Decreasing mortality and changes in treatment patterns in patients with acromegaly from a nationwide study

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Abstract

Context: New therapeutic strategies have developed for the management of acromegaly over recent decades. Whether this has improved mortality has not been fully elucidated.
Objective: The primary aim was to investigate mortality in a nationwide unselected cohort of patients with acromegaly. Secondary analyses included time trends in mortality and treatment patterns.
Design: A total of 1089 patients with acromegaly were identified in Swedish National Health Registries between 1987 and 2013. To analyse time trends, the cohort was divided into three periods (1987–1995, 1996–2004 and 2005–2013) based on the year of diagnosis.
Main outcome measures: Using the Swedish population as reference, standardized mortality ratios (SMRs) were calculated with 95% confidence intervals (CIs).
Results: Overall SMR was 2.79 (95% CI: 2.43–3.15) with 232 observed and 83 expected deaths. Mortality was mainly related to circulatory diseases (SMR: 2.95, 95% CI: 2.35–3.55), including ischemic heart disease (2.00, 1.35–2.66) and cerebrovascular disease (3.99, 2.42–5.55) and malignancy (1.76, 1.27–2.26). Mortality decreased over time, with an SMR of 3.45 (2.87–4.02) and 1.86 (1.04–2.67) during the first and last time period, respectively ($P = .015$). During the same time periods, the frequency of pituitary surgery increased from 58% to 72% ($P < 0.001$) and the prevalence of hypopituitarism decreased from 41% to 23% ($P < 0.001$).
Conclusions: Excess mortality was found in this nationwide cohort of patients with acromegaly, mainly related to circulatory and malignant diseases. Although still high, mortality significantly declined over time. This could be explained by the more frequent use of pituitary surgery, decreased prevalence of hypopituitarism and the availability of new medical treatment options.

European Journal of Endocrinology
(2018) **178**, 459–469

European Journal of Endocrinology

Introduction

Acromegaly is a rare disease caused by growth hormone (GH) hypersecretion mainly due to a benign pituitary adenoma (1). According to recent epidemiological data, acromegaly has an estimated prevalence of 2.8–13.7 cases/100 000 people and an annual incidence of 0.2–1.1 cases/100 000 people (2, 3, 4).

Chronic excessive GH secretion leads to a multisystem disorder characterized by acral overgrowth, musculoskeletal disease, metabolic disorders, myocardial hypertrophy and respiratory dysfunction (1, 5, 6, 7). These multiple comorbidities result in impaired quality of life and reduced life expectancy (8, 9, 10).

www.eje-online.org
https://doi.org/10.1530/EJE-18-0015

Published by Bioscientifica Ltd.

In 1970, Wright and colleagues (11) first described excess mortality in patients with acromegaly compared to the general population. Several studies have later confirmed this finding, displaying standardized mortality ratios (SMRs) between 1.2 and 3.3 (12). The excess mortality has been mainly related to cardiovascular, cerebrovascular and respiratory diseases, and in some studies, malignancies (8, 12).

Recent registry-based studies have shown that life expectancy in acromegaly is nowadays close to that of the general population (13, 14). A meta-analysis, including 16 studies conducted during different time periods, showed a lower mortality ratio in trials published from 1995 onward (SMR 1.62) compared to those published previously (SMR 2.11) (12). During recent decades, important achievements have been reached in the management of acromegaly, such as the introduction of microsurgical transsphenoidal techniques, and the development of new pharmacological therapies that may have improved biochemical remission and survival (5, 8, 12).

In this nationwide study, we aimed to investigate mortality in a large, unselected cohort of patients with acromegaly. Secondary aims were to analyse time trends in mortality and treatment patterns.

Patients and methods

Patients with acromegaly were identified in the Swedish National Patient Registry (Patient Registry), which contains information on every patient visit within the national hospital system in Sweden since 1987. Information on cause of death was obtained from the Swedish National Cause of Death Registry (Cause of Death Registry), which collects information on every death in Sweden since 1952. Data on medical treatment were available from July 1, 2005 when the Prescribed Drug Registry (Drug Registry) achieved national coverage. Using the unique personal identification number assigned to each Swedish resident, it is possible to obtain exhaustive and comprehensive healthcare data from national registers and databases. These registries are held by the National Board of Health and Welfare that maintains a high quality of the data (15, 16).

