; for women and men, the mean age was 83.9 (2.3) and 81.8 (2.2) years, respectively. The comparative age values for the general population were 79.1, 82.0 and 76.0 years and were significantly lower than for decedents with GCA ($P < 0.0001$ for all three comparisons). The mean age at death was 83.7 (2.3) and 83.0 (2.5) years for decedents with GCA recorded as UCD and NUCD, respectively. When restricting the analysis to decedents ⩾75 years old, the mean age at death was 84.9 (1.7) for decedents with GCA and did not differ from the mean age at death of 85.0 years for the general population ($P = 0.47$).

Fig. 2 plots the time trends of mean age at death for decedents with GCA and general population decedents ⩾55 years old: the mean age increased from 79.6 and 77.4 years old in 1980 to 86.2 and 80.7 years old in 2011. Spearman's correlation showed increasing trends of mean ages at death by calendar year in decedents with GCA and general population decedents (Spearman's ρ: 0.980 and 0.966; $P < 0.0001$ for both analyses). During the 32-year period, the difference in mean age at death between decedents with GCA and general population decedents increased significantly over time (Spearman's ρ: 0.958; $P < 0.0001$).

Causes of death and SMORs (period 2000–11)

We analysed 6313 GCA-related death certificates with individual multiple-cause-of-death data for the period 2000–11, all referring to decedents ⩾55 years old; 5917 (93.73%), 4417 (69.97%) and 4427 (70.12%) corresponded to decedents ⩾75 years old, females and death certificates listing GCA as NUCD, respectively. The

Fig. 1 Age- and sex-standardized death rates (per 100 000 inhabitants ⩾55 years) for GCA



The panels show mortality rate plots for all decedents combined and separately for those with GCA coded as an underlying and non-underlying cause of death (UCD and NUCD) in death certificates (**A**), and by sex (**B**) and age groups (**C**).

FIG. 2 Mean age at death for decedents with GCA and general population decedents ⩾55 years old

