Global epidemiology of acromegaly: a systematic review and meta-analysis

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Abstract

Objective: To date, no systematic reviews and meta-analysis on the global epidemiology of acromegaly are available in the literature. The aims of this study are to provide a systematic review and a meta-analysis of the global epidemiology of acromegaly and to evaluate the quality of study reporting for the identified studies.

Methods: MEDLINE, EMBASE and The Cochrane Library databases were searched for studies assessing the epidemiology of acromegaly from inception until 31 January 2020. We included original observational studies written in English, reporting acromegaly prevalence and/or incidence for a well-defined geographic area. Two reviewers independently extracted data and performed quality assessments. Prevalence and incidence pooled estimates were derived by performing a random-effects meta-analysis.

Results: A total of 32 studies were included in the systematic review, and 22 of them were included in the meta-analysis. The pooled prevalence of acromegaly was 5.9 (95% CI: 4.4–7.9) per 100 000 persons, while the incidence rate (IR) was 0.38 (95% CI: 0.32–0.44) cases per 100 000 person-years. For both prevalence and IR, considerable between-study heterogeneity was found (I^2 = 99.3 and 86.0%, respectively). The quality of study reporting was rated as the medium for 20 studies and low for 12 studies.

Conclusions: Although the largest amount of heterogeneity was due to the high precision of the studies' estimates, data source and geographic area could represent relevant study-level factors which could explain about 50% of the total between-study variability. Large-scale high-quality studies on the epidemiology of acromegaly are warranted to help the public health system in making decisions.

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Introduction

Acromegaly is a severe and chronic endocrine disease characterized by excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF1). The increase in GH and IGF1 levels is due in the vast majority of cases (>95%) to the presence of a GH-secreting pituitary tumor (1). Rarely, acromegaly can be associated with genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1), McCune–Albright syndrome (MAS) and

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Carney complex. Furthermore, acromegaly can present as a familial isolated pituitary tumor (FIPA), often due to mutations in the aryl hydrocarbon receptor-interacting peptide (AIP) gene (2). More recently, few cases of X-linked acrogigantism (X-LAG) have been described, as well (3).

Although acromegaly is characterized by evident visible clinical manifestations (4, 5), the onset usually emerges slowly and progressively, thus leading to a late diagnosis (6). In addition, the suspicion of acromegaly has to be confirmed by biochemical evaluation, showing increased IGF1 concentrations and GH levels not suppressed after an oral glucose tolerance test (OGTT) (4, 7, 8).

The multisystem comorbidities result in a reduction in quality of life (QoL) and premature mortality in acromegalic patients (7, 9, 10). Several studies have shown standardized mortality ratios (SMRs) between 1.2 and 3.3 compared to the general population (9). The excess mortality in acromegaly is mainly due to malignancies, cardiovascular diseases and respiratory problems (9, 10, 11), while it has been demonstrated that biochemical control may reduce the mortality risk to that of the general population (12).

Acromegaly is a rare condition, in line with the European Union (EU) definition as a disease affecting no more than 5 people per 10 000 people (13). Epidemiological studies are crucial to provide useful data for public health decision-makers. According to the recent epidemiological data, acromegaly has a prevalence ranging between 2.8 and 13.7 cases per 100 000 inhabitants and an annual incidence rate between 0.2 and 1.1 cases per 100 000 person-years (14, 15, 16). The mean age at diagnosis ranges between 40 and 47 years (14). In recent years, only one narrative review was conducted on the epidemiology of acromegaly, and it included 12 population-based studies conducted between 2004 and 2016, many of them in Europe (14). There are currently no systematic reviews also evaluating the quality of study reporting and in-depth investigating the sources of the observed heterogeneity. Moreover, no meta-analyses on the epidemiology of acromegaly are available in the literature. Therefore, the objective of this study was to evaluate the global epidemiology of acromegaly by conducting a meta-analysis of observational studies conducted worldwide, providing an assessment of the quality of study reporting.

