

Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis

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Abstract

Objective: To compare the acromegaly mortality rates with those expected for the general population from studies published before and after 2008.

Methods: We performed a systematic review and included observational studies in which the number of deaths observed in acromegaly was compared with the expected mortality for the general population mortality observed/expected (O/E). The following electronic databases were used as our data sources: EMBASE, MEDLINE and LILACS. From the observed and expected deaths, we recalculated all standardized mortality ratios (SMR) and their respective confidence intervals (95% CI), which were plotted in a meta-analysis using the software RevMan 5.3.

Results: We identified 2303 references, and 26 studies fulfilled our eligibility criteria. From the 17 studies published before 2008, the mortality in acromegaly was increased, while from the nine studies published after 2008, the mortality was not different from the general population (SMR: 1.35, CI: 0.99–1.85). In six studies where somatostatin analogs (SAs) were used as adjuvant treatment, acromegaly mortality was not increased (SMR: 0.98, CI: 0.83–1.15), whereas in series including only patients treated with surgery and/or radiotherapy, mortality was significantly higher (SMR: 2.11; CI: 1.54–2.91). In studies published before and after 2008, the mortality was not increased in patients who achieved biochemical control, while it was higher in those with active disease. Cancer has become a leader cause of deaths in acromegaly patients in the last decade, period in which life expectancy improved.

Conclusion: Mortality in acromegaly is normalized with biochemical control and decreased in the last decade with the more frequent use of SAs as adjuvant therapy. Increased life expectancy has been associated with more deaths due to cancer.

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Introduction

Acromegaly is a chronic systemic disease caused by the overproduction of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) (1). In the vast majority of cases, the disease is caused by a GH-secreting pituitary adenoma, which are macroadenomas (>10mm) at diagnosis in two-third of the patients. In a Mexican epidemiological study (2), the prevalence of acromegaly was estimated in 18 cases per million inhabitants (c.p.m.), contrasting to much higher estimates of 33.7 c.p.m in the Spanish Acromegaly

Registry (3), 40c.p.m. in a study carried out in Belgium and in Luxembourg (AcroBel study) (4) and 85 c.p.m. in a Danish population-based cohort study (5).

Microscopic and endoscopic transsphenoidal surgery is the primary choice of therapy for most acromegaly patients (6). In acromegaly patients who remain with disease activity after surgery, somatostatin analogs (SAs) are the first choice of adjuvant therapy. Primary therapy with SAs is usually recommended for patients with a low

chance of surgical cure, high surgical risk or who refuse surgery (1). Other pharmacological options to achieve biochemical control of the disease include cabergoline and the GH receptor antagonist (pegvisomant) (7). Radiotherapy is mainly reserved for patients harboring aggressive tumors that are not fully removed and controlled with surgery and medical therapies (1, 6).

Uncontrolled GH and IGF-1 hypersecretion in acromegaly is associated with increased risk for cardiovascular, respiratory, metabolic and neoplastic complications and higher mortality rates than in the general population (8). Abnormalities involving the cardiovascular system have traditionally been the most frequent complication in these patients, accounting for up to 60% of deaths. If present at diagnosis, heart disease leads to a 100% death rate in 15 years (9). Mortality due to respiratory disorders, such as hypopnea syndrome, obstructive sleep apnea, hypoventilation, hypoxia and lung infections, accounts for 25% of the cases (9), while malignant diseases are responsible for approximately 15–24% of deaths (10). In some, but not all studies, mortality associated with colorectal cancer was found to be increased in acromegaly (8).

Mortality in acromegaly was addressed by two systematic reviews published in 2008 in which standardized mortality ratios (SMRs) were found to be significantly higher in acromegaly patients than in general population (11, 12). In the last decade, however, some studies have reported on normalization of mortality rates (13, 14), while others still found increased SMR in acromegaly (15, 16). In the present systematic review and meta-analysis, our aim was to compare the SMR in acromegaly before and after 2008, with the hypothesis that SMR has decreased and even normalized due to improvement in surgical approaches, larger use of medical therapies and better control of comorbidities.

Methods

This systematic review was reported according to the MOOSE (meta-analysis of observational studies in epidemiology) Statement (17), and it was registered in the international prospective register of systematic reviews with number CRD42018084795.

Eligibility criteria

We included only observational studies where the number of deaths in patients with acromegaly could be determined.

The primary outcome was mortality presented as SMR, calculated as the ratio between the observed number of deaths in the study population and the number of expected deaths in that population (mortality observed/expected (O/E)), with adjustment for age and sex.

Search strategy

We searched the following electronic databases until February 2018 to identify the eligible studies: EMBASE (by Elsevier), MEDLINE (by PubMed) and LILACS (by Virtual Health Library). There was no language and year restriction. The following medical subject heading terms with their respective synonyms were used to construct the search strategies: Acromegaly, GH-secreting Tumor, Somatotropinoma, Gigantism and Mortality.

From the primary or secondary relevant studies, we checked for more eligible studies in their cited/included articles, and we also searched for eligible studies in the gray literature, including abstracts published in annals and proceedings of medical conferences and meetings.

We used the Mendeley software to download all references in order to remove duplicates and facilitate the selection process.

Study selection

Two reviewers (F B and A F N) independently screened the titles and abstracts identified by the literature search, and the studies potentially eligible for inclusion in the review were selected for complete reading. In case of disagreement in that selection process, a third reviewer was consulted (V S N N).

Data extraction and evaluation of risk of bias

The two reviewers independently extracted data from the articles that met the inclusion criteria. A standardized form was used to extract the following information: year of publication, type of study, participating centers, number of patients included, diagnostic criteria of the disease, average age at diagnosis, sex, main types of treatment, disease cure criteria, major chronic complications, mortality data in O/E and general SMR and divided by subgroups, base population for comparison for the calculation of the expected mortality rate, follow-up time and missing data.