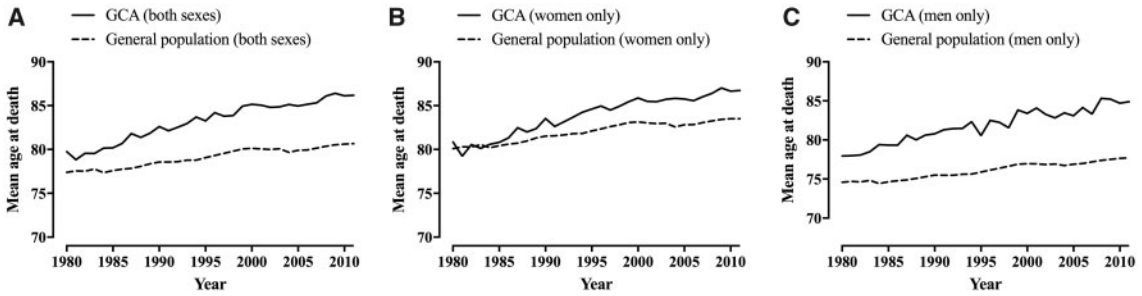


TABLE 1 Causes of death and SMORs for decedents with GCA

Underlying and non-underlying causes of death (ICD-10 codes)	Observed no. of deaths (%)		SMOR (95% CI)
	GCA (*N* = 6313)	General population (*N* = 5 653 629)	
Certain infectious and parasitic diseases (A00–B99)	765 (12.12)	433 487 (7.67)	1.76 (1.55, 2.00)
Malignant neoplasms (C00–C80/C97)	598 (9.47)	1 587 130 (28.07)	0.52 (0.45, 0.59)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue (C81–C96)	136 (2.15)	166 733 (2.95)	0.89 (0.73, 1.08)
Diabetes mellitus (E10–E14)	712 (11.27)	359 866 (6.37)	1.96 (1.72, 2.23)
Organic, including symptomatic, mental disorders (F00–F09)	535 (8.47)	292 172 (5.17)	1.35 (1.17, 1.55)
Other degenerative diseases of the nervous system (G30–G32)	417 (6.61)	292 502 (5.17)	1.06 (0.92, 1.23)
Hypertensive diseases (I10–I15)	1312 (20.78)	506 231 (8.95)	2.22 (1.97, 2.50)
Ischaemic heart diseases (I20–I25)	1044 (16.54)	686 942 (12.15)	1.45 (1.35, 1.64)
Pulmonary heart disease and diseases of pulmonary circulation (I26–I28)	301 (4.77)	173 230 (3.06)	1.58 (1.29, 1.85)
Other forms of heart disease (I30–I34/I36–I45/I47–I52)	2068 (32.76)	1 276 763 (22.58)	1.35 (1.21, 1.52)
Non-rheumatic aortic valve disorders (I35)	147 (2.33)	72 312 (1.28)	1.68 (1.39, 2.04)
Cerebrovascular diseases (I60–I69)	945 (14.97)	657 096 (11.62)	1.23 (1.09, 1.39)
Aortic aneurysm and dissection (I71)	117 (1.85)	44 002 (0.78)	3.09 (2.48, 3.82)
Influenza and pneumonia-other acute lower respiratory infections (J10–J22)	795 (12.57)	518 679 (9.17)	1.34 (1.18, 1.52)
Chronic lower respiratory diseases (J40–J47)	335 (5.31)	222 652 (3.94)	1.58 (1.36, 1.84)
Vascular disorders of intestine (K55)	97 (1.54)	52 683 (0.93)	1.69 (1.34, 2.10)
Paralytic ileus and intestinal obstruction without hernia (K56)	95 (1.51)	96 487 (1.71)	0.86 (0.68, 1.07)
External causes of morbidity and mortality (V01–Y98)	354 (5.61)	354 570 (6.27)	Control

SMOR calculations used the general population ⩾ 55 years old as the non-exposed group and deaths related to 'external causes of morbidity and mortality' as the control group. Percentages add up to >100 because of the multiple causes of death listed in death certificates. ICD-10: International Classification of Diseases, 10th revision; SMOR: standardized mortality odds ratios.

number of total death certificates registered for mainland France during 2000–11 was ∼5.7 million.

Table 1 shows the 17 selected causes and conditions of death and their respective crude frequencies in decedents with GCA and in the general population. Among people with GCA, the five most commonly listed UCDs or NUCDs were other forms of heart disease (32.76% of death certificates), hypertensive diseases (20.78%), ischaemic heart diseases (16.54%), cerebrovascular diseases (14.97%) and influenza and pneumonia-other acute lower respiratory infections (12.57%). Of note, deaths related to aortic aneurysm and dissection or non-rheumatic aortic valve disorders were listed in only 1.85 and 2.33% of death certificates, respectively.

The corresponding SMORs are in Table 1. The five highest SMORs, all statistically significant, were found for aortic aneurysm and dissection (SMOR: 3.09), hypertensive diseases (SMOR: 2.22), diabetes mellitus (SMOR: 1.96), certain infectious and parasitic diseases (SMOR: 1.76) and non-rheumatic aortic valve disorders (SMOR: 1.68). In contrast, the SMOR for malignant neoplasms showed significantly decreased risk (SMOR: 0.52). Therefore, we additionally calculated SMORs for the four sites of neoplasms with the highest incidence and mortality in France, namely breast, colorectal, lung and prostate cancer [14]. We found SMORs significantly lower than 1 for malignant neoplasms of digestive organs (ICD-10 codes: C15–C26) (SMOR: 0.45, 95% CI: 0.37, 0.53), malignant neoplasms of larynx, trachea, bronchus and lung (ICD-10 codes: C32–C34) (SMOR: 0.36, 95% CI: 0.27, 0.48) and malignant neoplasms of breast (ICD-10 code: C50) (SMOR: 0.54, 95% CI: 0.41, 0.69), but not malignant

prostate neoplasms (ICD-10 code: C61) (SMOR: 0.99, 95% CI: 0.76, 1.30).

Tables 2 and 3 show subgroup analyses by sex, age groups and time periods. Compared with decedents ⩾75 years old, those <75 years had significantly higher SMORs for aortic aneurysms and dissection (SMOR: 6.63 *vs* 2.90), vascular diseases of the intestine (SMOR: 4.35 *vs* 1.54) and cerebrovascular diseases (SMOR: 2.81 *vs* 1.16) (Table 2). SMORs by time periods did not show variations over time in the association of GCA with the analysed causes of death (Table 3).