Methods

Literature search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to improve the reporting of this systematic review and meta-analysis (Supplementary Table 1, see section on supplementary materials given at the end of this article). A literature search on the epidemiology of acromegaly was carried out using the bibliographic databases MEDLINE, EMBASE and The Cochrane Library from inception until 31 January 2020. The search terms were related to acromegaly, prevalence, incidence and epidemiology. The search results included citations, titles and abstracts that were exported into Endnote X9. The complete search strategy for each database is provided in Supplementary Table 2. Only original observational studies reporting numerical and well-defined data on the epidemiology of acromegaly, including the number of acromegaly cases, the underlying population and the observation period, were considered; furthermore, studies must have been written in English. Narrative or systematic reviews and meta-analyses, as well as book chapters, editorials and conference abstracts, were excluded. However, the references used in the narrative or systematic reviews and meta-analyses were screened to identify other potential studies to include. Studies were also excluded if they used pharmaco-economics or segregation analysis methods since, in the latter, epidemiological evaluations are based on mathematical models that make projections of the number of expected cases in a given population, thus concerning predicted and not actually observed incidence or prevalence (17). No geographic exclusion criteria were considered. After removing duplicates from the three different databases, four medically trained experts in endocrinology and pharmacoepidemiology (authors: S C, F S, N L, G G) screened individually the title and abstract of all records identified to remove articles, not of interest; the full texts of the articles were then reviewed by the experts to define whether they met inclusion criteria. Any disagreements were resolved through discussion or, if consensus was not yet reached, through the intervention of a fifth expert (G T).

Data extraction and quality of study reporting assessment

The information collected from the selected articles included author(s) and year of publication, study catchment area, data source (i.e. administrative databases, electronic hospital records, survey, etc.), prevalence type (i.e. annual or period), study population (i.e. all healthcare service beneficiaries, persons admitted to a particular hospital, etc.), study period, study design (i.e. cross-

sectional, survey, prospective or retrospective cohorts, etc.), acromegaly definition (i.e. assessed by clinical and biochemical features, MRI examination, specific disease codes, etc.) and the epidemiological estimate. For each considered study, prevalence of the disease was calculated by dividing the number of acromegaly cases by the individuals in the underlying source population, per 100 000 persons, while the reported incidence was defined as the number of new acromegaly cases per 100 000 person-years. The assessment of study reporting quality was carried out independently by two experts (S C, N L), who used a checklist specifically adapted for observational studies on the epidemiology of rare diseases from STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (18). Each study was then assigned an overall low, medium and high score (Supplementary document 1 for the complete algorithm) based on the following five fields: description of study design and setting, eligibility criteria, study population, outcomes and study participants. Disagreements in scoring were resolved through the intervention of a third expert (G T).

Statistical analysis

Meta-analysis of dichotomous data (i.e. prevalence) was performed in the framework of generalized linear mixed-effects models (19, 20), where a random-intercept logistic regression (i.e. a 'binomial-normal' model) was fitted to provide a pooled estimate of the disease prevalence. Specifically, for each included study, the number of cases is assumed to follow a binomial distribution (with unknown true probability of having the disease) given the study sample size. The 95% CI of each study-specific prevalence was calculated using the Clopper-Pearson exact method, based on the cumulative probabilities of the binomial distribution.

The logistic model provides the maximum (binomial) likelihood estimate of the pooled logit-transformed unknown probability (i.e. prevalence), as well as its S.E. The pooled prevalence, along with its 95% CI, was eventually computed by means of inverse logit formula. Standard Cochran's Q test and its derived measure of inconsistency (I^2) were used to assess between-study heterogeneity and it was declared as present when Cochran's Q-test *P*-value was <0.10 or $I^2 > 40\%$ (21). Given the presence of the (normally distributed) random intercept, it was expected that, in the case of non-negligible amounts of between-study heterogeneity, the CI around the pooled estimate was wider than the one achieved around a fixed effect pooled estimate. Meta-analysis of incidence rates (IRs) was performed assuming that each study-specific rate was normally distributed, and the correspondings.E. was derived on the basis of the reported 95% CI (or *P*-value). Therefore, a random-intercept linear mixed effect model was fitted to provide a pooled estimate of the incidence rate. In the presence of heterogeneity, a meta-regression analysis was further performed, with respect to different candidate study-level covariates (selected *a priori*), in order to quantify the contribution of each covariate in the reduction of the overall between-studies variability. Examination of sources of heterogeneity was based on the statistical significance (from omnibus Wald-type test) evaluated for each selected study-level covariate. Moreover, the proportion of the total between-studies variance (computed from the random effects MA, without the study-level covariate) that was reduced after the inclusion of some study-level covariate in the MA was defined as R^2. Both the study-specific as well as the pooled epidemiological estimates were graphically depicted, with their 95% CI, on a forest plot. To assess the presence of publication bias, a funnel plot showing the individual observed study outcome (on the x-axis) against the correspondings.E. (on the y-axis) was reported for each outcome at issue and the asymmetry of each funnel plot was evaluated by the rank correlation test, as proposed by Begg & Mazumdar (22). It is generally accepted that when there are fewer than ten studies in a meta-analysis,