Study population

All patients with an acromegaly diagnosis due to a pituitary tumor established between 1987 and 2013 were identified in the Patient Registry and included in the analysis. The following search criteria was used: the International Classification of Diseases (ICD) codes for acromegaly (E22.0 (ICD-10) or 253A (ICD-9)) in combination with neoplasm of pituitary gland (D35.2 or D44.3 (ICD-10) or 237A or 227D (ICD-9)). Using these conservative search criteria, only patients with both an acromegaly and a pituitary neoplasm diagnosis were included. The pituitary neoplasm diagnosis should have occurred no more than 5 years before, or any time after, the first acromegaly diagnosis. Patients diagnosed before the age of 18 years were excluded.

The patients were followed from the first diagnosis of acromegaly until death or the end of the study (December 31, 2013). Gender and pituitary tumor treatments as well as diagnoses of chronic hypopituitarism and diabetes insipidus were collected from the Patient Registry. Date and causes of death were gathered from the Cause of Death Registry. Data on mortality in the general population were obtained and analyzed in the same manner as for the patients.

To analyse the impact of treatments on mortality, data on radiotherapy and surgical procedures were retrieved from the Patient Registry through the treatment codes listed in the Supplementary Table 1 (see section on supplementary data given at the end of this article). Information on pharmacotherapy was collected from the Drug Registry for a subgroup of patients diagnosed with acromegaly after July 1, 2005. The following medical treatments were included: somatostatin analogs (SSAs), dopamine agonists (DAs) and GH receptor antagonists (GHRAs). Treatment duration for each patient was calculated as time from the first purchase of the drug to the end of treatment, death or the end of study. Medical treatment was defined as ended if there was no purchase for 6 consecutive months. In case of treatment that discontinued and restarted, the total treatment duration was calculated.

Ethics

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden and by the National Board of Health and Welfare, Sweden.

Statistics

Person-years at risk were calculated from study inclusion to death or end of study and stratified according to gender, 5-year age groups and 1-year calendar periods. The expected number of cases for each stratum was

calculated using the general Swedish population as a reference. The observed number of deaths among patients with acromegaly and the expected number of deaths in the general population were used to calculate SMRs. 95% CIs were calculated assuming a Poisson distribution of the observed numbers. SMRs for non-overlapping subgroups were compared to each other (17).

To analyse whether mortality has changed over time, the study cohort was divided into three groups based on the year of the acromegaly diagnosis (1987–1995, 1996–2004 and 2005–2013), which provided equal lengths of time and sufficient sample numbers in each period. Sub-analyses were performed on mortality regarding treatment patterns, age at diagnosis (< or ≥52 years, i.e. the median age of the study population) and level of surveillance (followed at a specialized care unit or not, the discontinuation of which was defined as 3 consecutive years without a visit to a specialist after the acromegaly diagnosis).

To analyse the differences between groups regarding diagnoses of hypopituitarism and diabetes insipidus as well as treatment patterns, chi-squared tests were used. The Cochran–Armitage test for trends was used to examine the differences between time periods. Finally, the effect of different follow-up times (different latency periods: 0–5, >5–10 and >10 years), that is the time between date of diagnosis and time of death, on mortality was analyzed (18). Continuous variables are presented as mean (±standard deviation (S.D.)) and categorical variables as count (%). All statistical analyses were carried out using SAS, version 9.4 (Cary, NC).

Results

Patient characteristics and gender differences

In total, 1089 patients with acromegaly due to a pituitary adenoma, diagnosed between 1987 and 2013, were identified with somewhat more women than men ($P=0.031$) (Table 1). The mean age at diagnosis was 51.6±15.1 years and the mean follow-up time was 11.8±7.5 years. There was a strong tendency toward a lower age at diagnosis among men than women ($P=0.052$). Men were more likely to receive surgery alone than women ($P=0.038$). Overall, pituitary surgery was performed in 700 (64%) patients and radiotherapy in 144 (13%) patients, with no differences between men and women. Neither surgery nor radiotherapy was recorded for 361 (33%) patients, including more women than men ($P=0.033$). In this group, 313 (87%) patients were followed at University Hospitals. Out of 1089 patients, the diagnosis of hypopituitarism and diabetes insipidus was recorded in 370 (34%) and 41 (4%), respectively (Table 1). The frequency of hypopituitarism was higher among men than women ($P=0.005$). In the group of patients treated with radiotherapy (67 men, 77 women), the mean age at diagnosis was lower than that in the group of patients without radiotherapy (47.2±14.8 vs 52.2±15.1; $P<0.001$), but the mean follow-up time was similar (12.3±7.1 vs 11.8±7.5; $P=0.33$). The frequency of hypopituitarism (41%) tended to be higher in patients treated with radiotherapy than in patients without radiotherapy (33%; $P=0.060$).