Table 4 shows the results of the sensitivity analyses with only UCDs as a cause of death considered; this analysis was carried out on the subset of 4427 death certificates that listed GCA as NUCD. The results were highly consistent with those produced by the multiple-cause-of-death analysis.

Discussion

We analysed the multiple causes of death for approximately 6300 French death certificates that mentioned GCA as an UCD or NUCD. As compared with French general population data, the age-, sex- and period-adjusted risk of dying from aortic aneurysms, other cardiovascular diseases and potentially treatment-related co-morbidities was increased with GCA listed on death certificates. Analysis of the entire ∼15 000 death certificates mentioning GCA over a 32-year period showed that age at death was not earlier for decedents with a mention of GCA than in the general population ⩾55 years old. This result adds support to the notion that a diagnosis of GCA does not negatively affect life expectancy of the general population, although it cannot be interpreted as an indication that a diagnosis of GCA has no impact on an individual's health prognosis.

The finding that aortic aneurysms and dissection yielded a high SMOR of 3.09 in GCA is not unexpected in light of the reported 2- to 17-fold higher incidence of thoracic aortic aneurysm or dissection with GCA than in the general population [15, 16]. Although not directly comparable [17], similar estimates for deaths related to large-vessel disease were reported from a nationwide study in Denmark that found a mortality rate ratio of 3.7 during the 2 years after GCA diagnosis [5] and from a retrospective US cohort study reporting a standardized mortality ratio of 2.6 [18]. However, aortic aneurysms or dissection as UCD or NUCD were reported in <2% of the analysed death certificates, which suggests large-vessel disease as an only minor cause of death in GCA. Non-rheumatic aortic

Table 2 SMORs for decedents with GCA stratified by sex or age group

Underlying and non-underlying causes of death (ICD-10 codes)	SMOR (95% CI)			SMOR (95% CI)		
	Women	Men	*P*-value[a]	<75 years	⩾75 years	*P*-value[a]
Certain infectious and parasitic diseases (A00–B99)	1.67 (1.44, 1.95)	1.98 (1.58, 2.50)	0.17	1.87 (1.19, 3.01)	1.78 (1.56, 2.03)	0.70
Malignant neoplasms (C00–C80/C97)	0.48 (0.40, 0.56)	0.61 (0.49, 0.78)	0.01	0.24 (0.15, 0.40)	0.51 (0.44, 0.59)	0.01
Diabetes mellitus (E10–E14)	1.81 (1.55, 2.11)	2.31 (1.84, 2.93)	0.09	2.55 (1.64, 4.08)	1.90 (1.67, 2.98)	0.16
Organic, including symptomatic, mental disorders (F00–F09)	1.29 (1.10, 1.52)	1.51 (1.62, 1.98)	0.35	2.40 (1.13, 4.73)	1.37 (1.19, 1.57)	0.15
Hypertensive diseases (I10–I15)	2.12 (1.85, 2.44)	2.45 (1.97, 3.07)	0.44	3.39 (2.21, 5.37)	2.18 (1.93, 2.46)	0.07
Ischaemic heart diseases (I20–I25)	1.44 (1.25, 1.67)	1.46 (1.17, 1.82)	0.60	1.65 (1.05, 2.67)	1.45 (1.28, 1.64)	0.77
Pulmonary heart disease and diseases of pulmonary circulation (I26–I28)	1.53 (1.28, 1.84)	1.72 (1.27, 2.30)	0.47	1.40 (0.75, 2.55)	1.61 (1.37, 1.89)	0.74
Other forms of heart disease (I30–I34/I36–I45/I47–I52)	1.30 (1.14, 1.49)	1.47 (1.20, 1.82)	0.47	1.73 (1.13, 2.74)	1.36 (1.21, 1.53)	0.33
Non-rheumatic aortic valve disorders (I35)	1.78 (1.42, 2.22)	1.43 (0.95, 2.09)	0.29	1.69 (0.50, 4.32)	1.73 (1.41, 2.10)	0.99
Cerebrovascular diseases (I60–I69)	1.16 (1.00, 1.34)	1.42 (1.13, 1.79)	0.15	2.81 (1.84, 4.44)	1.16 (1.03, 1.32)	<0.01
Aortic aneurysm and dissection (I71)	3.53 (2.67, 4.60)	2.57 (1.82, 3.58)	0.15	6.63 (3.43, 12.5)	2.90 (2.30, 3.63)	0.01
Influenza and pneumonia-other acute lower respiratory infections (J10–J22)	1.26 (1.09, 1.47)	1.50 (1.20, 1.89)	0.22	1.74 (1.06, 2.91)	1.34 (1.18, 1.53)	0.35
Chronic lower respiratory diseases (J40–J47)	1.58 (1.31, 1.91)	1.61 (1.26, 2.08)	0.67	1.66 (0.93, 2.94)	1.60 (1.37, 1.87)	0.72
Vascular disorders of intestine (K55)	1.81 (1.39, 2.32)	1.30 (0.77, 2.08)	0.18	4.35 (2.25, 8.21)	1.54 (1.20, 1.95)	0.01