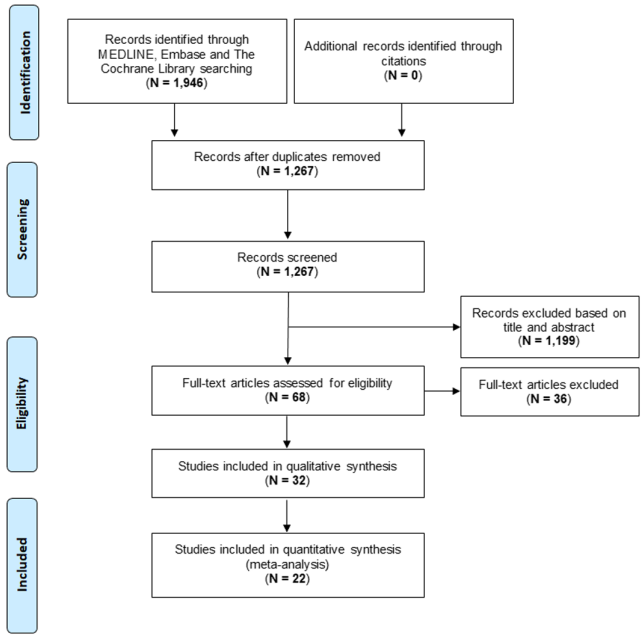

Figure 1
PRISMA flowchart showing the study selection process.

Table 1 Characteristics of the included studies investigating the acromegaly (AC) epidemiology.

Reference	Region	Data source	Population	Study years	Study design	Acromegaly definition	Estimate per 100 000 (95% CI)
(51)	Newcastle, UK	Questionnaire	Patients with AC diagnosis	1960–1971	Survey	Clinical, radiological and biochemical evidence (increased GH levels)	PP: 5.3 (4.6–6.2); PI: 0.28
(24)	W Sweden	Hospital medical charts	Patients with AC diagnosis	1955–1984	ROS	Progressive acral growth and typical facies and extremities increase heel-pad thickness and enlargement of the pituitary fossa	PP: 6.9 ; PI: 0.33
(52)	N Ireland	Secondary care EMRs	Patients with AC diagnosis	1959–1984	ROS	Biochemical and clinical evidence (increased GH levels)	AP (1984): 6.4 (5.2–7.8); PI: 0.41
(53)	Vizcaya, Spain	Data from 74 consecutive cases with a diagnosis of acromegaly in Vizcaya (Spain)	Patients with AC diagnosis	1970–1989	ROS	Typical signs and symptoms, elevated serum basal GH levels higher and/or no suppression of GH levels after oral glucose tolerance test and radiological evidence	PP: 6.0 (4.8–7.6); PI: 0.31
(25)	Spain	The Spanish Acromegaly Registry	Patients who were in the register	1997–2004	ROS	Biochemical evidence (increased GH and IGF1 levels)	PP: 3.4
(43)	Belgium, Luxembourg	Questionnaire	Patients with AC diagnosis after 1 January 2000	2003–2004	Survey	Failure of GH suppression and/or elevated IGF1 levels and radiological evidence	PP: 3.9 (3.5–4.2); PI: 0.19
(34)	Oxfordshire, UK	Primary care EMRs	Patients alive on 31 July 2006 and fulfilling diagnostic criteria for pituitary tumor	2006	CSS	Typical clinical and biochemical features and immunostaining for GH on tumor tissue	AP (2006): 8.6 (4.2–17.8)
(35)	Messina, Italy	Hospital medical charts; Sicilian referral center for pegvisomant treatment; Healthcare Agency of the province of Messina	Patients who were born and resided all their life in the province of Messina and alive till 31 December 2008	2008	ROS	Increased IGF1 and GH serum levels	AP (2008): 9.8 (7.7–12.5)
(26)	Vancouver, Canada	Hospital medical charts	Patients with AC diagnosis in the period 1980–2008	2009–2011	RCR	Typical signs and symptoms or GH hypersecretion or presence of comorbidities	PP: 2.9
(27)	Belo Horizonte, Brazil	Questionnaire and hospital medical charts	Patients aged >18 and <70 years in the period July–December 2010	July–December 2010	ROS	Retrospective survey	PP: 29.4
(44)	South Korea	Hospital medical charts	Patients who had visited secondary or tertiary medical institutes	2003–2007	ROS	Elevated GH and IGF1 levels and ≥ 1 typical clinical signs of acromegaly or confirmed pituitary tumor or medical history for transsphenoidal adenoidectomy/gamma knife surgery/radiotherapy	AP (2007): 2.8 (2.6–2.9); PI: 0.39