Table 1 Characteristics of patients with acromegaly in Sweden diagnosed between 1987 and 2013.

Characteristic	Total ($n=1089$)	Men ($n=509$)	Women ($n=580$)
Mean (±S.D.) age at diagnosis, year	51.6±15.1	50.6±13.9	52.4±16.1
Mean(±S.D.) follow-up time, year	11.8±7.5	11.8±7.7	11.8±7.3
Treatments			
All surgery	700 (64%)	340 (67%)	360 (62%)
Surgery alone	584 (54%)	290 (57%)	294 (51%)
All radiotherapy	144 (13%)	67 (13%)	77 (13%)
Radiotherapy alone	28 (3%)	17 (3%)	11 (2%)
Both surgery and radiotherapy	116 (11%)	50 (10%)	66 (11%)
Without both surgery and radiotherapy	361 (33%)	152 (30%)	209 (36%)
Hormonal status			
Patients with hypopituitarism	370 (34%)	195 (38%)	175 (30%)
Patients with diabetes insipidus	41 (4%)	14 (3%)	27 (5%)
Follow-up			
Patient followed at University Hospitals	781 (72%)	369 (73%)	412 (71%)
Patient who discontinued specialized health care contact	531 (49%)	242 (48%)	289 (50%)

Level of patient care

Pituitary surgery was performed at six University Hospitals in Sweden with a mean of 6.1 ± 4.0 operations per year per unit. For all 1089 patients, 72% had more than 50% of their visits after diagnosis at University Hospitals (Table 1). A total of 531 (49%) patients discontinued their care and follow-up at University Hospitals 23.3 ± 34.9 months after the diagnosis of acromegaly. During the entire study period, mean follow-up time was 16.3 ± 6.5 years in the group of patients who had discontinued specialized care and 7.5 ± 5.5 years in the group of patients who had not ($P < 0.001$). The proportion of patients who had received neither pituitary surgery nor radiotherapy was higher in the group who had discontinued follow-up at University Hospitals (41% vs 26%; $P < 0.001$).

Medical treatment patterns

Data on medical treatment were available for a subgroup of 338 patients (163 men; 175 women), diagnosed since July 1, 2005, when the Drug Registry achieved national coverage (Table 2). The mean age at diagnosis was 49.7 ± 15.5 years and the mean follow-up time was 4.2 ± 2.4 years. Pharmacotherapy was recorded in 151 (45%) patients, 106 (31%) had received both pituitary surgery and pharmacotherapy and pharmacotherapy without surgery was seen in 45 (13%) patients. Out of the 151 patients with pharmacotherapy, 119 (35%) received SSAs with a mean treatment duration of 31.9 ± 25.4 months. DAs were used by 50 (15%) and GHRAs by 30 (9%) patients for 21.7 ± 16.0 and 30.4 ± 21.5 months, respectively. There were no significant differences in medical treatments between women and men (Table 2).

Mortality

During the study period, 232 deaths were observed compared to an expected number of 83, resulting in an SMR of 2.79 (95% CI: 2.43–3.15) (Table 3). The overall SMR was similar between men (2.60, 95% CI: 2.11–3.09) and women (2.99, 95% CI: 2.46–3.51) ($P = 0.30$). The greatest number of deaths occurred from circulatory diseases ($n = 93$) and malignant neoplasms ($n = 49$) (Supplementary Table 2), with an SMR of 2.95 (95% CI: 2.35–3.55) and 1.76 (95% CI: 1.27–2.26), respectively (Table 3). A markedly increased SMR was found for death due to infectious diseases (7.91, 95% CI: 1.58–14.24). Mortality due to ischemic heart disease was only increased in women (2.85, 95% CI: 1.63–4.07), while mortality from malignant neoplasms was only increased in men (2.26, 95% CI: 1.41–3.11).

When the analysis was examined by treatment, excess mortality was found in all treatment groups, with SMR being the highest in patients only treated with radiotherapy (3.45, 95% CI: 1.20–5.71) (Table 3). The overall SMR was lower ($P = 0.029$) for patients treated with pituitary surgery 2.39 (95% CI: 1.92–2.86) than patients without 3.20 (95% CI: 2.66–3.75). Only three patients died during the first 30 days after the pituitary surgery (918 pituitary surgeries were performed in the study).

Although excess mortality was found in both patients who had discontinued specialized care (2.29, 95% CI: 1.90–2.70) and those who had not (3.84, 95% CI: 3.10–4.58), it was higher in the latter group ($P = 0.0002$) (Supplementary Table 3).