SMOR calculations used the general population ⩾55 years old as the non-exposed group and deaths related to 'external causes of morbidity and mortality' as the control group. [a]*P*-values refer to the effect of the interaction between GCA and sex or GCA and age group. ICD-10: International Classification of Diseases, 10th revision; SMOR: standardized mortality odds ratios.

Table 3 SMORs for decedents with GCA stratified by calendar periods

Underlying and non-underlying causes of death (ICD-10 codes)	SMOR (95% CI)				*P*-value[a]
	2000–02	2003–05	2006–08	2009–11	
Certain infectious and parasitic diseases (A00–B99)	1.65 (1.29, 2.12)	1.84 (1.44, 2.37)	1.62 (1.26, 2.10)	1.95 (1.51, 2.54)	0.49
Malignant neoplasms (C00–C80/C97)	0.52 (0.40, 0.67)	0.53 (0.41, 0.69)	0.46 (0.35, 0.60)	0.58 (0.44, 0.77)	0.70
Diabetes mellitus (E10–E14)	2.12 (1.66, 2.74)	1.87 (1.45, 2.42)	1.80 (1.39, 2.33)	2.05 (1.58, 2.69)	0.92
Organic, including symptomatic, mental disorders (F00–F09)	1.29 (0.99, 1.69)	1.32 (1.00, 1.74)	1.30 (0.98, 1.72)	1.48 (1.12, 1.95)	0.37
Hypertensive diseases (I10–I15)	2.16 (1.72, 2.73)	2.29 (1.83, 2.91)	1.91 (1.51, 2.44)	2.51 (1.99, 3.22)	0.37
Ischaemic heart diseases (I20–I25)	1.48 (1.18, 1.88)	1.54 (1.22, 1.96)	1.31 (1.03, 1.69)	1.46 (1.13, 1.90)	0.89
Pulmonary heart disease and diseases of pulmonary circulation (I26–I28)	1.50 (1.12, 2.03)	1.51 (1.11, 2.05)	1.55 (1.13, 2.12)	1.81 (1.31, 2.50)	0.45
Other forms of heart disease (I30–I34/I36–I45/I47–I52)	1.43 (1.16, 1.79)	1.45 (1.16, 1.82)	1.12 (0.90, 1.42)	1.42 (1.13, 1.82)	0.93
Non-rheumatic aortic valve disorders (I35)	2.12 (1.47, 3.01)	1.68 (1.12, 2.46)	1.39 (0.91, 2.07)	1.54 (1.03, 2.26)	0.22
Cerebrovascular diseases (I60–I69)	1.31 (1.04, 1.67)	1.23 (0.97, 1.57)	1.17 (0.92, 1.50)	1.20 (0.93, 1.57)	0.70
Aortic aneurysm and dissection (I71)	3.27 (2.16, 4.84)	2.46 (1.53, 3.81)	3.10 (2.00, 4.68)	3.69 (2.32, 5.68)	0.44
Influenza and pneumonia-other acute lower respiratory infections (J10–J22)	1.29 (1.01, 1.66)	1.45 (1.14, 1.86)	1.13 (0.87, 1.47)	1.50 (1.15, 1.95)	0.67
Chronic lower respiratory diseases (J40–J47)	1.57 (1.16, 2.11)	1.83 (1.37, 2.44)	1.26 (0.91, 1.74)	1.69 (1.23, 2.30)	0.96
Vascular disorders of intestine (K55)	1.54 (0.96, 2.38)	1.93 (1.25, 2.90)	1.59 (0.98, 2.48)	1.68 (1.01, 2.66)	0.94

SMOR calculations used the general population $\geqslant$ 55 years old as the non-exposed group and deaths related to 'external causes of morbidity and mortality' as the control group. [a]*P*-values refer to the effect of the interaction between GCA and time period. ICD-10: International Classification of Diseases, 10th revision; SMOR: standardized mortality odds ratios.

valve disorders, which may also signify dilation of the ascending aorta, were also rarely listed.