(28)	USA	Administrative claims from the HealthCore Integrated Research Database	Patients aged ≥20 years with AC diagnosis	2008–2012	RCS	≥2 independent diagnostic codes for acromegaly (ICD-9: 253.0x) or ≥1 acromegaly diagnostic code and ≥1 acromegaly-related procedure code or ≥1 acromegaly diagnostic code and ≥1 medical claim for an acromegaly-related therapy	PP: 4.2 ; AI (2011): 0.95
(45)	Iceland	Pituitary adenoma database	Patients with PA diagnosis	1955–2012	ROS	Clinical presentation and biochemical evidence according to international guidelines and consensus statements	AP (2012): 13.7 (10.2–18.4); PI (men): 0.8; PI (women): 0.4
(29)	Iceland	Secondary care EMRs	Patients with AC diagnosis	1955–2013	ROS	ICD-10 code: E22.0, typical clinical and physical signs of acromegaly, radiological tests	AP (2013): 13.3; PI: (2005–2013): 0.77
(46)	Nova Scotia, Canada	Halifax Neuropituitary and Capital Health Outpatient Clinics databases	Patients with a diagnosis of sellar masses in the period 2005–2013	2000–2013	RCS	Typical clinical features and elevated IGF1 levels; inability to suppress GH following a 75 g oral glucose load	AP (2013): 6.9(5.4–8.8); AI (2013): 0.38
(37)	Jeddah, Saudi Arabia	Secondary care EMRs	Patients with pituitary tumor diagnosis	2008–2015	ROS	MRI	PP: 3.3 (1.8–6.1)
(47)	Malta	Secondary care EMRs	Patients with amacroadenoma diagnosis	2000–2014	RPBCS	MRI	AP (2014): 13.6 (10.5–17.6); AI: 0.40 (0.27–0.60)
(36)	Mexico	MAR	Patients with AC diagnosis after 1990	Not reported	PBSRP	Typical clinical, biochemical (glucose-suppressed GH and increased IGF1 levels), hormonal and MRI	PP: 1.7 (1.7–1.8)
(30)	USA	MarketScan database and PharMetrics database	Patients aged <65 years with AC diagnosis	2008–2013	RCSS	≥2 ICD-9 codes 253.0 or 1 medical claim with acromegaly + 1 other claim for a pituitary tumor, hypophysectomy, or cranial stereotactic radiosurgery	AP (2013): 8.8 (MarketScan); 7.1 (PharMetrics); AI (2013): 1.2 (MarketScan); 0.83 (PharMetrics)
(31)	USA	Administrative claims data	Patients commercial health plan enrollees in the database in the period 2000–2012	2008–2012	ROS	≥2 medical claims on separate dates with a 253.0 ICD-9 code or 1 medical claim with an acromegaly diagnosis code + 1 medical claim with a pituitary tumor diagnosis code (ICD-9: 237.09) or 1 medical claim with an acromegaly diagnosis code + 1 medical claim for hypophysectomy or stereotactic radiosurgery	PP: 7.8; PI: 1.1
(48)	Denmark	Hospital medical charts of all patients diagnosed with acromegaly	Patients with AC diagnosis	1991–2010	RCS	ICD-8 codes: 25300 and 25301 ICD-10 code DE220 Increased GH and IGF1 serum levels Size of pituitary tumor	AP (2010): 8.5 (7.7–9.3); PI: 0.38 (0.37–0.40)
(49)	Buenos Aires, Argentina	Hospital Italiano Medical Care Program electronic database	All Hospital Italiano Medical Care Program patients aged >18 years	2003–2014	RCS	IGF1 elevated levels Unsuppressed GH in the oral glucose tolerance test	AP (2014): 14.1 (9.0–22.0); PI: 0.92 (0.44–1.41)

(Continued)

Table 1 Continued.

