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The changing landscape of acromegaly – an epidemiological perspective

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Abstract

Acromegaly is a rare disease and thus challenging to accurately quantify epidemiologically. In this comprehensive literature review, we compare different approaches to studying acromegaly from an epidemiological perspective and describe the temporal evolution of the disease pertaining to epidemiological variables, clinical presentation and mortality. We present updated epidemiological data from the population-based Danish cohort of patients with acromegaly ($Acro_{DEN}$), along with meta-analyses of existing estimates from around the world.

Based on this, we conclude that the incidence, prevalence and age at acromegaly diagnosis are all steadily increasing, but with considerable variation between studies. An increased number of incidental cases may contribute to the increase in incidence and age at diagnosis, respectively. The clinical features at presentation are trending toward a milder disease phenotype at diagnosis, and advances in therapeutic options have reduced the mortality of patients with acromegaly to a level similar to that of the general population. Moreover, the underlying cause of death has shifted from cardiovascular to malignant neoplastic diseases.

Keywords Acromegaly · Epidemiology · Prevalence · Incidence · Sex differences · Mortality

Abbreviations

GH	Growth Hormone
IGF-I	Insulin-like Growth Factor 1
ICD	International Classification of Disease
MRI	Magnetic Resonance Imaging
95%CI	95% Confidence Interval
AIP	Aryl hydrocarbon receptor-Interacting Protein
MEN1	Multiple Endocrine Neoplasia type 1
LAS	Liége Acromegaly Survey
SMR	Standardized Mortality Ratio

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1 Introduction

Acromegaly is caused by pituitary hypersecretion of growth hormone (GH) due to a GH-secreting adenoma, and the ensuing overproduction of insulin-like growth factor I (IGF-I) [1, 2]. Disease onset is insidious with a diagnostic delay of 3–10

years, often resulting in considerable morbidity at time of diagnosis [2–4]. Typical growth manifestations of acromegaly include enlargement of hands and feet, coarsening facial features, and less specific symptoms such as joint and muscular pain, excessive sweating, sleep apnea and headache [5]. Acromegaly is a rare disorder as it affects less than 500 individuals per 1,000,000 in the population [6]. Recent data indicates an increased incidence and a shift in phenotype towards a milder phenotype at diagnosis [4, 5, 7, 8]. A plausible explanation for this could be more frequent use of cerebral imaging, which has significantly increased the incidental findings of pituitary adenomas [7, 9], reportedly accounting for up to 30% of patients diagnosed with acromegaly within the last decade [7]. The biochemical threshold has also changed with the introduction of more sensitive GH and IGF-I assays, and the diagnosis of acromegaly with near normal GH but elevated IGF-I levels has been described [10]. Finally, it may be due to increased screening for acromegaly in patients with a cluster of symptoms and signs potentially related to acromegaly, as recommended by the Endocrine Society clinical guidelines [11].

Epidemiological data on acromegaly provides important information regarding impact on morbidity, socioeconomic factors and mortality [1, 12–14]. However, several sources of data are used, ranging from newly collected data from one or more centers with a specific research purpose [15], to secondary data retrieved from large databases such as governmental healthcare registries [16] or medical claims databases [17–19]. Each data source provides valuable data but is accompanied by distinct limitations. Whereas large databases and registries allow easy access, the data is rarely validated for research. On the other hand, small cohorts could be limited by selection bias or limited generalizability [20]. These different approaches with regard to study design may contribute to the heterogeneity found between various epidemiological studies [16, 20].

In this review, we aim to explore the epidemiological landscape of acromegaly focusing on the incidence rate, prevalence, clinical presentation and mortality including updated data from the National Danish Acromegaly cohort ($Acro_{DEN}$).

2 Epidemiological data sources and approaches

Most cohort studies reporting data on the epidemiology of acromegaly originate from Europe, although studies from Asia, North and South America and the Middle East have been published (Table 1). The methodological approach to conducting these epidemiological studies varies depending on factors such as the accessibility to national healthcare data, the availability of nationwide registries and the funding of healthcare systems. A range of data sources has been used, including insurance claims-based cohorts, population-based cohorts, national cohort studies, multi-center cohort studies, regional cohort studies, and single-center cohort studies, all of which are presented in Table 1.

2.1 Insurance-based databases

In countries with insurance-based healthcare services, extraction of data from insurance claims databases is a viable approach for conducting epidemiological studies. Burton et al. [17], Placzek et al. [22] and Broder et al. [18] reported epidemiological data using large US insurance claims databases, covering a large population, by using diagnosis and procedure codes. Similarly, Yun et al. [23], Park et al. [24], Wu et al. [25] and Matsubayashi and Kawakami [26] reported data from national health insurance databases in South Korea, Taiwan and Japan, respectively, covering a population of several million, as shown in Table 1. An important distinction is that Asian insurance databases have near-complete coverage, whereas the American cohorts derive from several independent insurance companies without national coverage.

A limitation of this approach is that insurance claims-based databases are designed mainly for administrative and financial purposes and contain limited clinical information at the individual level. Acromegaly cases are usually identified by combining variables such as surgical procedures, use of medical treatment and acromegaly-related treatment codes. This could introduce the risk of false positive cases, and the risk of missing prevalent cases in remission after surgery that are monitored without active treatment. Moreover, US insurance claims databases mainly include selected working age individuals, which may impede generalizability.

2.2 Multi-center and national cohorts

Another epidemiological approach is to combine multicenter national studies. Constituting one of the first, large acromegaly registries, the Spanish Acromegaly Registry contains data on 1219 acromegaly patients [27]. Reporting to this database was voluntary, and large regional variations were noted, along with declining data reports over time. The AcroBel cohort [28] contains 418 cases of acromegaly across 37 medical centers in Belgium and Luxembourg. However, not all centers contributed to the study, precluding national coverage. After publication of these studies, several European multi-center cohorts have been presented, such as the German [29], French [8], Italian [30] and British [31] national databases. As the catchment areas of cases are not always well defined in multicenter cohort studies (this can especially be the case if reference centers provide cases), valid estimation of incidence and prevalence of acromegaly may be hampered.