Deaths related to ischaemic heart and cerebrovascular diseases were less strongly associated with GCA, with SMORs of 1.45 and 1.23, respectively, but were listed in 17 and 15% of death certificates. These results corroborate cohort studies and meta-analyses indicating GCA to be associated with increased risk of coronary artery disease [19–22], myocardial infarction [23] and cerebrovascular disease [19, 21, 23–25], and death from cardiovascular diseases [5, 6]. Our finding that excess cardiovascular mortality appeared to be increased in the younger age group of people with GCA, which has been reported previously [6, 26], could agree with the more widespread vessel involvement observed with young age at GCA diagnosis [27, 28]. Thus, whether the cardiovascular excess mortality with GCA takes into account vessel inflammation, pre-existing arteriosclerosis, therapy toxicity or several of these factors that act in combination or sequentially over the course of the disease is unknown [29]. Data for RA suggest the systemic inflammatory response as the main driver in cardiovascular disease [30], but glucocorticoids also promote the incidence and progression of atherogenesis [31]. Of note, our study showed an increased reporting of diabetes, hypertension and infection in death certificates also mentioning GCA, which highlights the untoward effects of immunosuppressive therapy on GCA mortality.

Strikingly, we found a SMOR of 0.52 for deaths related to solid neoplasms in GCA, which closely agrees with the 2-fold lower risk of cancer deaths observed in a nationwide study in Denmark [5]. The lower-than-expected cancer mortality in GCA in our study could imply a well-known bias of multiple-cause-of-death analysis due to the lesser reporting of co-morbidities in death certificates of people dying from conditions known for their high mortality [32]. Thus, this phenomenon cannot explain the similar observations in the Danish study, which relied on linkage of different registries [5], nor the fact that we found reduced mortality for solid neoplasms overall but not haematological malignancies or prostate cancer. A potential reason for a truly reduced cancer mortality with GCA may include earlier detection and better cure of cancers in patients followed for a chronic illness. The lesser cancer mortality might also reconcile the observations that life expectancy in GCA is not substantially different from that in the population in general [4] despite the increased cardiovascular mortality.

The time trend of death rates over 1980–2011 showed a peculiar bell-shaped curve, with a peak for 1995–2000 and a subsequent steady decline. A study using Canadian administrative health data found the standardized mortality rates for GCA more than halved in 2005–12 as compared with 1997–2004 [33]. Which factors or interventions could have contributed to this steady improvement in survival in the 20 years is not known, and we did not find temporal changes in SMORs for the most common causes of deaths. Alternatively, the rise and fall in the death rates we observed could also reflect temporal changes in the recognition or true incidence rates of GCA.

TABLE 4 Sensitivity analysis considering only the death causes listed as underlying cause of death