Reference	Region	Data source	Population	Study years	Study design	Acromegaly definition	Estimate per 100 000 (95% CI)
(50)	Guayaquil, Ecuador	Hospital medical charts	Patients with AC diagnosis attending endocrinology clinics	2000–2014	ESPRD	Biochemical evidence (increased GH and IGF1 levels)	AP (2014): 1.9 (1.4–2.5); PI: 0.13
(15)	Piedmont Region, Italy	Administrative Health Databases	Patients with ≥2 claims suggesting AC	2012–2016	RCS	Subjects identified in at least two of the following databases: ICD-9 code: 253.0 Exemptions code: 001 ≥ 1 pharmacy claim for: octreotide (ATC: H01CB02), lanreotide (ATC: H01CB03), pegvisomant (ATC: H01AX01), pasireotide (ATC: H01CB05) ≥ 1 prescription for these radiological tests: facial bone NMR (codes 88.91.3–88.91.4); cranial (sella turcica, orbit) CT (codes 87.03–87.03.1)	PP: 8.3 (7.5–9.2); PI: 0.53 (0.42–0.67)
(16)	Italy	Health Search Database	Patients aged ≥18 years registered in the GP lists at 1 January 2000 and with ≥1 year of recorded history prior to the start of the study	2000–2014	ROS	ICD-9 code: 253.0 and ≥ 1 recorded event for GH evaluation (national code: 90.35.1), IGF1 evaluation (code: 90.40.6) or MRI of the sella turcica (code: 88.97)	PP: 6.9 (5.5–8.7); PI: 0.31
(32)	Hong Kong, China	Hospital medical charts	Patients with AC diagnosis	1984–1992	RCR	Failure of suppression of GH during an extended oral glucose tolerance test	PI: 0.38
(38)	N Finland	Diagnosis, operation, and outpatient visit hospital registries	Patients with PA diagnosis	1992–2007	RCS	Diagnosis codes Transsphenoidal operation codes	PI: 0.34 (0.23–0.44)
(39)	Ringkøbing, Aarhus, Viborg, Denmark	Danish National Registry of Patients and Hospital records	Patients with AC diagnosis	1991–2009	RPBS	ICD-8: 25300, 25301 ICD-10: E22.0 Elevated IGF1 and GH serum concentrations or visible pituitary tumor	PI: 0.45 (0.36–0.55)
(40)	Vastra Gotaland, Sweden	Swedish Pituitary Registry and hospital records review	Patients with pituitary tumor diagnosis	2001–2011	ROS	ICD-10 code: E22.0	PI: 0.35 (0.25–0.45)
(33)	New Deli, India	Secondary care EMRs	Patients with pituitary disorders diagnosis	1990–2015	RCR	ICD codes	PI: 0.49
(41)	Taipei, Taiwan	NHIRD	Patients hospitalized for AC	1997–2013	RCS	ICD-9 code: 253.0	PI: 0.28 (0.26–0.29)
(42)	Republic of Korea	HIRA Claims Database	Patients with AC diagnosis	2010–2013	RPBCS	ICD-10 code: E22.0 Presence of treatment related to acromegaly within 2 years of the first diagnosis of acromegaly	PI: 0.36 (0.33–0.40)

AI, annual incidence; AP, annual prevalence; ATC, anatomical therapeutic chemical; CSS, cross-sectional study; EMRs, electronic medical records; ESPRD, epidemiological study using prospectively and retrospectively collected data; GH, growth hormone; HIRA, health insurance review and assessment; ICD, International Classification of Diseases; IGF1, insulin-like growth factor-1; MAR, Mexican Acromegaly Registry; NHIRD, National Health Insurance Research Database; PA, pituitary adenoma; PBSRP, population-based study using retrospectively and prospectively collected data; PI, period incidence per 100 000; PP, period prevalence per 100 000; RCR, retrospective chart-review; RCRS, retrospective chart-review study; RCS, retrospective cohort study; RCSS, retrospective cross-sectional study; ROS, retrospective observational study; RPBCS, retrospective population-based cohort study.

both meta-regression (21) and test for publication bias (23) should not be considered. Two-sided P values< 0.05 were considered for statistical significance. Statistical analyses were performed using R Foundation for Statistical Computing (version 4.0, package: metafor).

Results

Study selection and characteristics

The study selection flowchart is shown in Fig. 1. A total of 1946 studies were identified through the literature search. After removal of duplicates ($n=679$), 1267 (65.1%) abstracts were initially screened and, of them, only 69 (5.4%) full-text articles were retained for further evaluation. Among these, 32 (46.4%) studies met the inclusion criteria and were thus finally included in the systematic review. The characteristics of the included studies are summarized in Table 1. Just over half of these studies ($n=17$; 53.2%) were conducted in Europe, while the remaining studies were conducted in North America ($n=6$; 18.7%), South America ($n=3$; 9.4%) and Asia ($n=6$; 18.7%). Acromegaly was defined by clinical, biochemical and radiological evidence in 17 studies (53.2%). In three studies (9.4%), acromegaly was defined using only diagnostic codes (mainly International Classification of Disease codes), in four studies (12.5%) using diagnostic codes and/or procedure codes, while in five studies (15.5%) using both diagnostic codes and biochemical/radiological findings. Finally, three studies (9.4%) defined acromegaly using diagnostic codes, national healthcare co-pay exemption codes and pharmacy claims for drugs related to the treatment of acromegaly. Overall, 21 studies (65.6%) were based on secondary use of healthcare data that were collected during routine clinical practice. Specifically, 9 (42.9%) used electronic medical records (EMRs), 8 (38.1%) used claims databases and 4 (19.0%) used patient/disease registries (Table 2). The remaining studies ($n=11$; 34.4%) used other data sources (i.e. questionnaires and paper-based hospital records). Of the 32 studies included in the systematic review, 10 (24, 25, 26, 27, 28, 29, 30, 31, 32, 33) were excluded from the meta-analysis because neither the 95% CI nor the total number of subjects (denominator) were reported in the full-text articles.