For each study selected, the risk of bias was evaluated according to the criteria described by Newcastle–Ottawa Scale (case–control studies), which considers three domains: selection (four items), comparability (one item)

and exposure (three items). A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, a maximum of two stars can be given for comparability (18).

Synthesis and analysis of the data (meta-analysis) and quality of evidence

From the number of observed deaths in patients with acromegaly and the expected mortality rate for the population used as a basis for comparison, all the SMRs and their respective 95% CI were recalculated according to the Boice–Monson method (19).

The SMRs recalculated with their respective CI were plotted in a meta-analysis, using the Review Manager 5.3 software. The random effect was chosen as a model of analysis. The inverse of the variance was the statistical method used to weigh the SMRs of the included studies. The inconsistency between the results was determined through the visual inspection of the forest plot (no overlapping of CIs around the estimates of the effect of individual studies) and also through Higgins' inconsistency test or I^2 , in which $I^2 > 50\%$ indicates a moderate probability of heterogeneity (20).

The potential causes of heterogeneity were evaluated by performing the following subgroups analysis: SMR from studies published before and after 2008, according to the cure criteria, cause of death (cerebrovascular, respiratory, cardiovascular and neoplasia) and according to treatment modality (predominantly surgery, radiotherapy and availability of pharmacological treatment, in special SAs). We also performed subgroup analysis according to gender and study setting (multicenter vs single-center study).

We used only the available data in the published articles, and when necessary, we contacted the authors of the original studies to obtain missing information.

The quality of evidence of the acromegaly SMR result was generated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (21).

We evaluated publication bias by visual inspection of funnel plot, and we considered the presence of this bias as an observation of an asymmetrical rather than a symmetrical graph (22).

Results

From the searches of databases, 2303 references were identified (Fig. 1). Thirty articles were potentially eligible

for inclusion in the review, and from these, 26 publications were included in the final analysis (4, 8, 13, 14, 15, 16, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42). Two studies were excluded because the authors did not provide mortality data in O/E for SMR calculation (3, 5). We excluded other two studies due to duplication data: the study by Sherlock *et al.* (16) that included patients from the study by Ayuk *et al.* (43), and the study from Ritvonen *et al.* (44) that were previously published by Kauppinen-Mäkelin *et al.* (29).

The main characteristics of the included studies are presented in Table 1. All studies were observational, including patients followed by one or several centers of a particular region, and the mortality information was obtained through hospital records, contact with family members or doctors monitoring these patients or via death certificates. In the study by Colao *et al.* (39) comparing cohorts from two different countries, data from Naples was included in another publication of a multicenter study in Italy (13), and then only data from patients followed in Bulgaria in that publication were included in our analysis (b).

From the 26 studies included, 17 were published before and 9 after 2008, with a total of 10 770 acromegaly patients (4, 8, 23, 24, 26, 28, 29, 30, 31, 33, 35, 36, 37, 38, 41, 42). From the 17 studies published before 2008, 5152

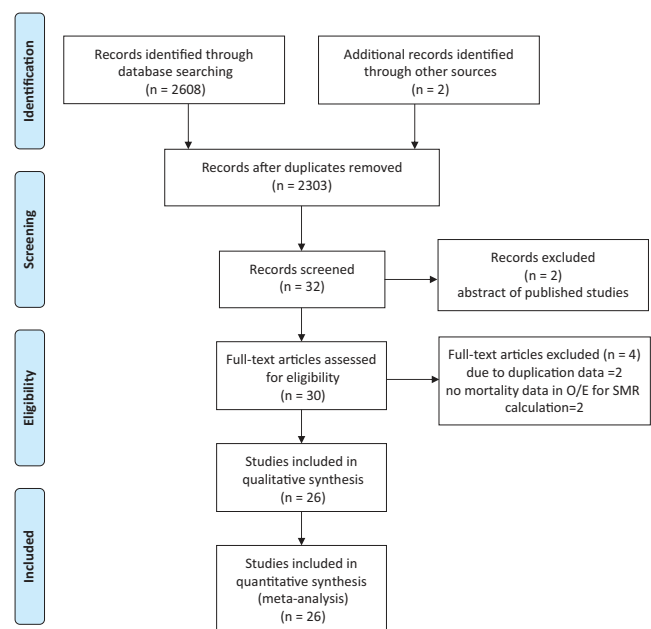


Figure 1

Flowchart for identifying eligible studies. SMR, standardized mortality ratios. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0255>.

Table 1 Main characteristics of the 26 studies included in the meta-analysis.

Study/year	Sample size	Lost to follow-up	F/M	Centers	Follow-up time	SMR (95% CI)	O/E	Base population for comparison	Cure criteria	GH test	Treatment modality
(23)	194	-	105/89	5 hospitals (Hammersmith, King's College, Middlesex, The Royal Sussex County, University College), England and Wales	1937–1967	1.89 (1.44–2.49)	54/28.5	General population of England and Wales	-	-	No treatment, radiotherapy, TSS or TCS
(33)	164	-	94/70	Newcastle Regional Hospital, England	1960–1971	3.31 (2.46–4.45)	45/13.6	General population of England and Wales from 1969	-	-	-
(34)	256	15	123/133	Middlesex Hospital, England	1963–1984	1.26 (0.94–1.69)	47/37.2	General population of England and Wales from 1982	Random GH <10 mU/L*, nadir after OGTT <4 mU/L	-	TSS, radiotherapy
(35)	166	-	89/77	Sahlgrenska Hospital, Sweden	1955–1984	1.80 (1.50–2.16)	62/34.4	Population of Sweden from 1955–1985	Random GH <10 U/L	-	No treatment, TSS or TCS, radiotherapy, bromocriptine associated with surgery or radiotherapy
(36)	74	-	48/26	Hospital de Cruces, Spain	1970–1989	3.23 (1.72–6.07)	10/3.1	Population of Vizcaya in 1987	Random GH <5 ng/mL** and/or nadir after OGTT <5 ng/mL	RIA	TSS, radiotherapy, bromocriptine or octreotide
(37)	79	-	50/29	North Staffordshire, United Kingdom	1967–1991	2.68 (1.85–3.88)	28/10.44	General population of England and Wales	Random GH <10 mU/L	RIA	No treatment, TSS or TCS, radiotherapy, bromocriptine
(38)	254	-	105/149	University of California, United States	1974–1992	1.28 (0.88–1.86)	29/22.7	Population of the United States from 1995	Random GH <5 nG/mL	-	TSS, radiotherapy, bromocriptine or SA
(8)	1362	-	-	15 tertiary reference centers, United Kingdom	-	1.60 (1.44–1.78)	366/228.81	General population of England and Wales	-	-	-
(42)	979	-	-	142 hospitals, Japan	1988–1993	2.10 (1.76–2.51)	84/40	-	-	-	TSS or TCS, radiotherapy, pharmacotherapy
(30)	149	2	-	Massachusetts General Hospital, United States	1978–1996	1.16 (0.66–2.04)	12/10.34	Population of the United States	Normal IGF-1 or random GH <2.5 ng/mL	-	TCS, radiotherapy, pharmacotherapy