In patients diagnosed since 2005, SMR was 2.03 (95% CI: 0.62–3.44) among medically treated patients, 0.98 (95% CI: 0.00–2.35) in patients treated with both

Table 2 Distribution of treatment modalities in patients with acromegaly diagnosed between July 1, 2005 and December 31, 2013.

Treatment	Total ($n = 338$)	Men ($n = 163$)	Women ($n = 175$)
Surgery alone	200 (59%)	103 (63%)	97 (55%)
Radiotherapy alone	3 (1%)	2 (1%)	1 (1%)
Both surgery and radiotherapy	47 (14%)	20 (12%)	27 (15%)
Neither surgery nor radiotherapy	88 (26%)	38 (23%)	50 (29%)
Pharmacotherapy	151 (45%)	70 (43%)	81 (46%)
Somatostatin analogs	119 (35%)	58 (36%)	61 (35%)
Dopamine agonists	50 (15%)	21 (13%)	29 (17%)
Pegvisomant	30 (9%)	14 (9%)	16 (9%)
Pharmacotherapy in combination with surgery	106 (31%)	51 (31%)	55 (31%)
Pharmacotherapy without surgery	45 (13%)	19 (12%)	26 (15%)
No pharmacotherapy	186 (55%)	93 (57%)	93 (53%)
With surgery	141 (42%)	72 (44%)	69 (39%)
Without surgery	46 (14%)	21 (13%)	25 (14%)
Without surgery or radiotherapy	44 (13%)	20 (12%)	24 (14%)

Table 3 Standardized mortality ratio in patients with acromegaly in Sweden between 1987 and 2013.

Mortality	No. observed	No. expected	SMR (95% CI)	*P* value
Overall mortality				
Acromegalic patients (*n* = 1089)	232	83.0	2.79 (2.43–3.15)	<0.0001
Men (*n* = 509)	107	41.2	2.60 (2.11–3.09)	<0.0001
Women (*n* = 580)	125	41.9	2.99 (2.46–3.51)	<0.0001
Cause-specific mortality (ICD chapters)				
ICD-10 Chapter 1, Infectious disease	6	0.8	7.91 (1.58–14.24)	0.032
Men (*n* = 509)	2	0.3	NC	NC
Women (*n* = 580)	4	0.4	9.67 (0.19–19.16)	0.073
ICD-10 Chapter 9, Circulatory disease	93	31.5	2.95 (2.35–3.55)	<0.0001
Men (*n* = 509)	38	16.6	2.29 (1.56–3.02)	0.0005
Women (*n* = 580)	55	14.9	3.69 (2.71–4.66)	<0.0001
ICD-10 Chapter 10, Respiratory disease	14	4.2	3.31 (1.58–5.04)	0.009
Men (*n* = 509)	5	1.9	2.64 (0.33–4.96)	0.16
Women (*n* = 580)	9	2.3	3.85 (1.33–6.36)	0.026
Cause-specific mortality (specific causes)				
Ischemic heart disease	36	18.0	2.00 (1.35–2.66)	0.0027
Men (*n* = 509)	15	10.6	1.41 (0.70–2.13)	0.26
Women (*n* = 580)	21	7.4	2.85 (1.63–4.07)	0.0029
Cerebrovascular disease*	25	6.3	3.99 (2.42–5.55)	0.0002
Men (*n* = 509)	9	2.6	3.52 (1.22–5.82)	0.032
Women (*n* = 580)	16	3.7	4.31 (2.20–6.42)	0.0021
Malignant neoplasms	49	27.8	1.76 (1.27–2.26)	0.0025
Men (*n* = 509)	27	12.0	2.26 (1.41–3.11)	0.0038
Women (*n* = 580)	22	15.9	1.39 (0.81–1.97)	0.19
Malignant neoplasm of brain	3	1.0	3.02 (0.00–6.44)	0.25
Overall mortality in subgroups				
All patients treated with surgery (*n* = 700)	100	41.8	2.39 (1.92–2.86)	<0.0001
Men (*n* = 340)	46	21.2	2.17 (1.54–2.80)	<0.0001
Women (*n* = 360)	54	20.6	2.62 (1.92–3.31)	<0.0001
Patients treated with surgery alone (*n* = 584)	91	36.5	2.49 (1.98–3.00)	<0.0001
Men (*n* = 290)	41	18.2	2.25 (1.56–2.94)	0.0004
Women (*n* = 294)	50	18.3	2.73 (1.97–3.49)	<0.0001
All patients treated with radiotherapy (*n* = 144)	18	7.9	2.28 (1.23–3.33)	0.017
Men (*n* = 67)	10	4.8	2.07 (0.79–3.36)	0.101
Women (*n* = 77)	8	3.1	2.60 (0.80–4.41)	0.082
Patients treated with radiotherapy alone (*n* = 28)	9	2.6	3.45 (1.20–5.71)	0.033
Men (*n* = 17)	5	1.9	2.67 (0.33–5.01)	0.16
Women (*n* = 11)	4	0.7	5.43 (0.11–10.76)	0.10
Patients treated with both surgery and radiotherapy (*n* = 116)	9	5.3	1.70 (0.59–2.82)	0.22
Men (*n* = 50)	5	3.0	1.70 (0.21–3.18)	0.36
Women (*n* = 66)	4	2.3	1.71 (0.03–3.39)	0.41
Patients treated without both surgery and radiotherapy (*n* = 361)	123	38.6	3.19 (2.62–3.75)	<0.0001
Men (*n* = 152)	56	18.1	3.09 (2.28–3.90)	<0.0001
Women (*n* = 209)	67	20.5	3.27 (2.49–4.05)	<0.0001