Epidemiology of acromegaly

Seven studies (21.9%) reported the prevalence of acromegaly (25, 26, 27, 34, 35, 36, 37), 7 studies (21.9%) reported the incidence of acromegaly (32, 33, 38, 39, 40, 41, 42) and 18 studies (56.2%) reported both parameters (15, 16, 24, 28, 29, 30, 31, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53). All the seven studies estimating only acromegaly prevalence reported period prevalence. Three of them were European (25, 34, 35), three American (26, 27, 36) and one was Asian (37). Of the seven studies reporting acromegaly incidence, four reported age-standardized incidence (38, 40, 47, 49). Of these, three were European (38, 39, 40) and four were Asian (32, 33, 41, 42). Of the remaining 18 studies evaluating both prevalence and incidence of acromegaly, 11 were European (15, 16, 24, 29, 43, 45, 47, 48, 51, 52, 53), 6 American (28, 30, 31, 46, 49, 50) and 1 was Asian (44). Overall, the prevalence of acromegaly among the studies included in the systematic review ranged from 1.7 (95% CI: 1.7–1.8) (36) to 29.4 (95% CI not reported) (27) cases per 100 000 persons. The pooled prevalence of the studies included in the meta-analysis was 5.9 (95% CI: 4.4–7.9) per 100 000 persons (Fig. 2). Considerable heterogeneity was found among these studies (Cochrane's $Q=2161.80$, $P<0.001$; $I^2=99.3\%$), and this was due to the fact that most of the included studies were characterized by a very precise estimate (i.e. narrow confidence limits), because of their large sample size.

The IR of acromegaly ranged from 0.1 (50) to 1.2 (30) cases per 100 000 person-years; 95% CIs were not reported for both estimates. The pooled IR was 0.38 (95% CI: 0.32–0.44) per 100 000 person-years (Fig. 3). Considerable heterogeneity was detected among these studies ($Q=49.88$, $P<0.001$; $I^2=86.0\%$), and this is due to the same reasons described above. In this case, it was not possible to investigate both the source of heterogeneity and the presence of publication bias, as only eight studies (fewer than ten) were included in the meta-analysis (23).

Exploration of sources of heterogeneity and the assessment of publication bias

In order to explore possible sources of heterogeneity, which could be of help in reducing the total between-study variance, a meta-regression analysis was performed for prevalence only, using the following study-level covariates: the geographic area, data source, prevalence type (i.e. annual or period prevalence), the mean age at disease diagnosis and the study period. As for the latter, only studies that reported the prevalence computed within a specific calendar period (instead of a single calendar year) were considered. As shown in Table 3, only the data source ($P<0.001$) and the geographic area ($P=0.013$) significantly reduced the largest quote (i.e. 59.2 and 48.4%, respectively) of the total between-study variance. No publication bias was detected in the funnel plot and according to both

Table 2 Included studies using real-world data. Data are presented as *n* (%).

	EMRs, *n* = 9	Claims DB, *n* = 8	Registers, *n* = 4	Total, *n* = 21
Countries				
Europe	5 (55.6%)	3 (37.5%)	3 (75.0%)	11 (52.4%)
North America	1 (11.1%)	3 (37.5%)	1 (25.0%)	5 (23.8%)
South America	1 (11.1%)	–	–	1 (4.8%)
Asia	2 (22.2%)	2 (25%)	–	4 (19.0%)
Publication year				
1990–1995	1 (11.1%)	–	–	1 (4.8%)
1996–2001	–	–	–	–
2002–2007	–	–	1 (25.0%)	1 (4.8%)
2008–2013	1 (11.1%)	1 (12.5%)	–	2 (9.5%)
2014–2020	7 (77.8%)	7 (87.5%)	3 (75.0%)	17 (80.9%)
Study design				
Prospective cohort study	–	–	1 (25.0%)	1 (4.8%)
Retrospective cohort study	7 (77.8%)	7 (87.5%)	3 (75.0%)	17 (80.9%)
Cross-sectional study	2 (22.2%)	1 (12.5%)	–	3 (14.3%)
Identification of acromegaly				
Diagnosis codes	1 (11.1%)	1 (12.5%)	1 (25.0%)	3 (14.3%)
Pharmacy claims	–	–	–	–
Procedure codes	–	–	–	–
Diagnostic exams	7 (77.8%)	1 (12.5%)	2 (50.0%)	10 (47.6%)
More than one of the above	1 (11.1%)	6 (75.0%)	1 (25.0%)	8 (38.1%)

DB, databases; EMRs, electronic medical records.