Clinical Study				F Bolfi and others	Mortality in acromegaly in the last decade	179:1	63				
(26)	103	4	43/60	Notre-Dame Hospital, Canada	1970–1999	2.14 (1.34–3.42)	18/8.4	Population of Quebec from 1998	Normal IGF-1 for age and sex and/or nadir GH after OGTT <1 µg/L if IRMA or <2 µg/L if RIA and random GH <2.5 µg/L	Until 1993 GH evaluated by RIA and after IRMA	Radiotherapy, TSS, octreotide
(24)	154	–	77/77	Hiroshima University, Japan	1977–2000	1.17 (0.64–2.14)	11/9.4	Japanese Population from 1985 to 1995	Random GH <5 ng/mL and/or high IGF-1	until 1985 GH RIA, from 1985 GH IRMA/log Y=0.949 log X+0.064 (Y=RIA e X=IRMA); 1985–1994: IGF-1 RIA, from 1994 IGF-1 IRMA	TSS, octreotide, bromocriptine or adjuvant radiotherapy
(28)	208	–	83/125	Auckland Hospital, New Zealand	1964–2000	2.7 (2.13–3.42)	72/26.7	Population of New Zealand	–	RIA up until 1995 and IRMA from then on	TSS or TCS, radionuclide implantation, radiotherapy
(41)	164	–	73/91	Leiden University, the Netherlands	1977–2002	1.33 (0.91–1.94)	28/21.1	Population of the Netherlands	Random GH <5 mU/L, nadir GH after OGTT <1 µg/L if IRMA or <2.5 µg/L if RIA for age and sex	GH until 1992 RIA conversion factor (CF)=2 to transform mU/L in µg/L; GH from 1993 22 kDa specific GH conversion factor (CF)=2.6 to transform mU/L in µg/L	TSS, radiotherapy and/or SA
(29)	334	–	173/161	5 University hospitals of Finland	1980–1999	1.16 (0.85–1.58)	56/48.3	Population of Finland in 2002	Random GH <2.5 µg/L, immunofluorometric assay and chemiluminescence	1980–1999: GH dosed in five laboratories with seven different kits. The authors cite the differences and correlations between the GH assays; IGF-1 RIA and IRMA, with results on average 1.5 times higher in IRMA than in RIA	TSS or TCS, radiotherapy, SA, DA
(31)	94	–	49/45	University Hospital of Bern, Switzerland	1971–2003	1.34 (0.77–2.33)	13/9.72	Population of Switzerland from 1990	Normal IGF-1 for age and sex and nadir GH after OGTT <1.0 µg/L or random GH <2.5 µg/L	GH until 1994 RIA, 1994–2002 IRMA and after 2002 ELISA; IGF-1 1995–1997 RIA and after 1998 IRMA	TSS, radiotherapy, DA and/or SA, GHRA
(4)	418	–	205/213	37 hospitals in Belgium and Luxembourg	2000–2004	1.39 (0.96–2.04)	27/19.4	General population of Belgium from 2001 to 2003	Normal IGF-1 for age and sex and average GH <2 µg/L	–	No treatment, TSS, radiotherapy, DA and/or SA, GHRA
(16)	501	–	275/226	16 centers of West Midlands, United Kingdom	1990–2006	1.69 (1.45–1.97)	162/95.9	General population of England and Wales	–	RIA	TSS or TCS, radiotherapy
(15)	142	–	68/74	Taipei Veterans General Hospital, Taiwan	1979–2007	1.93 (1.22–3.05)	18/9.31	General population of Taiwan from 1986 to 2006	Normal IGF-1 and random GH <2 µg/L	RIA up until 1999, immunofluorometric assay from then on	TSS

(Continued)

Table 1 Continued.