Table 1 Overview of studies presenting incidence and prevalence estimates, gender composition and/or age at diagnosis

Author, year of publication	Country	Type of cohort	Period	Population	Cases	Incidence (cases/10^6/year)	Prevalence (cases/10^6)	Female (%)	Age at diagnosis (years)
Present study	Denmark	National cohort	1977–2021	5.867.412	889	4.6	108	52%	48 (F48, M48)
Robért et al. 2023 [55]	Sweden	National cohort	1991–2018	10.200.000	1034	5.1		49%	52 (F53, M50)
Falch et al. 2023 [59]	Norway	Regional cohort	1999–2019	3.000.000	262	4.7	83	50%	52 (F52, M51)
Aagaard et al. 2022 [7]	Denmark	Regional cohort	1992–2021	600.000	72	4.6	127	58%	50
Zaina et al. 2022 [45]	Israel	Regional cohort	2000–2020	800.000	77		155	48%	51 (F53, M49)
Arnardóttir et al. 2022 [54]	Sweden	National cohort	1991–2011	9.500.000	698	3.7		51%	
Yun et al. 2021 [23]	South Korea	National health insurance claims database	2013–2017	51.000.000	1093	4.2	32	46%	48 (F47, M48)
Matsubayashi and Kawakami 2020 [26]	Japan	National health insurance claims database	2013–2017	105.100.000	28,936	4.9	92	57%	45 (F46, M43)
AlMalki et al. 2020 [38]	Saudi Arabia	Multi-centre	2017–2019	33.400.000	195		6	41%	46 (F48, M44)
Park et al. 2020 [24]	South Korea	National health insurance claims database	2010–2013	51.000.000	718	3.6		57%	46
Wu et al. 2020 [25]	Taiwan	National health insurance claims database	1997–2013	29.900.000	1195	2.8	43	50%	51
Caputo et al. 2019 [19]	Italy	Regional cohort	2012–2016	4.400.000	369	5.3	83	60%	50
Gatto et al. 2018 [34]	Italy	General Practice database	2000–2014	1.066.871	74	3.1	69	65%	47
Maione et al. 2017 [8]	France	Multi-centre (national registry)	1977–2012		999		17*	54%	46 (F49, M43)
Al-Dahmani et al. 2016 [44]	Canada	Regional cohort	2000–2013	945.061	65	3.8	69	53%	49
Dal et al. 2016 [2]	Denmark	National cohort	1991–2010	7.200.000	405	3.8	85	47%	49
Burton et al. 2016 [17]	USA	Health insurance claims database	2008–2012	50.000.000	2241	11	78	52%	
Aljabri et al. 2016 [46]	Saudi Arabia	Single-centre	2008–2015	300.000	10		33		
Broder et al. 2016 [18]	USA	Health insurance claims database	2008–2013				88		52
Fainstein Day et al. 2016 [47]	Argentina	Single-centre	2003–2014	150.000	19	9.2	141	76%	41

Table 1 (continued)

Author, year of publication	Country	Type of cohort	Period	Population	Cases	Incidence (cases/10^6/year)	Prevalence (cases/10^6)	Female (%)	Age at diagnosis (years)
Portocarrero-Ortiz et al. 2016 [36]	Mexico	Multi-centre (national registry)	1990–2012	119.000.000	2057		18	59%	47
Gavilanez et al. 2016 [37]	Ecuador	Multi-centre	2000–2014	2.560.505	48	1.3	19	65%	45
Hoskuldsdottir et al. 2015 [58]	Iceland	National cohort	1955–2013	321.857	52	7.7	133	39%	49
Placzek et al. 2015 [22]	USA	Health insurance claims database	2008–2012	18.112.675	757		42	54%	45 (F44, M45)
Agustsson et al. 2015 [57]	Iceland	National cohort	1955–2012	321.857	53		137	40%	
Tjörnstrand et al. 2014 [52]	Sweden	Regional cohort	2001–2011	1.590.640	53	3.5		49%	50
Dal et al. 2014 [56]	Denmark	Regional cohort	1991–2009	1.300.000	110	4.5		48%	
Gruppetta et al. 2013 [33]	Malta	National cohort	2000–2011	417.608	58	3.1	125	58%	44 (F46, M42)
Kwon et al. 2013 [39]	South Korea	National cohort	2003–2007	48.456.369	1350	3.9	28	54%	43
Vallette et al. 2013 [78]	Canada	Multi-centre (national registry)	1980–2011		649		17*	49%	45 (F47, M44)
Howlett et al. 2013 [31]	United Kingdom	Multi-centre (national registry)	1980–2011		2572		46*	50%	47
Petrossians et al. 2017 [4]	Cross-national	Multi-centre	1990–2015		3173			55%	45 (F46, M45)
Arosio et al. 2012 [30]	Italy	Multi-centre (national registry)	1980–2002		1512		60*	59%	45 (F47, M43)
Schöfl et al. 2012 [29]	Germany	Multi-centre (national registry)	1960–2006		1344		19*	58%	44 (F47, M41)
Mercieca et al. 2012 [32]	Malta	National cohort	1979–2008		47	4.0	114	53%	45 (F47, M43)
Almalki et al. 2012 [102]	Canada	Single-centre	1980–2008		130		29	49%	47 (F45, M 49)
Fernandez et al. 2010 [35]	United Kingdom	Multi-centre	-2006	81.449	7		86	43%	46
Cannavó et al. 2010 [43]	Italy	Regional cohort	-2008	654.601	64		97	55%	41 (F38, M41)
Raappana et al. 2010 [51]	Finland	Regional cohort	1992–2007	733.000	54	3.4		40%	45–50
Carlsen et al. 2008 [101]	Norway	Multi-centre	1999–2004	4.500.000	83	3.6		50%	44 (F46 M42)
Bex et al. 2007 [28]	Belgium / Luxembourg	Multi-centre	2000–2004	10.850.000	418	1.9	59	49%	48

Table 1 (continued)