*No deaths caused by cerebrovascular disease were observed in patients treated with radiotherapy.
CI, confidence interval; NC, not calculated; SMR, standardized mortality ratio.

pharmacotherapy and surgery and 0.45 (95% CI: 0.00–1.08) among those only treated with surgery.

Time trends

The frequency of pituitary surgery increased from 58% to 63% and 72% during the first, second and last time periods, respectively ($P < 0.001$) (Table 4). The prevalence of hypopituitarism declined from 41% during the first time period to 23% during the last period ($P < 0.001$). Mortality also decreased over time, with an SMR of 3.45 (95% CI: 2.87–4.02) and 1.86 (95% CI: 1.04–2.67) during the first and last follow-up period, respectively ($P = .015$) (Fig. 1 and Table 5). Among patients treated with surgery alone, SMR declined from 3.51 (95% CI: 2.64–4.37) to 1.90 (95% CI: 1.17–2.62) from the first to the second

Table 4 Hypopituitarism and treatment with pituitary surgery and radiotherapy in patients with acromegaly in Sweden followed between 1987 and 2013.

Characteristics	Time of diagnosis			Trend analysis*
	1987–1995 (*n*=359)	1996–2004 (*n*=370)	2005–2013 (*n*=360)	*P* value
Mean (±S.D.) age at diagnosis, year	50.6±14.8	54.0±14.6	50.0±15.8	0.61
Mean(±S.D.) follow-up time, year	19.0±6.6	12.0±3.6	4.5±2.6	<0.001
Treatment				
All surgery	209 (58%)	233 (63%)	258 (72%)	<0.001
Men	103 (61%)	110 (64%)	127 (75%)	0.023
Women	106 (56%)	123 (62%)	131 (69%)	0.026
Surgery alone	184 (51%)	191 (52%)	209 (58%)	0.067
Men	92 (55%)	91 (53%)	107 (63%)	0.13
Women	92 (48%)	100 (50%)	102 (54%)	0.28
All radiotherapy	37 (10%)	52 (14%)	55 (15%)	0.12
Men	17 (10%)	26 (15%)	24 (14%)	0.35
Women	20 (11%)	26 (13%)	31 (16%)	0.24
Radiotherapy alone	12 (3%)	10 (3%)	6 (2%)	0.36
Men	6 (4%)	7 (4%)	4 (2%)	0.66
Women	6 (3%)	3 (2%)	2 (1%)	0.29
Both surgery and radiotherapy	25 (7%)	42 (11%)	49 (14%)	0.004
Men	11 (7%)	19 (11%)	20 (12%)	0.108
Women	14 (7%)	23 (12%)	29 (15%)	0.015
Without both surgery and radiotherapy	138 (38%)	127 (34%)	96 (27%)	0.001
Men	59 (35%)	54 (32%)	39 (23%)	0.014
Women	79 (41%)	73 (37%)	57 (30%)	0.021
Hypopituitarism	147 (41%)	139 (38%)	84 (23%)	<0.001
Men	78 (46%)	72 (42%)	45 (27%)	<0.001
Women	69 (36%)	67 (34%)	39 (21%)	0.0017

*Cochran-Armitage test for trend.

time period (*P*=.012). Mortality in patients who received neither surgery nor radiotherapy remained unchanged during the study period (Table 5).

The analysis of the effect of different length of follow-up (0–5, 5–10 and >10 years) on mortality showed excess mortality in all latency periods, with an SMR of 9.28 (95% CI: 6.83–11.73), 3.27 (95% CI: 2.43–4.11) and 2.00 (95% CI: 1.64–2.36) during the first, second and third periods, respectively.