Study/year	Sample size	Lost to follow-up	F/M	Centers	Follow-up time	SMR (95% CI)	O/E	Base population for comparison	Cure criteria	GH test	Treatment modality
(25)	1512	-	888/624	24 reference centers, Italy	1980-2002	1.15 (0.90-1.47)	61/53	General population of Italy from 2008	Random GH <2.5 µg/L and/or nadir GH after OGTT <1 µg/L and normal IGF-1 for age and sex	GH and IGF-1 assays changed over time	SA, DA, radiotherapy, TSS or TCS
(13)	438	-	249/189	University of Pisa and University Federico II Nápoles, Italy	1966-2009	0.70 (0.45-1.09)	20/28.57	General population of Italy from 1999 to 2009	1980-1990: GH <5 µg/L, 1990-1997: GH <2 µg/L, 1997-2009: nadir GH <1 µg/L after OGTT and normal IGF-1 for sex and age	1980-1990: RIA, 1990-1997: IRMA, 1997-2009: chemiluminescence	TSS or TCS, radiotherapy, SA
(9)	627 (220a and 407b)	-	380/247	Naples, Italy (a) and Sofia, Bulgaria (b)	1999-2008	0.66 (0.31-1.39) a 2.01(1.59-2.54)b	7/10.6(a) 71/35.4(b)	Population of Campania (a) and Bulgaria (b)	Random GH <2.5 µg/L and/or nadir GH after OGTT <1 µg/L and normal IGF-1 for age and sex	Until 1992, in Bulgaria, GH dosed by RIA with conversion factor (FC)=2 to transform mIU/L in µg/L; IGF-1 was transformed from the result to ULN of each assay used	TSS or TCS, radiotherapy, DA, SA, GHRA
(14)	442	-	289/153	Hospital de Especialidades, Mexico	1990-2012	0.76 (0.50-1.16)	22/29	General population of Mexico	Nadir GH after OGTT <0.4 ng/ml and IGF-1 <1.2 of the limit over normality	-	TSS, octreotide, cabergoline
(32)	88 (new cohort)	-	41/47	University Hospitals of North Midlands	1992-2012	1.0 (0.57-1.75)	12/12	General population of England and Wales	Two consecutive GH values from random samples or mean of GH day profile or mean of GH values on OGTT were <1.7 µg/L (equivalent of 5 IU/L) I and normal IGF-1 for age and sex	RIA, before 2009 were reported in IU/L and a multiplying conversion factor of 0.33 was used	TSS, radiotherapy, pharmacotherapy (SAs and DAs)
(40)	999	165	539/460	33 centers in France and also in French-speaking areas of Switzerland and Belgium	1977-1999 retrospectively and 1999-2012 prospectively	1.05 (0.77-1.43)	41/39	French population	1.2-1.3x ULN IGF-1 levels or random GH <1 ng/mL or a GH nadir <0.4 ng/mL after OGTT suppression	-	Surgery, radiotherapy, pharmacotherapy (SAs, DAs, GHRA)
(27)	1089	531	580/509	Swedish National Health Registries	1987-2013	2.79 (2.46-3.18)	232/83	Swedish population	-	-	Surgery, radiotherapy, pharmacotherapy (SAs, DAs, GHRA)

*1 mIU/L \approx 2 ng/mL; **1 ng/mL = 1 µg/L.

-, not described in the text; F/M, Female/Male; OGTT, Oral Glucose Tolerance Test; GH, growth hormone; IGF-1, insulin-like growth factor type 1; O/E, mortality observed/expected; SA, somatostatin analogs; SMR, standardized mortality ratio; CI, confidence interval; RIA, radioimmunoassay; IRMA, immunoradiometric assay; ELISA, enzyme-linked immuno-adsorbent assay; TCS, transcranial surgery; TSS, transphenoidal surgery; ULN, upper limit of normal; DA, dopamine agonist; GHRA: GH receptor antagonist.

patients were included with 962 deaths during a median follow-up period of 15 years. From the nine studies published in the last decade (13, 14, 15, 16, 25, 27, 32, 39, 40), 5618 acromegaly patients were included with 639 deaths in a median follow-up period of 24 years. All studies provided the number of deaths in relation to the expected mortality rate for the population, with adjustment for age and sex, allowing recalculation of all SMRs with their respective CI. In the studies by Mercado *et al.* (14) and Esposito *et al.* (27), we contacted the correspondent authors by email to ask about the number of observed and expected deaths in patients with acromegaly according to the disease control (controlled vs uncontrolled) and treatment modality respectively.

Regarding risk of bias by Newcastle–Ottawa Scale, all included studies achieved the same score: three stars for selection domain, one for comparability and one for exposure, resulting in this review a total of five stars (maximum nine).

The SMR observed in patients with acromegaly in the studies published before 2008 was significant higher than in the general population (SMR: 1.76, CI:1.52–2.4, $P < 0.00001$, Fig. 2). Although there is a high heterogeneity among studies ($I^2 = 77\%$), CIs around the effect estimates of individual studies have the same direction.

In the nine studies published after 2008, the meta-analysis showed no differences in the SMR between acromegaly patients and the general population (SMR: 1.35, 95% CI: 0.99–1.85; $P = 0.06$; $I^2 = 93\%$, Fig. 2). The high heterogeneity among the studies was further evaluated in a subgroup analysis according to treatment modality. In six studies in which SA was available as adjuvant treatment (13, 14, 25, 27, 32, 40), mortality in acromegaly was not different from general population (SMR: 0.98; CI: 0.83–1.15, $I^2 = 9\%$, Fig. 3). On the other hand, in four studies where only surgery and radiotherapy were available (15, 16, 27, 39), mortality was significantly higher in acromegaly (SMR: 2.11; CI: 1.54–2.91; $I^2 = 90\%$, Fig. 3). Although the study by Esposito *et al.* (26) was published in 2018, the authors provided SMR from 2005, when data on medical treatment were available and drug registry achieved national coverage, and before 2004, where only surgery and radiotherapy were accessible. We used the O/E of patients treated with both pharmacotherapy and surgery (80% of patients in pharmacotherapy received SAs).

We also performed SMR comparisons before and after 2008 according to the cure criteria and cause of death. For the studies published after 2008, only four studies evaluated the SMR according to the status of the disease