Author, year of publication	Country	Type of cohort	Period	Population	Cases	Incidence (cases/10^6/year)	Prevalence (cases/10^6)	Female (%)	Age at diagnosis (years)
Kauppinen-Mäkelin et al. 2005 [50]	Finland	National cohort	1980–1999		334	4		52%	45
Mestrón et al. 2004 [27]	Spain	Multi-centre	1997–2004		1219	2.1	34	61%	51 (F52, M50)
Ko et al. 1999 [48]	Hong Kong	Single-centre	1984–1992	1.000.000	34	3.8		71%	44 (F46, M40)
Etxabe et al. 1993 [42]	Spain	Regional cohort	1970–1989	1.183.000	74	3.1	60	65%	40
Ritchie et al. 1990 [40]	Northern Ireland	Regional cohort	1959–1984	1.490.000	131	4.1	63	50%	46
Bengtsson et al. 1988 [53]	Sweden	Regional cohort	1955–1984	1.500.000	166	3.3	69	54%	
Alexander et al. 1980 [41]	United Kingdom	Regional cohort	1960–1971	3.092.200	164	2.8	53	57%	45 (F48 M46)

*denotes estimates retrieved from Kerbel et al. [21] (F = Female, M = Male)

The Liège Acromegaly Survey (*LAS) Database* [4] was originally developed and validated as a single-center study but subsequently expanded to include several European centers allowing comparisons of patient characteristics and outcomes between countries, but it does not provide valid estimates of incidence and prevalence for reasons outlined above. Two studies [32, 33] report the incidence and prevalence of pituitary adenomas in Malta, by way of central hospital registries, making this effectively a population-based study with validated cases of acromegaly. Using a rather unique approach, Gatto and colleagues [34] derived data from a large database based on approximately 1,000 general practitioners with a catchment population of approximately 1 million patients across Italy. The cases were identified using an algorithm based on diagnosis and procedure codes. Such an approach is at risk of both false positive and missing cases (see above). By means of data from 16 general practice clinics [35] the epidemiology of acromegaly in the British town of Banbury has been reported.

The Mexican Acromegaly Register constitutes one of the largest registries outside of Europe [36] and includes retro- and prospectively collected data across 24 tertiary care centers. Gavilanez et al. [37] present the epidemiology of acromegaly patients in the city of Guayaquil, Ecuador. However, as the authors note, not all medical centers within the city participated in the study, likely underestimating the number of acromegaly cases. Clinical, biochemical and epidemiological data from 9 tertiary healthcare centers in Saudi Arabia are reported by AlMalki et al. [38], while Kwon and colleagues [39] conducted a four-year nationwide survey of acromegaly in South Korea, encompassing 74 secondary- and tertiary-level medical centers, having every case confirmed by the staff of each center. However, it is not specified how cases were identified.

A common drawback of these multi-center studies is the voluntary nature of data reporting, whereby individual physicians or entire centers can opt out of participating, introducing the risk of incomplete case coverage; this would especially bias the full picture if mainly specific cases are reported (such as for example only the most severe cases). Only few and relatively small studies present data on prevalence from population-based cohorts and include validated cases with national coverage.

2.3 Single-center and regional cohorts

Several studies report epidemiological data from smaller regional cohorts from variably defined geographical catchment areas. The acromegaly cases are usually validated by scrutinizing data from individual patient charts. Two of the first studies reporting data on the epidemiology of acromegaly originate from the United Kingdom in 1980 and 1990; Ritchie and colleagues [40] presented data on patients with acromegaly from Northern Ireland over a 25-year period, while Alexander and colleagues [41] used a survey to identify patients with acromegaly in the Newcastle region. In their 1993 paper, Etxabe and colleagues [42] covered the incidence, prevalence and outcome of

patients with acromegaly in the Vizcaya region of Spain, though it was not detailed how the cases were identified. More recently, two studies from Italy [19, 43] examined the epidemiology of acromegaly in the Piemonte region and Messina province, respectively, covering a combined population of approximately 5,000,000. In the former study, cases were identified by combining four healthcare registries with acromegaly-related diagnosis or treatment codes, whereas the latter consulted regional medical archives. In a 2016 study, Al-Dahmani et al. [44] used two local prospectively constructed databases to assess the prevalence of sellar masses in the region of Nova Scotia in Canada, including patients with acromegaly, and Zaina et al. [45] reported case-validated data from a health insurance database encompassing the regions of Haifa and the western Galilee district.

Few studies were performed as single-center studies, and results were extrapolated to estimate a national incidence and prevalence. These included the 2016 study by Aljabri and colleagues [46], in which the epidemiology of sellar masses, including acromegaly, was reported. Similarly, Fainstein Day and colleagues [47] described the epidemiology of pituitary tumors derived from a single tertiary care center, catering to approximately 150,000 people in Buenos Aires, Argentina. The authors cite the lack of a well-defined geographical catchment area as the study's main weakness. Finally, Ko et al. performed a chart review-based study of all acromegaly patients attending the Prince of Wales Hospital of Hong Kong with a reported catchment population of approximately one million subjects [48]. A limitation of this approach is the potential lack of generalizability, since the single centers are often highly specialized, tertiary-level care centers.

2.4 Population based approaches: Scandinavian cohorts

The Scandinavian countries have many things in common including relatively small and homogenous populations covered by tax-supported universal healthcare, and they maintain extensive nationwide healthcare registries based on unique ID numbers for all inhabitants, ensuring virtually complete follow-up [49]. Furthermore, the Scandinavian healthcare systems are well structured, and medical centers have well-defined catchment areas, conducive to epidemiological research. The healthcare systems are also tax-supported, and citizens have free and equal access to medical aid, minimizing potential barriers to seeking medical care.