Underlying causes of death (ICD-10 codes)	Observed no of deaths (%)		SMOR
	GCA ($N = 4427$)	General population ($N = 5\,653\,629$)	(95% CI)
Certain infectious and parasitic diseases (A00–B99)	171 (3.86)	107 542 (1.90)	1.84 (1.51, 2.25)
Malignant neoplasms (C00–C80/C97)	373 (8.43)	1 429 175 (25.27)	0.47 (0.40, 0.56)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue (C81–C96)	84 (1.90)	137 432 (2.43)	0.85 (0.65, 1.09)
Diabetes mellitus (E10–E14)	177 (4.00)	127 132 (2.25)	1.65 (1.35, 2.00)
Organic, including symptomatic, mental disorders (F00–F09)	162 (3.66)	141 650 (2.51)	1.02 (0.83, 1.26)
Other degenerative diseases of the nervous system (G30–G32)	175 (3.95)	181 255 (3.21)	0.89 (0.73, 1.09)
Hypertensive diseases (I10–I15)	196 (4.43)	97 609 (1.73)	2.02 (1.67, 2.45)
Ischaemic heart diseases (I20–I25)	473 (10.68)	450 162 (7.96)	1.26 (1.08, 1.48)
Pulmonary heart disease and diseases of pulmonary circulation (I26–I28)	66 (1.49)	60 231 (1.07)	1.18 (0.89, 1.55)
Other forms of heart disease (I30–I34/I36–I45/I47–I52)	422 (9.53)	477 658 (8.45)	0.91 (0.77, 1.07)
Non-rheumatic aortic valve disorders (I35)	67 (1.51)	41 138 (0.73)	1.68 (1.27, 2.19)
Cerebrovascular diseases (I60–I69)	482 (10.89)	392 687 (6.95)	1.30 (1.11, 1.53)
Aortic aneurysm and dissection (I71)	58 (1.31)	32 102 (0.57)	2.72 (2.01, 3.62)
Influenza and pneumonia-other acute lower respiratory infections (J10–J22)	150 (3.39)	164 492 (2.91)	0.91 (0.74, 1.12)
Chronic lower respiratory diseases (J40–J47)	114 (2.58)	104 688 (1.85)	1.40 (1.11, 1.75)
Vascular disorders of intestine (K55)	41 (0.93)	27 252 (0.48)	1.64 (1.16, 2.26)
Paralytic ileus and intestinal obstruction without hernia (K56)	42 (0.95)	32 720 (0.58)	1.29 (0.92, 1.78)
External causes of morbidity and mortality (V01–Y98)	232 (5.24)	291 564 (5.16)	Control

SMOR calculations used the general population $\geqslant 55$ years old as the non-exposed group and deaths related to 'external causes of morbidity and mortality' as the control group. ICD-10: International Classification of Diseases, 10th revision; SMOR: standardized mortality odds ratios.

Indeed, findings from several recent population-based studies suggest that incidence rates of GCA, previously described as increasing [34], have plateaued [35] and even declined since the 1990s [26, 36, 37].

Limitations of our study are related to the declarative nature of information reported in death certificates, which makes it vulnerable to selection and other biases [38]. As compared with an earlier annual incidence estimate of 9/100 000 people $\geqslant 50$ years old reported from France [39], the observed annual death rate of 3.16/100 000 people indicates that our analyses may have captured less than half of all cases of GCA. Thus, the consistency of our findings with those from other studies using different methodologies suggests no major selection bias, although we cannot exclude that our data might preferentially reflect the mortality associated with recently diagnosed or still-active GCA. Another limitation of our study is the lack of clinical data in death certificates, which prevented investigation of previous indications of increased mortality in the first year after GCA diagnosis [5] or the subset of GCA patients with large-vessel manifestations [18]. Also, we recognize that our use of midpoints of 10-year age-class intervals for age at death calculations represent approximations of the exact values, even though this did not likely result in significant inaccuracies.

In conclusion, this comprehensive analysis of quantitative and qualitative aspects of GCA mortality should help guide the management of GCA. The low occurrence of lethal aortic complications must be kept in mind to devise the most cost-effective screening for GCA-related aortic disease. Studies are warranted to elucidate the mechanisms underlying the cardiovascular disease risk in GCA and whether glucocorticoid-sparing agents may reduce the cardiovascular and treatment toxicity-related burden in GCA. Potential temporal changes in GCA-associated mortality warrant further investigation and attention because they may hold important clues to the factors involved in the natural history of the disease.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234–45.

2 Weyand CM, Goronzy JJ. Clinical practice. Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med 2014;371:50–7.

3 Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003;49:703–8.

4 Hill CL, Black RJ, Nossent JC *et al*. Risk of mortality in patients with giant cell arteritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2017;46:513–9.

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

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

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

8 Schmidt J, Smail A, Roche B *et al*. Incidence of severe infections and infection-related mortality during the course of giant cell arteritis: a Multicenter, Prospective, Double-Cohort Study. Arthritis Rheumatol 2016;68:1477–82.

9 Miettinen OS, Wang JD. An alternative to the proportionate mortality ratio. Am J Epidemiol 1981;114:144–8.

10 Johansson L, Pavillon G, Trotter M. A comparison and analysis of ICD-10: underlying cause coding differences among three coding systems: manual coding, ACME system and Styx system. In: Minino AM, Rosenberg HM, eds. *Proceedings of the International Collaborative Effort on Automating Mortality Statistics*, Vol. 2. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2001:71–5.