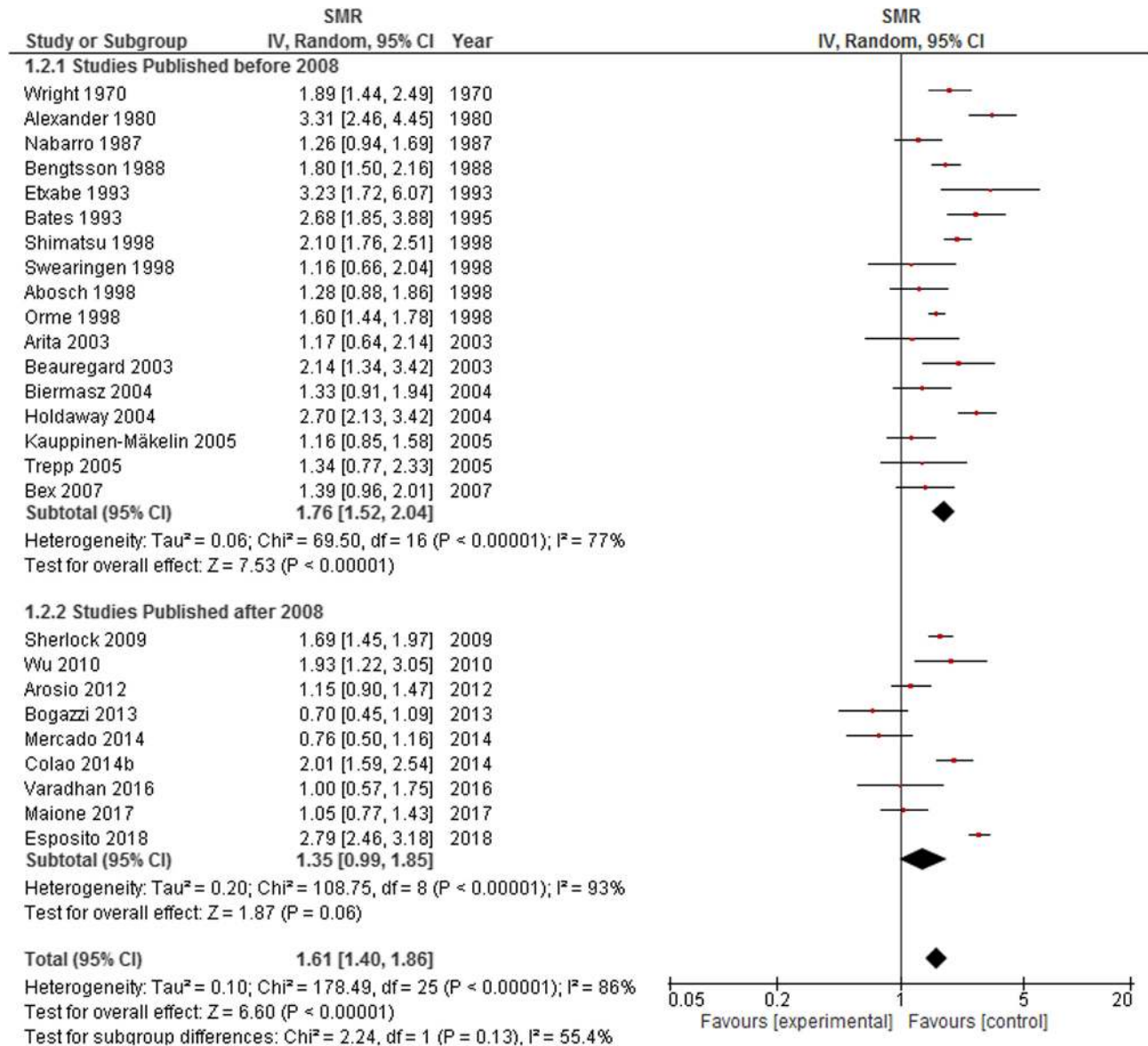
(14, 15, 25, 39). Three studies considered as ‘controlled patients’ those who exhibited normal IGF-1 associated with random GH ≤ 2.5 ng/mL (15, 25, 39), and one (14) considered as ‘controlled patients’ those who achieved IGF-1 levels below 1.2 times the upper limit of normal. In the meta-analysis of controlled patients, observed deaths were not significantly different from the expected deaths in general population (SMR: 0.71, CI: 0.41–1.22, $I^2 = 62\%$, Fig. 4). The inconsistency was solved separating studies according to adjuvant use of SAs (14, 25) or not (15, 39). In studies with SAs as adjuvant therapy, mortality was significantly lower than in normal population (SMR: 0.55, CI: 0.37–0.82, $I^2 = 0\%$), while no difference was observed in the studies where SA therapy was not used (SMR: 0.94, CI: 0.77–1.84, $I^2 = 7\%$). In uncontrolled acromegaly patients, SMR was significantly higher than that in the general population (SMR: 1.96, CI: 1.25–3.05, $I^2 = 78\%$, Fig. 4). The heterogeneity was attributed to the Mexican study, in which observed deaths in acromegaly were not different from general population, despite that only 36% of patients in their cohort were controlled. Excluding the Mexican study, the SMR increased to 2.4 (CI: 1.91–3.01) and the heterogeneity falls to 13%.

Before 2008, four studies evaluated SMR according to cure criteria (26, 30, 31, 41), and controlled disease was defined by normal IGF-1 and random GH < 2.5 ng/mL. In these patients, mortality was not different from general population (SMR: 0.94, CI: 0.76–1.16, $I^2 = 8\%$, Fig. 4). In contrast, active disease was associated with higher mortality (SMR: 2.11, CI: 1.13–3.97, $I^2 = 73\%$, Fig. 4). The high heterogeneity occurred due to Beauregard’s study, but, in this case, the estimated effect in mortality showed similar directions in all four studies, namely higher in acromegaly.

Nine studies evaluated the SMR in relation to cardiovascular death (8, 16, 23, 27, 28, 29, 33, 36, 39), three published after and six before 2008. In both periods of time the mortality was higher in acromegaly (SMR: 2.38, CI: 1.81–3.14, $I^2 = 72\%$ and SMR: 1.67, CI: 1.35–2.05, $I^2 = 48\%$ respectively, Fig. 5).

The SMR due to respiratory causes included three studies published before 2008 (8, 23, 33) and two after 2008 (16, 27), and mortality was higher in acromegaly in both periods (SMR: 2.64, CI: 1.60–4.35, $I^2 = 61\%$ and SMR: 2.40, CI: 1.31–4.41, $I^2 = 68\%$, Fig. 5).