In their 2005 paper, Kauppinen-Mäkelin and colleagues [50] examined retrospectively the medical records of all patients with acromegaly over a 20-year period across five university hospitals, covering the entire country of Finland. In a 2010 study also from Finland [51], authors used nationwide registries on diagnosis and procedure codes to identify potential cases, and subsequently validated each case patient chart in the northern Finland region. In 2014, Tjörnstrand and colleagues [52] presented data from the Swedish Pituitary Register as well as a national healthcare registry, describing the epidemiology of pituitary adenomas, including acromegaly, in a specific region of southwest Sweden. In 1988, Bengtsson and colleagues [53] were among the first to describe the epidemiology of this disease in the same region. In 2022, Arnardóttir et al. [54] published their epidemiological findings on acromegaly, using data from the Swedish Pituitary Registry, and this cohort has subsequently been improved and enriched by including data from the National Patient Registry [55].

Two Danish studies published regional epidemiological data on acromegaly [7, 56] covering a population of approximately 2,000,000. In these studies, potential cases were identified with the use of a national healthcare registry and subsequently validated. An algorithm was constructed based on ICD8 and ICD10 (International Classification of Disease, 8th and 10th revisions) codes, allowing the identification of a population-based cohort. The positive predictive value of these codes was found to be approximately 50% at most, so each case was subsequently validated by individual chart review [56]. This gave rise to the $Acro_{DEN}$ cohort which was initially presented in 2016 [2] and recently updated in 2022 (Table 1). In Iceland, a similar approach was applied [57, 58], using diagnosis codes to map all patients with pituitary adenomas in Iceland over a six-decade period, followed by chart reviews. Recently, Falch et al. [59] reported the first epidemiological data from Norway, based on individuals from a previous study cohort [60] and a regional, internal quality registry from Oslo University Hospital, covering South-Eastern Norway.

The data quality from the Scandinavian registries depends on correct and consistent coding of diseases. Whereas the diagnosis of acromegaly can be confirmed by patient chart review, false negative cases, i.e. patients with acromegaly who are not coded as such, is more problematic. As shown above, there are different strategies to mitigate this challenge. One way is to combine different data sources i.e. the use of pituitary surgery or the use of acromegaly specific medical treatment [55, 56].

3 Incidence and prevalence of acromegaly

Our literature review revealed a relatively constant incidence rate across studies, with a tendency toward a gradual increase with time. The incidence rate ranged between 2–7 cases per million and a recent meta-analysis reported a pooled incidence rate of 3.8 cases per million person-years (95% CI: 3.2–4.4) [20]. During the 1960–1980 period, the reported incidence rate ranged between 2–4 cases per million [61],

whereas more recent publications report incidence rates of 4–5.5 cases per million [20] (Table 1), suggesting a slight increase. In the $Acro_{DEN}$ cohort, a similar time-dependent increase in incidence rate was observed, with incidence rates increasing from 3.0 cases per million person-years in the 1990s to 4.6 cases per million person-years in the last decade (Fig. 1). The largest increase in incidence rate was observed in 1980, where it increased from 1.5 to 3.0 cases per million person-years, which was ascribed to the introduction of IGF-I measurements and increased use of pituitary imaging by MRI (Fig. 1). During the 1990 – 2010 period, the incidence rate plateaued around 3.8 cases per million person-years [2]. A similar observation was made by Demir et al. [62], where the number of newly diagnosed acromegaly patients gradually increased from 1980 until 2010 and then reached a plateau. Interestingly, a decrease in incidence rate has been reported in a recent study from Turkey, probably linked to the COVID-19 pandemic with a reduction in physical patient appointments, and the widespread use of face masks which may have disguised facial features suggestive of acromegaly [62]. A particularly high incidence rate, however, was reported from an American insurance claims database [18], which may represent selection bias due to overrepresentation of working-age individuals – the age group where the incidence of acromegaly is highest. Other reports showing particularly high incidence rate often originate from small cohorts (19–52 cases) where only few cases are diagnosed each year [47, 57, 58]; as such, estimates from these studies are often uncertain with wide confidence intervals.

There is considerable variation in the reported prevalence estimates on acromegaly, ranging from 18 to 141 cases per million. A meta-analysis including 22 studies from 1980–2020 reported a pooled prevalence of 59 (95% CI: 44–79) per million cases with wide between-study heterogeneity [20]. A robust prevalence estimate depends on the completeness of true cases with acromegaly without loss to follow-up, updated information on mortality and a well-defined catchment area [55]. A review from 1999 [61] suggested a prevalence of 53–69 cases/million in studies from 1960–1980 [40–42, 53, 61]. Our literature review indicates a time-dependent increase in acromegaly over the last decades (Table 1, Fig. 1), which is likely a reflection of the increased incidence. Among prevalence studies, numbers exceeding 120 cases per million are most often based on small cohorts (7–77 cases), potentially hampering the validity.

Large national acromegaly registries originating from countries such as Germany (n = 1543 [29, 63, 64]), France (n = 999 [8]), and Mexico (n = 2715 [21, 36, 65]), have contributed to the epidemiological picture. Despite the large number of participants, these registries report a notably lower prevalence compared to the meta-analysis mentioned above [20], ranging from 17 to 19 cases per million (Fig. 2). While these figures represent important data, they may not accurately represent the general population prevalence. An explanation could be the need to actively enter data into these registries, potentially leading to underreporting. Similarly, a review by Kerbel et al. in 2023 [21] presented data from 9 nationwide acromegaly cohorts from