Discussion

This is the first study to investigate mortality, time trends and treatment patterns in a nationwide cohort of patients with acromegaly. Although mortality in acromegaly was still increased compared to that for the general population, it showed that the excess mortality has significantly declined during recent decades. Also, noteworthy changes were recorded in treatment patterns, with an increasing use of pituitary surgery over time; concurrently, a decreasing prevalence of hypopituitarism was observed.

Mortality in acromegaly has only been described in one previous population-based study with 405 patients, displaying an adjusted hazard ratio of 1.3 (95% CI: 1.0–1.7) (2). Changes in the management of acromegaly and improvements in long-term outcomes have been recently reported in some registry-based studies, concluding that mortality in acromegalic patients no longer exceeds that of the general population (13, 14). The French Acromegaly Registry, for example, has displayed an SMR of 1.05 (95% CI: 0.70–1.42) in a cohort of 999 patients followed between 1999 and 2012. However, since the majority of centers that participated in that survey were tertiary referral centers, mortality might be underestimated compared to that for the general French acromegalic population. In addition, 17% of patients were lost to follow-up and the deaths in that group were not recorded.

We found excess mortality in patients with acromegaly mainly due to circulatory diseases, including ischemic heart disease and cerebrovascular disease, as well as malignancies. Cardiovascular and cerebrovascular diseases are reported to be the main causes of death in most studies of acromegaly (6, 19, 20). Conversely, data on cancer-related mortality are controversial (21,

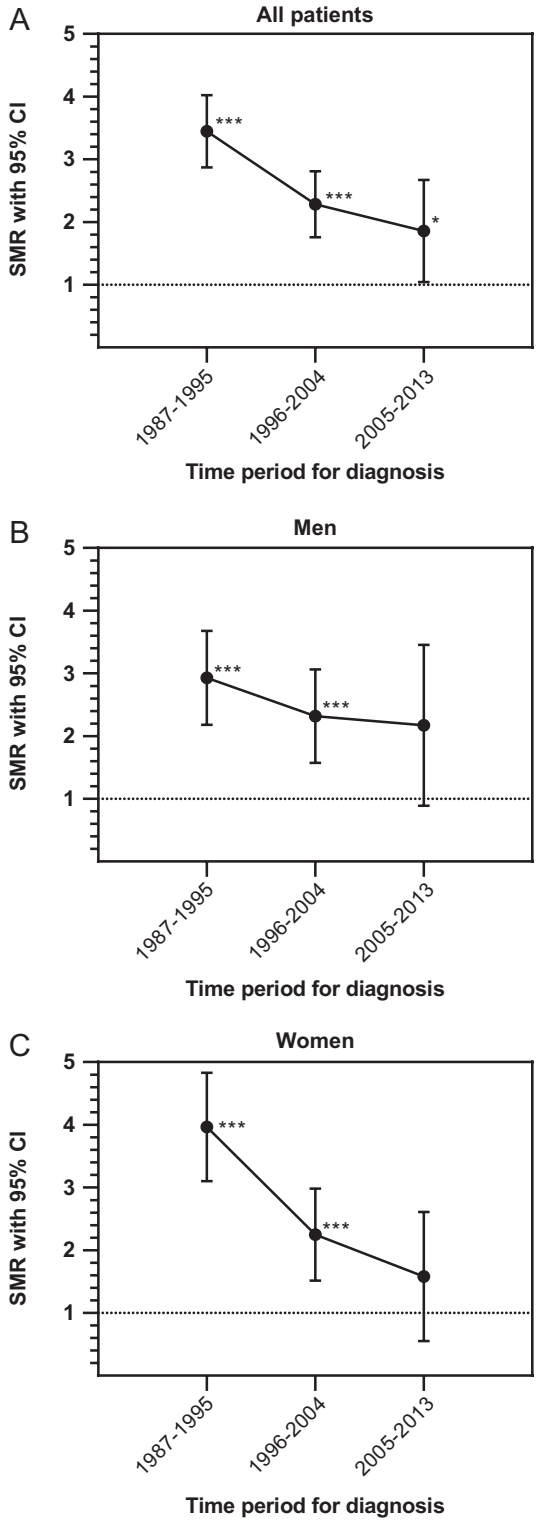

Figure 1

Mortality in patients with acromegaly in Sweden followed between 1987 and 2013. Overall mortality in the entire cohort of patients (A), men (B) and women (C) with acromegaly. ***$P<0.001$; and *$P<0.05$.