11 CépiDc—Centre d'épidémiologie sur les causes médicales de décès. http://www.cepidc.inserm.fr/site4/ (8 July 2017, date last accessed).

12 Insee—Institut national de la statistique et des études économiques. http://www.insee.fr/fr/themes/tableau.asp?reg_id=0&ref_id=NATnon02150 (8 July 2017, date last accessed).

13 Pace M, Lanzieri G, Glickman M, Grande E, Zupanic T, Wojtyniak B *et al*. Revision of the European Standard Population, Report of Eurostat's task force. Luxembourg: Publications Office of the European Union: 2013.

14 Évolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. http://www.invs.sante.fr/publications/2003/rapport_cancer_2003 (8 July 2017, date last accessed).

15 Evans JM, Bowles CA, Bjornsson J, Mullany CJ, Hunder GG. Thoracic aortic aneurysm and rupture in giant cell arteritis. A descriptive study of 41 cases. Arthritis Rheum 1994;37:1539–47.

16 Robson JC, Kiran A, Maskell J *et al*. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. Ann Rheum Dis 2015;74:129–35.

17 Stewart W, Hunting K. Mortality odds ratio, proportionate mortality ratio, and healthy worker effect. Am J Ind Med 1988;14:345–53.

18 Kermani TA, Warrington KJ, Crowson CS *et al*. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis 2013;72:1989–94.

19 Tomasson G, Peloquin C, Mohammad A *et al*. Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. Ann Intern Med 2014;160:7380.

20 Ray JG, Mamdani MM, Geerts WH. Giant cell arteritis and cardiovascular disease in older adults. Heart 2005;91:324–8.

21 Amiri N, De Vera M, Choi HK, Sayre EC, Avina-Zubieta JA. Increased risk of cardiovascular disease in giant cell arteritis: a general population-based study. Rheumatology (Oxford) 2016;55:33–40.

22 Ungprasert P, Koster MJ, Warrington KJ. Coronary artery disease in giant cell arteritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2015;44:586–91.

23 Li L, Neogi T, Jick S. Giant cell arteritis and vascular disease-risk factors and outcomes: a cohort study using UK Clinical Practice Research Datalink. Rheumatology (Oxford) 2017;56:753–62.

24 Robson JC, Kiran A, Maskell J *et al*. Which patients with giant cell arteritis will develop cardiovascular or cerebrovascular disease? A Clinical Practice Research Datalink Study. J Rheumatol 2016;43:1085–92.

25 Ungprasert P, Wijarnpreecha K, Koster MJ, Thongprayoon C, Warrington KJ. Cerebrovascular accident in patients with giant cell arteritis: a systematic review and meta-analysis of cohort studies. Semin Arthritis Rheum 2016;46:361–6.

26 Mohammad AJ, Nilsson JA, Jacobsson LT, Merkel PA, Turesson C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. Ann Rheum Dis 2015;74:993–7.

27 Muratore F, Kermani TA, Crowson CS *et al*. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford) 2015;54:463–70.

28 Czihal M, Zanker S, Rademacher A *et al*. Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. Scand J Rheumatol 2012;41:231–6.

29 Mackie SL, Dasgupta B. Vasculitis syndromes: dealing with increased vascular risk and mortality in GCA. Nat Rev Rheumatol 2014;10:264–5.

30 Meissner Y, Zink A, Kekow J *et al*. Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis. Arthritis Res Ther 2016;18:183.

31 Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol 2007;157:545–59.

32 Fedeli U, Zoppini G, Goldoni CA *et al*. Multiple causes of death analysis of chronic diseases: the example of diabetes. Popul Health Metr 2015;13:21.

33 Belvedere LM, Choi HK, Dehghan N, Sayre EC, Avina-Zubieta JA. OP0280 improved survival in giant cell arteritis: a Population-Based Study. Ann Rheum Dis 2016;75:164.

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

35 Chandran AK, Udayakumar PD, Crowson CS, Warrington KJ, Matteson EL. The incidence of giant cell arteritis in Olmsted County, Minnesota, over a 60-year period 1950-2009. Scand J Rheumatol 2015;44:215–8.