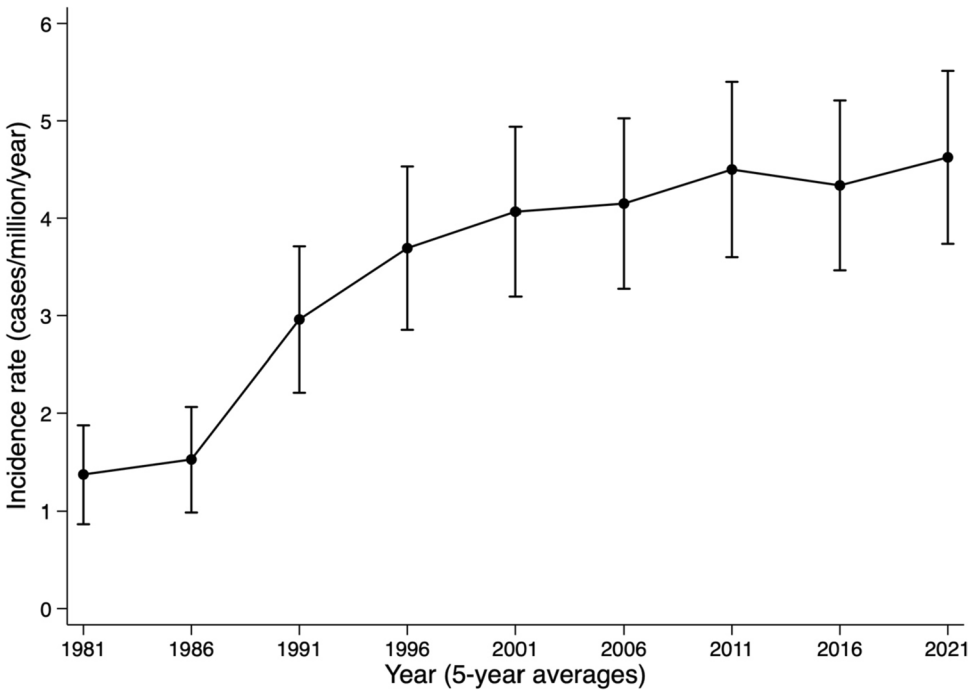

Fig. 1 Incidence rates ± standard error (number of cases/10^6 persons/year) based on the Danish $Acro_{DEN}$ national cohort of acromegaly patients (5-year averages)

several countries comprising a total of 13,416 individuals with acromegaly. These studies reported prevalence rates between 17 – 60 cases per million. The source of this variation was discussed, and it was suggested that despite most registries being open to patients seen by private endocrinologists, many cases were managed by highly specialized tertiary-care referral centers, potentially underestimating prevalence figures. Maione and colleagues published a review in 2019 [16], encompassing cohorts from 19 different nations with various study designs, covering more than 16,000 acromegaly cases. However, only a limited number of studies included in the review reported prevalence data. The prevalence ranged from 20 to 80 cases per million, with the highest prevalence originating from the $Acro_{DEN}$ cohort [2]. In another recent review published in 2022, focusing on acromegaly in Central and Eastern Europe, Israel, and Kazakhstan, a panel of experts from 13 specialist centers in these regions estimated prevalence rates ranging from 50 to 85 cases per million. Regional disparities were observed, with figures ranging from 23 to 90 cases per million in Russia and 40 to 70 cases per million in Kazakhstan [66].

In 2022, the nationwide Danish $Acro_{DEN}$ cohort was updated (n = 889), yielding a prevalence of biochemically confirmed cases of 108 per million (95%CI: 100; 116). In support of a time-dependent increase, a prevalence of 85 cases per million was reported from the same cohort in 2010. Although the Scandinavian countries all report high incidence rates, only studies from Iceland and Denmark have recently reported prevalence figures. Interestingly, the highest prevalence rates often originate from smaller populations with well-defined catchment populations, such as Malta or Iceland. There has, however, been speculations whether the accumulation of familial cases might contribute to these particularly high figures. In the northern region of Denmark, a similarly high prevalence was reported in 2022; however, in this cohort, all cases of early-onset acromegaly underwent genetic screening, revealing no cases of AIP or MEN1 mutations [7].

A theoretical maximum prevalence based on an incidence rate of 5 cases per million per year and the calculation of disease duration by combining mean age at diagnosis (50 years) with a normal life expectancy (80 years) would be estimated to 115 cases per million (5*(80–50)). This is very close to recent findings (Fig. 2).

The epidemiological pattern of other rare endocrine diseases also seems to exhibit changes over time; a similar trend of an increasing incidence rate and milder disease presentation has been reported for adrenal adenomas. In a population-based study from 2020, the incidence of adrenal tumors increased 10-fold between 1995 and 2017. This was mainly ascribed to the increasing use of abdominal scans [67]. In line with this, a 5-fold increase in pheochromocytomas and 50% increase in the incidence of Cushing's disease cases were observed in two population-based studies [68, 69]. Furthermore, patients with pheochromocytomas are older at the time of diagnosis and presented with fewer symptoms during the last decade. The increase in acromegaly incidence rate is less pronounced, which could be due to a less widespread use of cerebral imaging, and because small pituitary incidentalomas could be missed by a standard scan of the cerebrum.

4 Change in age at acromegaly diagnosis, clinical presentation and co-morbidity

The clinical characteristics of acromegaly populations across 19 national registries are quite homogeneous, as regards pituitary adenoma size, GH and IGF-I levels [16]. However, data suggests a time-dependent change toward a milder phenotype with lower hormone levels at the time of diagnosis within cohorts covering longer periods. Three recent single-center studies by Demir et al. [62], Aagaard et al. [7] and Ohno et al. [9] all report such a trend with decreasing IGF-I levels, and GH during the periods 1980–2023, 1977–2022 and 2006–2015, respectively. In a surgical series including 548 patients with acromegaly during the period 1975–2015, Fernández Mateos et al. [70], report a similar time-dependent decrease in GH and IGF-I levels by almost 50%, and a decrease in pituitary adenoma size and tumor invasiveness. In another surgical series focusing on pituitary adenomas, 112 of 1839 cases were incidentally diagnosed with acromegaly based on the histological examination. The histologically diagnosed cases of acromegaly presented with lower IGF-I and GH levels, and the incidence rate was reported to increase by threefold during the study period [71]. In the large LAS Survey [4] including a total of 3174 patients with acromegaly, GH levels at time of diagnosis decreased significantly, driven in part by lower GH levels at diagnosis among female patients during the last decade. Changes in hormone levels over a long time period should be interpreted with some caution since different assays and cut-off levels have been used [72]. However, IGF-I measurements were expressed as either multiples of 'Upper Limit of Normal' (ULN) or IGF-I SDS (Standard Deviation Score), based on each assay's age- and sex-specific reference levels. GH measurements remain challenging since both the assay methodology and the definition of disease control changed during the study period [72].