Egger's regression test ($P=0.235$) and Begg and Mazumdar rank correlation test for asymmetry ($P=1.000$) (Fig. 4).

Quality of study reporting assessment

Quality of study reporting assessment was performed for the 32 included studies (Supplementary Table 3). The quality of study reporting was estimated as medium for 20 (62.5%) studies and as low quality for 12 (37.5%) studies, while no studies were estimated as having a high quality of study reporting. Most of the studies considered to be of medium quality was based on secondary use of already existing healthcare data ($n=16$, 80.0%). Study design and setting were adequately reported in just over half of the included studies ($n=17$, 53.1%), being unclear in the remaining studies ($n=15$, 46.9%). The description of the acromegaly definition was clear in the majority of the studies included ($n=31$, 97.0%), while only 4 (12.5%) studies reported an adequate characterization of the study participants (i.e. no studies reported more than patients age and gender).

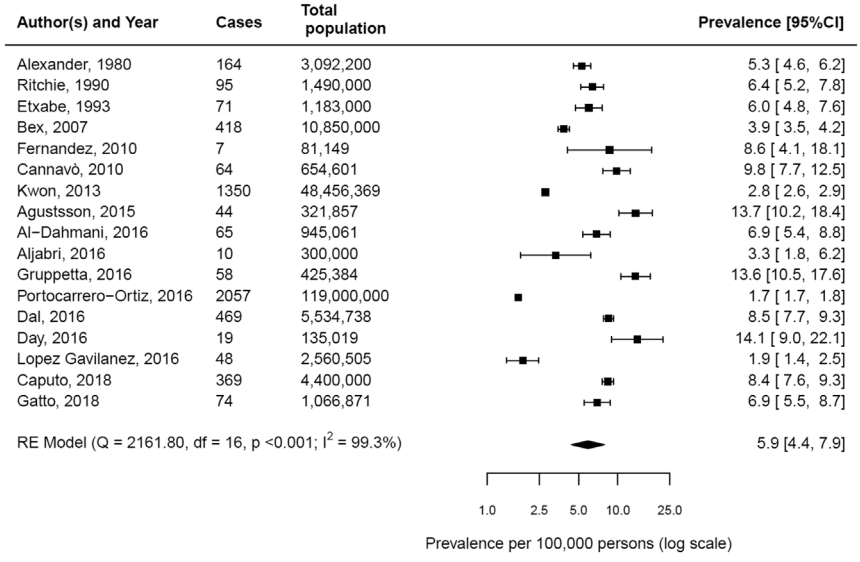

Figure 2
Forest plot of the estimated acromegaly prevalence per 100 000 cases with 95% CI: RE, random effects; df, degree of freedom.

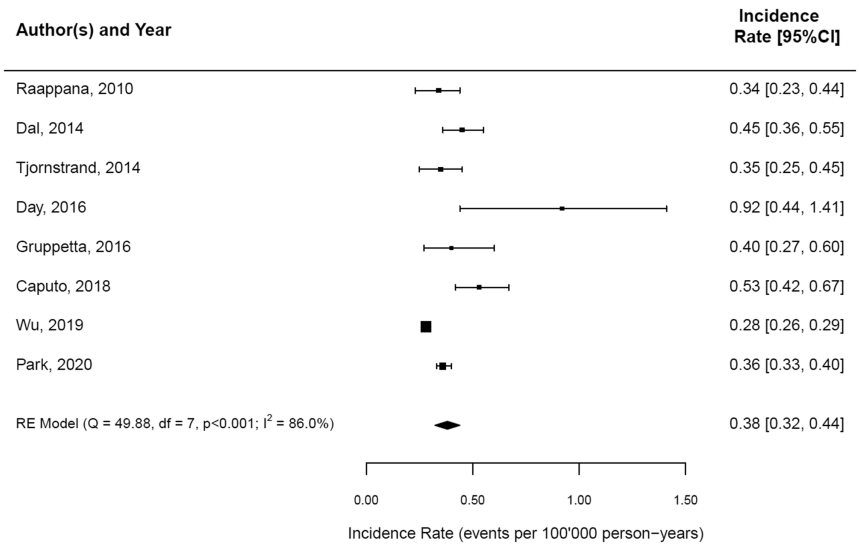

Figure 3
Forest plot of the estimated acromegaly incidence per 100 000 cases with 95% CI. RE, random effects; df, degree of freedom.