22). Available data suggest that 15–24% of deaths in acromegaly are due to malignancies (6, 23). In line with this, we observed that 21% of deaths in our population were related to malignant neoplasms and mainly due to lung, colorectal and breast cancer. In contrast, no excess mortality for cancer was found in a cohort of 333 Finnish patients after 20 years of follow-up (24).

Little information exists on mortality time trends in acromegaly. In the current study, mortality was increased in all study periods, but a significant decrease was recorded over time. An increasing use of pituitary surgery throughout the study from 58% in the first time period (1987–1995) to 72% in the last period (2005–2013) could explain this finding. Our results stand in contrast to the Belgian Acromegaly Register (25), which showed that the frequency of surgery declined from 84% to 61% between 1980 and 2000. However, in the French Registry, the proportion of patients treated with pituitary surgery from 2001 to 2012 remained stable (13).

In our study, the prevalence of hypopituitarism declined from 41% to 23%, which may be related to the improvement in surgical techniques and, the increasing use of pharmacotherapy as the first-line therapy, as recently reported by Maione and co-authors (13). It is well known that hypopituitarism itself has excess mortality (26, 27, 28); it is therefore plausible that the reduced prevalence of hypopituitarism, together with the increasing use of pituitary surgery, have improved mortality in acromegaly over recent decades. The diagnosis of hypopituitarism was recorded in 34% of patients during the entire study period, which agrees with previous studies. For instance, hypopituitarism was found in 31% and 26% of acromegalic patients in the French and Spanish Registry, respectively (13, 29). The current study found a higher frequency of hypopituitarism among men than women. A possible explanation is that men have larger tumors than women, leading to more frequent hormonal deficiency (30).

The highest risk of death in our cohort of patients was recorded during the first 5 years after the diagnosis. This was not related to the perioperative mortality rate as only three deaths occurred within 30 days after pituitary surgery. One plausible explanation is that, in more severe cases, the death occurs within 5 years after the diagnosis. In addition, the delay between the onset of symptoms and the acromegaly diagnosis (7–10 years) leads to a prolonged exposure to GH and insulin-like growth factor-I (IGF-I), which may cause multiple complications leading to death in the first period after the diagnosis. In agreement with this hypothesis, Dal and colleagues (2) showed an increased morbidity in the 3-year prediagnostic period

and the highest mortality risk in the first year after the diagnosis.

During the entire study period, two-third of our patients were treated with pituitary surgery and only 13% received radiotherapy, which agrees with other recent reports (13, 25, 31, 32, 33). This is also in line with the current guidelines that recommend radiation therapy in patients with residual tumor mass after pituitary surgery if pharmacotherapy is unavailable, unsuccessful or not tolerated (5). Earlier studies have shown that radiotherapy is associated with an increased mortality mainly due to cerebrovascular disease (14, 28, 34). It seems logical since radiation therapy in the management of acromegaly has mostly been used for persistent or recurrent disease, which *per se* may affect mortality (12). In this study, we did not observe any deaths from cerebrovascular disease in patients treated with radiotherapy. However, the number of events was too small to provide any useful analysis of the potential link between radiotherapy and mortality. During the observation period, 33% of patients received neither pituitary surgery nor radiotherapy. Even though one might speculate that some of those patients probably received medical therapy, data supporting this were not available before July, 2005.

In the current study, medical treatment was used by half of patients in the subgroup diagnosed with acromegaly since 2005. As in other registries, SSAs were the most commonly used medical treatment, followed by DAs and GHRAs. Mortality data in patients with medical treatment are lacking; thus, it is still unclear whether pharmacotherapy may further improve long-term outcome in acromegaly. Interestingly, in our study, an SMR of 2.03 was recorded among medically treated patients, 0.98 among patients treated with both pharmacotherapy and surgery and 0.45 among those only treated with surgery. However, these data do not allow conclusions on the optimal treatment pattern in acromegaly, since the number of events were too few and those patients treated with different therapeutic strategies have different degrees of tumor burden and disease severity.

Most studies have shown that GH concentration is the strongest predictor of mortality in acromegaly (21, 28, 35); thus, the goal of treatment is to achieve biochemical remission in acromegalic patients, which signifies age-normalized serum IGF-I and random GH <1.0 µg/L (5).

Table 5 Time trends in mortality in patients with acromegaly in Sweden followed between 1987 and 2013.