Another indication of a shift towards a milder phenotype is the notion of acromegaly with normal GH levels but elevated IGF-I levels, for which the term "micromegaly" has been suggested [10, 73]. In one study including 16 patients with micromegaly, the patients presented with physical signs of acromegaly and pituitary adenomas. However, this group of patients presented with a remarkably low burden of comorbidities such as diabetes (2 of 16) and sleep apnea

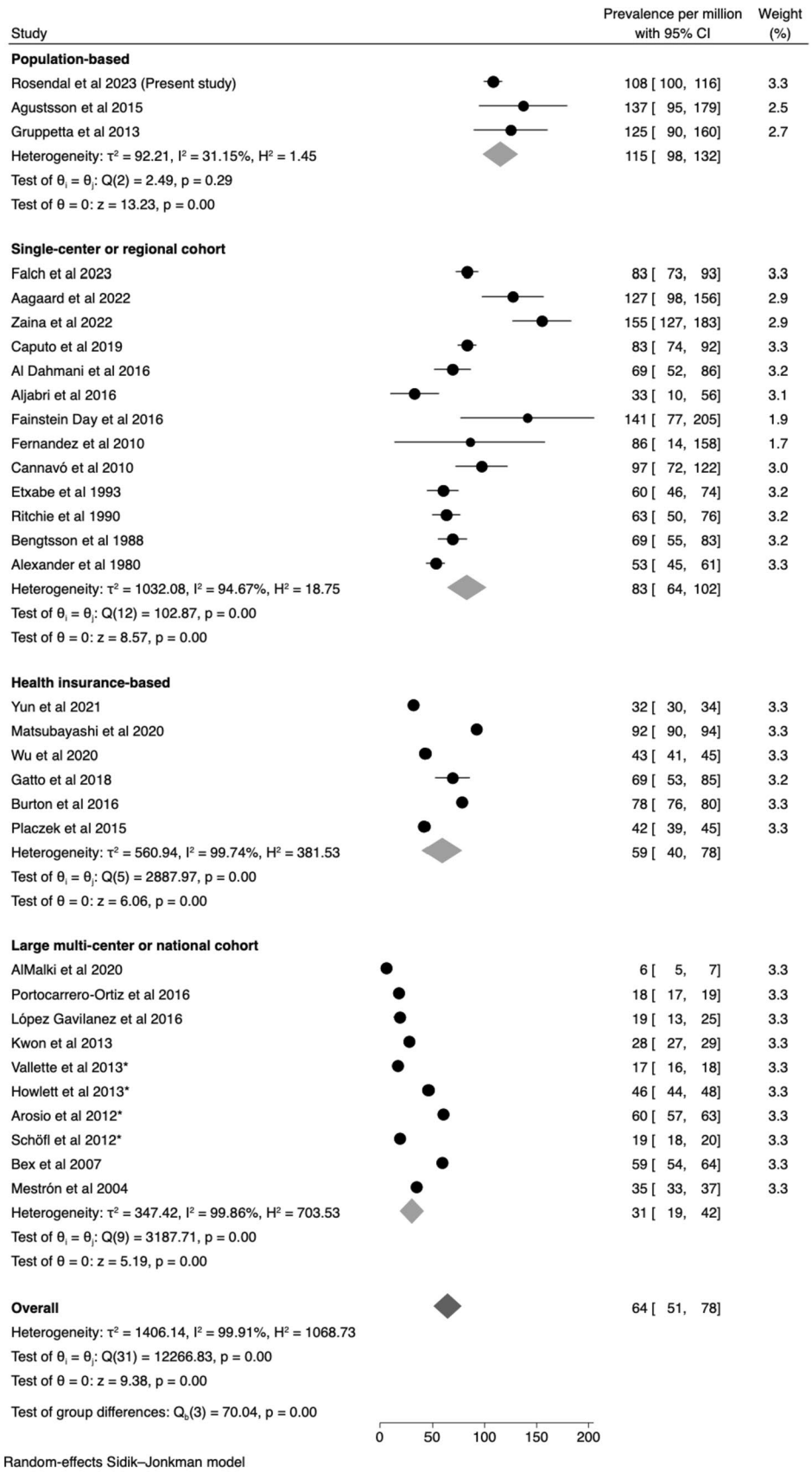

Fig. 2 Forest plot of reported prevalence estimates (cases per 10^6 persons) by cohort type. Prevalence figures and 95%CI were recalculated based on population and prevalence numbers (see Table 1). Only one study for each cohort was included. * denotes prevalence estimates derived from Kerbel et al. [21]

(3 of 16) suggesting a milder variant or a shorter disease duration [10]. Further supporting this trend, Demir et al. [62] observed a decrease in the frequency of certain comorbidities, such as diabetes, hypertension, colon polyps, and thyroid cancer, and a significantly lower burden of co-morbidities in the last decade [62]. This observation is made despite a concomitantly increasing focus on screening of co-morbidities [74]. However not all studies report such a change in phenotype, as a study by Reid et al. did not observe any changes in clinical presentation or burden of comorbidities during the period 1981 to 2006 [75].

According to the present review, the average age at the time of acromegaly diagnosis ranges from 40 to 52 years. As with the calendar time-dependent increase in prevalence, a trend toward an increasing mean age at time of diagnosis is observed (Table 1). During the 1960–1980 period, Holdaway et al. reported a mean age at diagnosis of 44 years [61], whereas more recent studies report average ages close to 50 years (Table 1). This is especially true for studies showing a high incidence or prevalence, possibly indicating a high degree of data completeness or a higher awareness of mild cases. In the LAS cohort and the $Acro_{DEN}$ cohort, the mean age at diagnosis increased gradually by nearly ten years during the last decades [4] (Fig. 3). In a recent review by Ambrosio et al. focusing on acromegaly in the elderly patients, it is reported that older patients present with a milder phenotype of acromegaly including milder disease features and hormonal abnormalities, but a higher response to medical treatment [76]. Although the number of studies focusing on the clinical presentation in elderly patients in comparison with younger subjects is limited [76]. In the LAS cohort, they further explored this triangular relation between higher age at diagnosis, smaller tumors, and lower diagnostic GH values [4].