In the eight studies that cerebrovascular diseases were evaluated (8, 16, 23, 27, 28, 29, 33, 39), five were published before and three were published after 2008. The SMR was 2.76 (CI: 1.90–4.02, $I^2 = 82\%$, Fig. 5) and increased mortality was observed in both periods.

**Figure 2**

Meta-analysis of SMR in acromegaly of the 26 included studies, with subgroup analysis of the studies published before 2008 vs after 2008. SMR, standardized mortality ratios. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0255>.

In the six studies published before 2008, where the mortality in acromegaly was significantly higher (8, 23, 28, 29, 33, 35), the SMR due to malignancies was not increased. In three studies published after 2008 (16, 27, 39), period which life expectancy in acromegaly has improved, we observed a change in the causes of deaths in acromegaly, an increasing number of deaths due to cancer (Fig. 5).

From the 17 studies published before 2008, 12 were single center and 5 were multicenter. In both settings, mortality in acromegaly was significantly higher than in

the general population (SMR: 1.64, CI: 1.36–1.97; SMR: 1.83, CI: 1.47–2.29 respectively). After 2008, five studies were multicenter and four single center, and again there was no difference in mortality according to the study setting (SMR: 1.35, CI: 0.87–2.11; SMR: 1.34, CI: 0.81–2.21 respectively).

Six studies published before 2008 had SMR calculated according to gender (26, 29, 33, 34, 36, 38), and in both men and women, mortality was higher in acromegaly than in the general population. Three studies published after 2008 provided SMR according to gender (13, 14, 27),

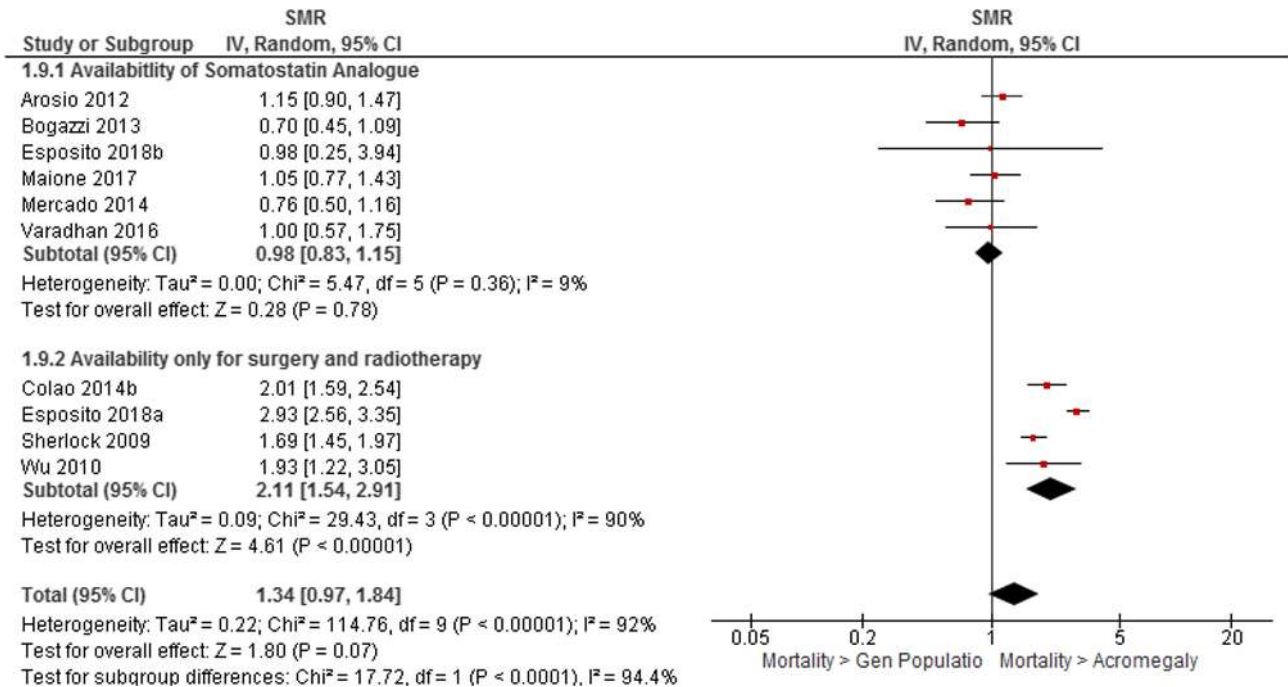


Figure 3

Meta-analysis of SMR in acromegaly of studies published after 2008, with subgroup analysis according to treatment modality (adjuvant therapy with somatostatin analogs vs therapy only with surgery and/or radiotherapy). SMR, standardized mortality ratios. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0255>.

and for both men and women, mortality did not differ between acromegaly and control population.

Applying GRADE, for all estimated effects of acromegaly in mortality rates (represented by SMRs plotted in the meta-analysis), the quality of evidence was very low.

We provided a funnel plot of the SMRs from all 26 studies included, and by visual inspection, we considered improbable the presence of publication bias (Fig. 6).

Discussion

The first evidence for a higher mortality rate in acromegaly patients came from the report by Wright *et al.* in 1970 (23). Since then, other studies have found similar results, indicating mortality rates three to four times higher in acromegaly in comparison with individuals of the same gender and age.