Mortality	No. observed	No. expected	SMR (95% CI)	*P* value
Overall mortality				
1987–1995	139	40.3	3.45 (2.87–4.02)	<0.0001
1996–2004	73	32.0	2.28 (1.76–2.81)	<0.0001
2005–2013	20	10.8	1.86 (1.04–2.67)	0.039
Men				
1987–1995	59	20.1	2.93 (2.18–3.68)	<0.0001
1996–2004	37	16.0	2.32 (1.57–3.06)	0.0005
2005–2013	11	5.1	2.17 (0.89–3.46)	0.074
Women				
1987–1995	80	20.2	3.96 (3.10–4.83)	<0.0001
1996–2004	36	16.0	2.25 (1.51–2.98)	0.0009
2005–2013	9	5.7	1.58 (0.55–2.61)	0.27
Patients treated with surgery alone				
1987–1995	63	18.0	3.51 (2.64–4.37)	<0.0001
1996–2004	26	13.7	1.90 (1.17–2.62)	0.016
2005–2013	2	4.9	NC	NC
Patients treated with radiotherapy alone				
1987–1995	4	1.0	4.21 (0.08–8.34)	0.13
1996–2004	4	1.0	4.08 (0.08–8.07)	0.13
2005–2013	1	1.0	NC	NC
Patients treated with both surgery and radiotherapy				
1987–1995	4	1.6	2.45 (0.05–4.85)	0.24
1996–2004	3	2.8	1.08 (0.00–2.29)	0.90
2005–2013	2	0.9	NC	NC
Patients treated without both surgery and radiotherapy				
1987–1995	68	19.8	3.44 (2.62–4.26)	<0.0001
1996–2004	40	14.5	2.76 (1.91–3.62)	<0.0001
2005–2013	15	4.4	3.43 (1.70–5.17)	0.006

CI, confidence interval; NC, not calculated (for groups with less than 3 deaths); SMR, standardized mortality ratio.

According to recent studies, the rate of disease control has increased over time (13), which may be explained with the advent of additional therapeutic options or with the adoption of new recommended criteria for biochemical remission (36). However, we could not analyse disease control, as data on biochemical disease activity were not available in our population.

The proportion of acromegalic patients discontinuing follow-up has been evaluated in only a few studies (37, 38). Delemer and colleagues (37) displayed a prevalence of loss to follow-up of 21% to any Endocrine Department. The proportion of patients in our study who did not have any visits to university hospital care for 3 consecutive years at any time during the follow-up was 49% and the mean follow-up time before discontinuing this care was 23 months. This group had a higher proportion of patients who received neither surgery nor radiotherapy. Surprisingly, the mean follow-up during the entire study period was longer in the group who discontinued specialized care, and excess mortality was significantly lower compared to patients who had not discontinued. One might hypothesize that patients discontinuing specialized follow-up visits had milder disease not requiring advanced tumor treatments. Therefore, once achieving disease control, these patients may have been referred to local medical care that seems consistent with a mean follow-up time of approximately 2 years before discontinuing specialized care.

The main strength of this study lies in the large nationwide population and the long follow-up period. Also, data were obtained from official national registers that have a very high yield. In addition, the characteristics of our population were similar to those described in previous registries and large series (13, 14, 29, 30, 31), supporting the reliability of the applied identification criteria. There are, however, some limitations to be considered. Detailed data on clinical characteristics and tumor size were not available in the registers. Similarly, data on post-treatment remission status and details on the degree of hypopituitarism and its treatment were not available. Finally, we did not perform an internal validation of the acromegaly diagnosis, but in our previous studies on pituitary adenoma and craniopharyngioma, the search criteria were validated with good results (39, 40).

In conclusion, excess mortality was found in this nationwide cohort of unselected patients with acromegaly, mainly related to circulatory and malignant diseases. Although mortality is still high, it gradually declined during recent decades, which may be explained by the increasing use of pituitary surgery, decreasing prevalence of hypopituitarism and the availability of new additional treatment options.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-18-0015.

Declaration of interest
D E and O R have nothing to declare. D G and T M are employed by Nordic Health Economics. G J has received lecture fees from Novartis, Novo Nordisk, Pfizer, Sandoz, Merck Serono and Otsuka as wells as consultancy fees from Astra Zeneca and Shire. D S O has been a consultant for Sandoz, Ipsen and Pfizer.

Funding
This study was supported by the Swedish government under the ALF agreement.

Acknowledgment
The authors are indebted to the National Board of Health and Welfare for their excellent collaboration. The authors would like to acknowledge all the help we have received from Nordic Health Economics, Gothenburg, Sweden, which has performed the mortality calculations. They also would like to thank Peter Todd (Tajut Ltd., Kaiapoi, New Zealand) for third-party writing assistance in drafting of this manuscript, for which he received financial compensation from ALF funding.

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Received 8 January 2018
Revised version received 15 February 2018
Accepted 26 February 2018