A recent meta-analysis reported that females were on average 3 years older than males, at time of diagnosis [77]. In three cohort studies, a shift in sex distribution was observed from initial female predominance to a more even sex balance [4, 77, 78]. At the same time, the age gap between males and females decreased [4, 77, 78]. This is in line with our literature review where more recent, population-based surveys report only minor sex differences [2, 23, 24]. Despite a trend toward an increasing age at time of diagnosis, a simultaneous decrease in diagnostic delay has been reported [4], further supporting the notion of a shift in the phenotype of acromegaly. The diagnostic delay is defined as the period from the first symptom or sign of acromegaly until the time of diagnosis. Three older series including data for the years 1960–1983, reported a mean diagnostic delay of 7 to 10 years [41, 53, 79]. More recent series suggest that the diagnostic delay is now reduced to 3–6 years [3, 4, 7, 75, 80, 81] This data is, however, often not uniformly reported and assessed, and historical information provided by the patient may be subject to recall bias. The discrepancy between the patient's experience of physical changes in acromegaly and the physician-reported manifestations were found to be as high as 36% for specific types of signs and manifestations of acromegaly [5].

Esposito et al. used the Swedish healthcare databases to explore the use of hospital services during the pre-diagnostic period [3]. A correlation between a decreasing diagnostic

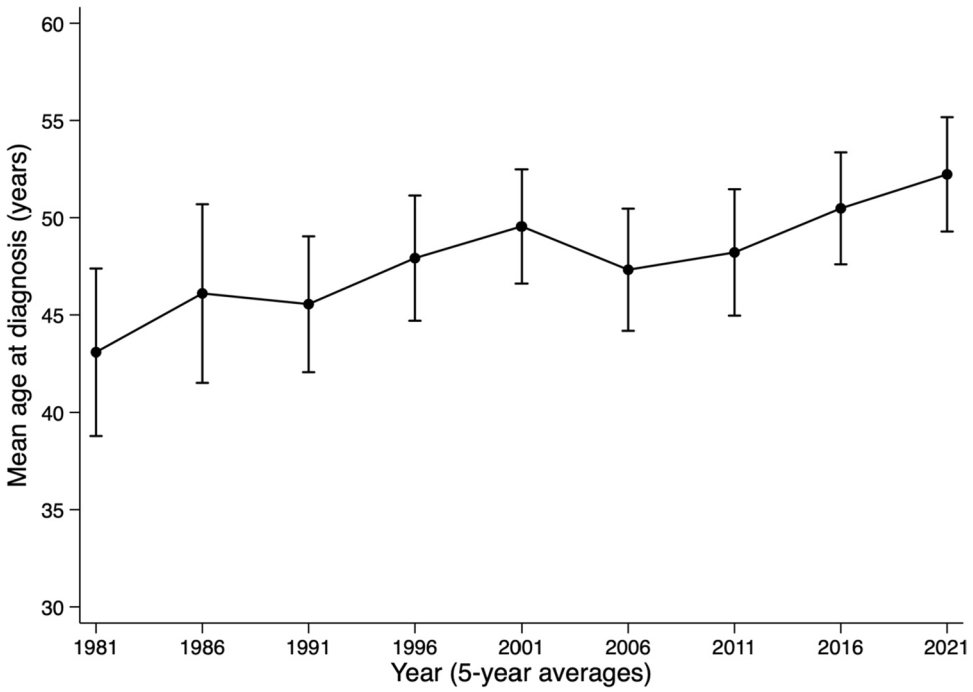

Fig. 3 Mean age at diagnosis ± standard error (years) of the $Acro_{DEN}$ cohort (5-year averages)

delay and a lower burden of comorbidities was observed, also suggesting that patients are now diagnosed with a phenotypically milder acromegaly. A prolonged diagnostic delay was observed in women compared to men, which was supported by a recent meta-analysis [77]. The fact that female patients with acromegaly are slightly older at the time of diagnosis, and also experience a longer diagnostic delay, could be related to sex-specific differences in the clinical presentation. The most common symptoms of active acromegaly leading to the initial diagnosis are growth changes [5]. However, as opposed to males, women are more likely to present with less specific symptoms such as headache and musculoskeletal pain possibly due to the suppressive effect of estrogen on IGF-I excess [5, 7]. Moreover, symptoms such as sweating and amenorrhea could be interpreted as menopausal in female patients, thereby contributing to a delay in the diagnosis. In line with this, female patients are known to have consulted more doctors before being diagnosed with acromegaly [82]. A longer diagnostic delay and a prolonged GH exposure in females are supported by an increased burden of co-morbidities during this pre-diagnostic period. Metabolic changes induced by GH excess are also more prevalent in females at the time of diagnosis, and females have an increased risk of type 2 diabetes and hypertension [3, 21, 83, 84].

5 Mortality

The first reports showing an excess mortality in acromegaly were conducted in the 1970s and 1980s and showed an increased Standardized Mortality Ratio (SMR) ranging from 1.3–3.3 indicating an increased mortality risk compared to the general population [14, 41, 79, 85]. These levels of increased mortality were subsequently confirmed by others. In 2008, all published data was collected in two meta-analyses published by Dekkers et al. and Holdaway et al., respectively [86, 87], showing a slightly increased mortality risk in acromegaly According to our meta-analysis based on registry-based studies published after year 2010, the SMR further decreased [2, 59, 88, 89] and the life expectancy in acromegaly is now approaching that of the general population (Fig. 4) [8, 25, 30, 54, 89–96].