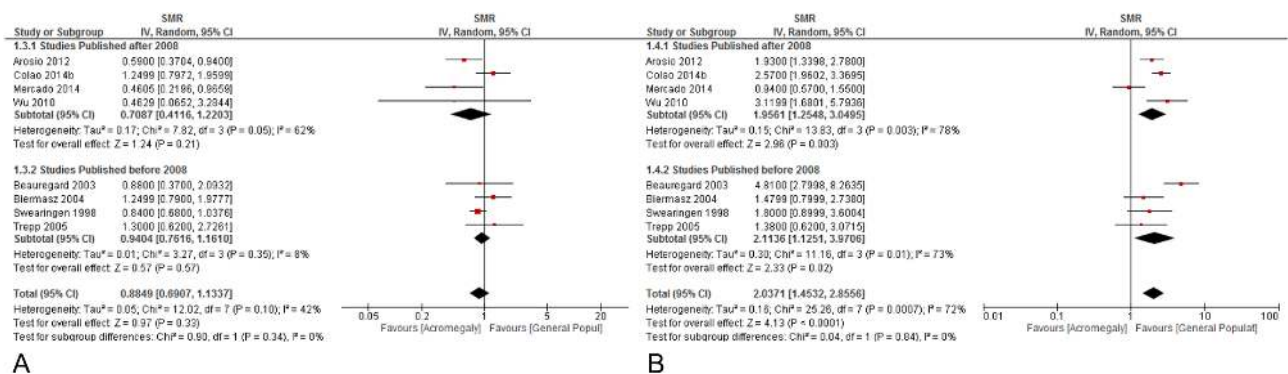


Figure 4

Meta-analysis of SMR in acromegaly of studies published after 2008 and before 2008, with subgroup analysis according to disease activity. (A) Controlled Patients. (B) Uncontrolled Patients. SMR, standardized mortality ratios. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0255>.

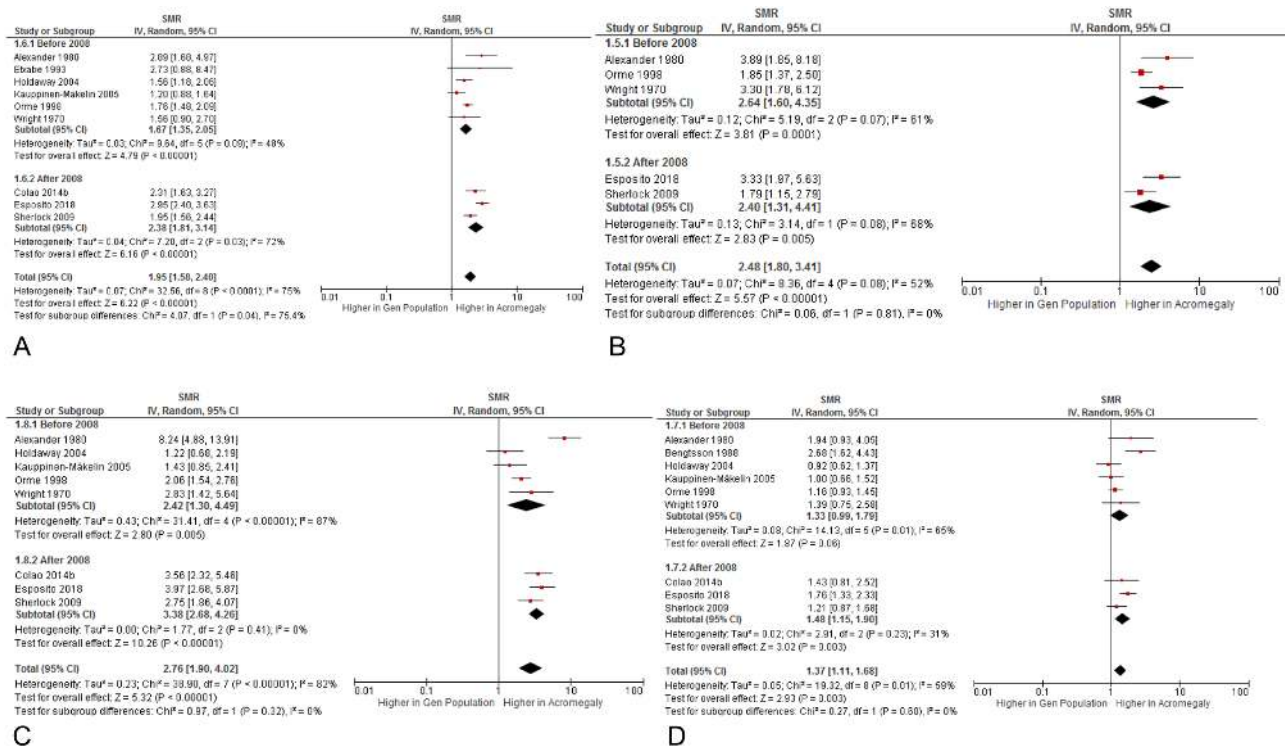


Figure 5

Meta-analysis of SMR according to causes of deaths, with a subgroup analysis of the studies published before 2008 vs after 2008. (A) Deaths due to cardiovascular diseases. (B) Deaths due to respiratory diseases. (C) Deaths due to cerebrovascular diseases. (D) Deaths due to cancer. SMR, standardized mortality ratios. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0255>.

The increased mortality at that time was due to scarce treatment options, which included only surgery and radiotherapy. Besides the improvement of the surgical results over the years, pharmacological therapy of acromegaly, especially the introduction of SAs in the 1980, has been claimed to exert an important impact on mortality. The first studies with the prolonged release formulation of SAs were published only in 1995 (45) and even many years after their introduction in the market, the wider use of SAs has been limited in many countries due to the high costs of the treatment. For instance, in the study by Colao *et al.* (39) published in 2014, mortality was much higher in acromegaly patients followed in Bulgaria compared to those followed in Italy, and this was attributed to the use of SAs since 1988 and the GHR antagonists since 2004 in Italy, while in Bulgaria these drugs were not available until 2008, with a significantly higher proportion of patients treated with radiotherapy than in the Italian center.

Two meta-analyses published in 2008 showed an increased mortality rate in acromegaly patients compared to the general population (11, 12). In our review, in the

studies published after 2008, mortality in acromegaly was not significantly different from that expected in the general population. There was, however, a high heterogeneity in the meta-analysis. Such inconsistency was solved by a separate sub-analysis of the six studies (13, 14, 25, 27, 32, 40) in which mortality rate was not different from that in the general population and the four studies where mortality rate was higher (15, 16, 27, 39). We found that in the former, the authors included SAs as complementary treatment for patients uncontrolled by surgery, while in the later, patients were treated only with surgery and radiotherapy, showing that the use of SAs had a positive impact in reducing mortality in acromegaly.