36 Diamantopoulos AP, Haugeberg G, Amundsen L *et al*. The incidence rate of giant cell arteritis in Southern Norway is lower than previous reported: a result of temporal variations or a sign of a true shift in incidence rates? Abstract FRI0447. Ann Rheum Dis 2014;73(Suppl 2):549.

37 Catanoso M, Macchioni P, Boiardi L *et al*. Incidence, prevalence and survival of biopsy-proven giant cell arteritis in Northern Italy during a 26-year period. Arthritis Care Res 2017;69:430–8.

38 Redelings MD, Wise M, Sorvillo F. Using multiple cause-of-death data to investigate associations and causality between conditions listed on the death certificate. Am J Epidemiol 2007;166:104–8.

39 Barrier J, Pion P, Massari R *et al*. Epidemiologic approach to Horton's disease in the department of Loire-Atlantique. 110 cases in 10 years (1970-1979) [French]. Rev Med Interne 1982;3:13–20.

Clinical Vignette

Rheumatology 2018;57:1055
doi:10.1093/rheumatology/kex479
Advance Access publication 17 January 2018

Central retinal vein occlusion in temporal arteritis: red sign or red herring?

A 74-year-old female with biopsy-proven temporal arteritis in remission after prednisone treatment for 18 months presented with blurred vision. Fluorescein angiography revealed unilateral central retinal vein occlusion (CRVO). Elevated CRP was noted. Her cardiovascular risks factors included past smoking and advanced age. Thrombophilia assessment was negative.

Three months later she complained of arthralgias. Inflammation markers were elevated. CT with angiography revealed evidence of extensive large vessel vasculitis of the thoracic/abdominal aorta and its branches. Steroid treatment was reintroduced, MTX and AZA initiated.

CRVO is known to be related to cardiovascular risk factors, hypercoagulable states or intraocular hypertension, but not to GCA. Various CRVO scenarios have been reported in the context of GCA—possible association to central retinal artery occlusion or as a presenting as well as a late event of GCA—but a constant feature remains, elevated sedimentation rate [1]. Chronic inflammation affecting endothelial function may explain the tendency for venous thrombosis [2].

Our case highlights that occurrence of CRVO in elderly people, in the presence of elevated inflammation parameters, should suggest the diagnosis of GCA. The impact of early steroid treatment on visual acuity in this context is still unknown.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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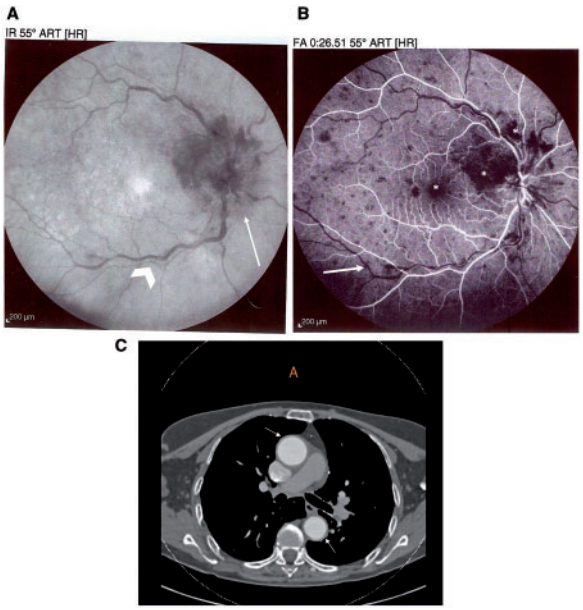
Fig. 1 Retinal imaging demonstrating right eye central vein occlusion



(A) An infrared image of the right eye posterior pole demonstrating a central retinal vein occlusion. Note that the optic disc is obscured by oedema and haemorrhages (arrow), the dilated and torturous veins (arrow head). (B) An early phase fundus fluorescein angiography demonstrating delayed retinal venous filling as well as extensive hypofluorescence lesions around the optic disc correlating to retinal haemorrhages (*). (C) CT with angiography shows the enlarged wall of the thoracic aorta (arrow).

References

1 Zaldivar RA, Calamia KT, Bolling JP. Retinal vein occlusion in giant cell arteritis [abstract]. Invest Ophthalmol Vis Sci 2004;45:1589.

2 Ly KH, Liozon E, Dalmay F *et al*. Venous thrombosis in patients with giant cell arteritis: Features and outcomes in a cohort study. Joint Bone Spine 2017;84:323–26.