In a meta-analysis from 2018, Bolfi et al. [14] divided the included publications according to the year of publication as either before or after year 2008. Among 17 studies published before 2008, the pooled mortality in acromegaly was increased (SMR 1.8), whereas for nine later studies published between 2008 and 2018 [8, 30, 89, 92, 94–98], mortality risk was lower (SMR: 1.35, 95%CI: 0.99; 1.85) in line with the findings from the $Acro_{DEN}$ cohort in 2016 [2]. Furthermore, in six studies showing data on patients treated with a somatostatin analog

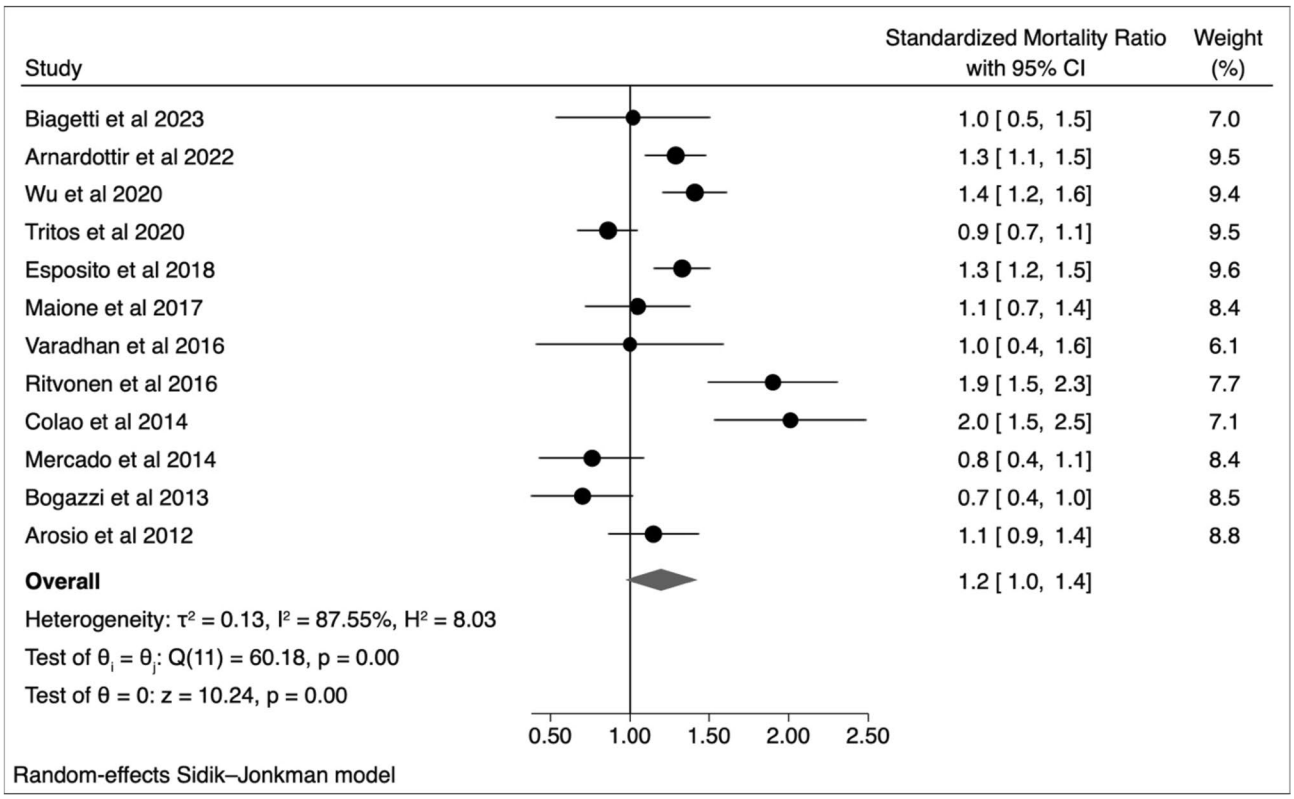

Fig. 4 Forest plot of reported mortality rates since 2010 expressed as Standardized Mortality Ratio (SMR)

[8, 30, 89, 92, 95, 96], mortality risk further decreased to a level similar to the general population (SMR: 0.98, 95%CI: 0.83; 1.15). However, among patients with active disease the mortality remained increased (SMR: 2.0, 95%CI: 1.3; 3.0) [14]. A dose-dependent positive correlation between increased IGF-I or GH and increased mortality was demonstrated [87, 99]. Besides the advances in surgical techniques and results over the last decades, new pharmacological treatments of acromegaly have been claimed to exert an important impact on biochemical disease control and mortality [7, 8].

The cause underlying the increased mortality in uncontrolled acromegaly is still debated [14]. In the first series, the excess mortality was mainly related to cardiovascular [41, 42, 50, 85, 99, 100], cerebrovascular [41, 50, 85, 99, 100] and respiratory diseases [41, 85, 100], and, to a lesser extent, malignancies [41, 50, 53, 85, 99, 100]. However, in recent epidemiological studies where the mortality risk in acromegaly has been normalized and life expectancy increased, the main causes of deaths have shifted to cancer similar to the general population [8, 30, 95, 96]. In recent studies, the types of cancer in question include a wide range of malignancies that are not traditionally related to acromegaly [8, 15, 95]. Thus, studies indicate that when mortality in acromegaly declines as a result of more effective treatment, causes of death in acromegaly shift towards those of the general population.

6 Conclusion

In conclusion, the prevalence and incidence rate of acromegaly has been steadily increasing toward more than 100 cases per million, but with considerable between-study variation. In addition, a new subpopulation of patients presenting at an older age and with a milder phenotype is emerging, probably as a result of the increased use of brain imaging in the elderly leading to the incidental diagnosis of hitherto unrecognized and milder cases of acromegaly. A moderate sex difference prevails in terms of a longer diagnostic delay in women, although this gap seems to be narrowing. Within the recent decades, increased awareness and advances in the treatment of acromegaly have led to a decline in mortality to a level comparable to the reference population. Moreover, the cause of death in patients with acromegaly has shifted from a preponderance of cardiovascular diseases to malignant causes, similar to the background population.

Author contributions All authors contributed to the study conception and design, as well as the establishment of the database from which the presented original epidemiological data is derived. The first draft of the manuscript was written by J.D. and C.R. and all authors commented on previous versions of the manuscript. All authors read, critically revised and approved the final manuscript.

Data availability Data from the present study is available from the authors upon request.

Declarations

Competing interests JD: Unrestricted research grant from Pfizer and Ipsen.

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