Our results showed a clear evidence that mortality in acromegaly is strongly related to disease control, as observed by normal SMR in controlled patients in both periods of the study, and increased SMR in uncontrolled patients, even in the most recent studies published in the last decade.

The reduced life expectancy in acromegaly has been attributed to vascular and respiratory diseases, and most published studies have provided the O/E so that the

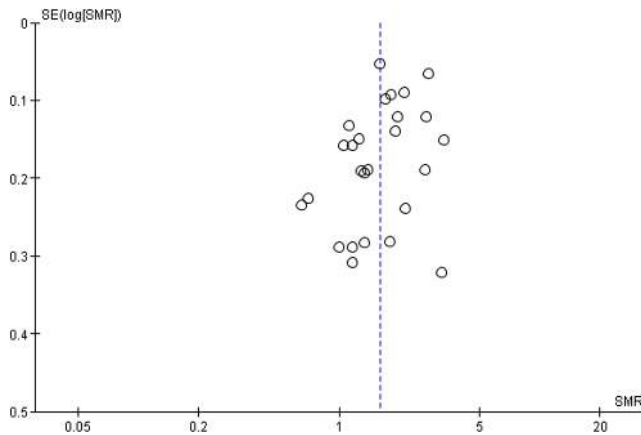


Figure 6

Funnel plot of acromegaly SMR in all 26 studies included. SMR, standardized mortality ratios. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0255>.

SMR and the corresponding CI could be recalculated (8, 16, 23, 27, 28, 29, 33, 36, 39). We observed that cardiovascular, respiratory and cerebrovascular mortality was significantly higher in acromegaly patients than in the general population, both before and after 2008. However, in recent epidemiological studies where mortality in acromegaly has been normalized and life expectancy increased, the main causes of deaths have changed from cardio and cerebrovascular complications to cancer. In the Mexican cohort (14), the most prevalent cause of mortality was cancer in 27.2% of patients, followed by respiratory and cardiovascular disease, responsible for 14% and 9% deaths respectively. In the finish cohort with a follow-up of 20 years, Ritvonen *et al.* (44) observed that deaths to cardiovascular diseases decreased from 44% in the first decade of follow-up to 23% in the second decade of follow-up, while deaths due to cancer increased from 28 to 35% respectively. Similar findings were observed in the study by Maione *et al.* (40), where the causes of death, in decreasing order, were cancer, vascular events and respiratory disease; Arosio *et al.* (25), in which 27.9% patients died from cardiovascular diseases and 36% from malignancies and Bogazzi *et al.* (13), where 20% of patients died due to cardiovascular diseases, 25% due to cerebrovascular complications and 30% due to cancer. These results show that when SMR declines, there is a shift in the causes of death in acromegaly related to aging in the same direction as observed in the general population. Moreover, in recent studies, the type of cancers related to death in acromegaly include a wide range of different malignancies, including anaplastic thyroid carcinoma,

glioblastoma, ovarian adenocarcinoma, uterine, lung, liver, prostate, breast, ovary, brain, gastric, pancreatic, hematological and melanoma (8, 16, 23, 27, 28, 29, 33, 36, 39). These malignancies are not those traditionally related to acromegaly, such as colon and differentiated thyroid carcinoma, but instead those characteristically associated with age, genetic and environmental factors.

Two epidemiological studies evaluated mortality in acromegaly patients, but they were excluded from our review because mortality data in O/E for SMR calculation were not provided (3, 5). In Mestrón *et al.* (3) published in 2004, 56 deaths were observed in 1219 patients. Mortality was greater in patients treated with radiotherapy and in those with active disease and uncontrolled GH and IGF-I concentrations. The deaths in patients never treated with SAs was significantly higher than in those exposed to SA treatment any time during the follow-up (66% compared with 34%; $P=0.016$). In Dal *et al.* (5), the authors included 405 acromegaly patients and 4050 age- and gender-matched controls. During the mean follow-up of 10.6 years, the mortality rate was marginally higher in acromegaly (hazard ratio (HR) of 1.3 (95% CI: 1.0–1.7)) and uninfluenced by treatment modality. However, the HR for mortality was higher in the first year after diagnosis than subsequent years (HR: 1.2 (95% CI: 0.9–1.6)).

There are some limitations in our review that may have influenced the results. First, only retrospective studies were included, in which failure in obtaining information often occurs. For instance, in our sub-analysis separating controlled and uncontrolled patients, it is possible that some patients were not included because they did not have IGF-1 and/or GH measured in their last appointment. Moreover, lost to follow-up is common in retrospective studies which might influence the analysis of general mortality. The presence of comorbidities also plays a significant role on life expectancy in patients with acromegaly, and their management is as important as the normalization of GH and IGF1 levels. Unfortunately, we could not assess the influence of some acromegaly related comorbidities, such as diabetes mellitus and arterial hypertension, or lifestyle (smoking, alcohol intake) on the mortality data. The delay in acromegaly diagnosis has improved over time, and we could not evaluate if this was associated with decrease in mortality rate.

We considered improbable the presence of publication bias due to no visualization of asymmetry in the funnel plot, by the huge search in the literature for eligible studies and because we included studies with differences and no differences in the comparison of mortality in acromegaly with the expected in general population.

In the GRADE approach, observational studies start as low-quality evidence, but it can be rated down if most of the relevant evidence comes from studies that suffer from a high risk of bias (21). Due to methodological limitations in the included studies, we rated down one level of quality of evidence in all our results, and the final quality of evidence was very low.

In conclusion, our study showed that mortality rates in acromegaly are normalized with biochemical control of the disease, and in comparison with studies published before 2008, SMR decreased in the last decade especially due to the most frequent use of SAs as adjuvant therapy in patients not controlled with surgery. Normalization of SMR in acromegaly seems to change the causes of mortality, with larger proportion of deaths due to malignancies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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