Discussion

To our knowledge, this is the first systematic review and meta-analysis of epidemiologic studies of acromegaly worldwide, which also provided the assessment of the quality of study reporting. Our study reported a pooled global prevalence of acromegaly equal to 5.9 (95% CI: 4.4–7.9) per 100 000 persons and a pooled global IR of 0.38 (95% CI: 0.32–0.44) per 100 000 person-years. Each included study used different data sources (i.e. newly collected or based on secondary use of already existing healthcare databases), acromegaly definitions, inclusion criteria, study design, which altogether can account for the high heterogeneity of the findings from various epidemiologic studies. As shown by meta-regression analysis, the large amount of between-study variance among prevalence estimates was mainly due to the different data sources and the different geographic zone.

In general, the heterogeneity observed in studies conducted in different geographic areas could be determined by several factors. For example, a selection bias could be related to the places where the studied subjects were selected, since some studies evaluated patients referred to tertiary centers only, while others included the cases followed-up outside these structures. Furthermore, it is worth mentioning the role of peculiar genetic clusters, as observed in Ireland and Northern Ireland where the presence of the R304* variant of aryl hydrocarbon receptor-interacting protein (AIP) was related to the higher prevalence of acromegaly in some families (54, 55). In some

Table 3 Results from meta-regression analysis of acromegaly prevalence.

Meta-regression analysis		Heterogeneity assessment				
Covariate selected	*P**	Cochran's Q (df)	*P* (Q test)	I^2 (%)	Between-study variance#	R^2 (%)†
All studies (*n* = 17)						
None (random-effects MA)	–	2161.804 (16)	<0.001	99.26	0.379	–
Geographic area°	0.013	249.575 (11)	<0.001	95.59	0.196	48.36
Data source^	<0.001	532.737 (12)	<0.001	97.75	0.155	59.19
Prevalence type (annual vs period)	0.115	1859.270 (15)	<0.001	99.19	0.335	11.54
Mean age at diagnosis	0.273	642.702 (13)	<0.001	97.98	0.378	0.18
Studies reporting only PP (*n* = 7)						
None (random-effects MA)	–	1118.380 (6)	<0.001	99.46	0.248	–
Study year (begin) + Study duration	0.239	278.598 (4)	<0.001	98.56	0.173	30.23

°Geographical areas were classified on the basis of subcontinents as follows: Northern America (Nova Scotia and Mexico) (two studies), Southern America (Argentina and Ecuador) (two studies), Northern Europe (UK, Ireland, Denmark, Iceland) (five studies), Southern Europe (Italy and Malta) (four studies), Western Europe (Spain and Belgium/Luxembourg) (two studies), Asia (South Korea and Saudi Arabia) (two studies); ^Data source were categorized as follows: claims databases (three studies), electronic medical records (seven studies), hospital charts (four studies), survey (two studies), registry (one study); **P* values from omnibus Wald-type test of parameters (i.e. study-level covariates included into the model); #Total and residual between-study variance: the overall heterogeneity corresponds to the total between-study variance estimated from random effects; MA whereas the residual heterogeneity corresponds to between-study variance explained by the study-level covariates included into meta-regression model; †R^2 is the proportion of the overall heterogeneity (i.e. the total between-study variance) which is 'explained' (i.e. reduced) by the effect of the included study-level covariate. df, degrees of freedom referred to the Cochran's Q test; I^2, measure of inconsistency; MA, meta-analysis; PP, period prevalence.

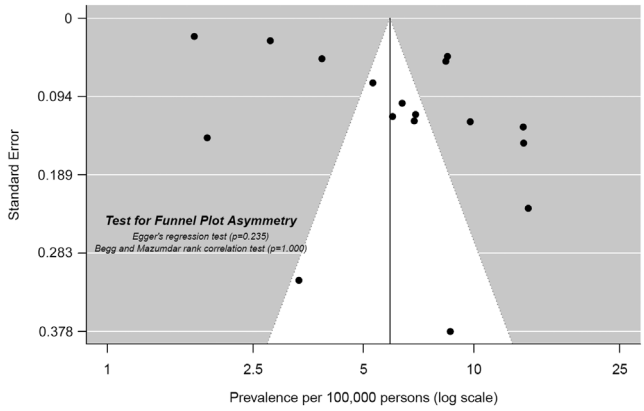

Figure 4
Funnel plot for the estimated acromegaly prevalence.

circumstances, the heterogeneity was due to the different methods used for acromegaly identification. For example, Hoskuldsdottir *et al.* evaluated acromegaly epidemiology in Iceland in a broad period (1955–2013), combining the records from the only University Hospital in the island with two other hospitals, the information from consulting endocrinologists in the country, and the related diagnostic codes (29). Another factor to be considered is the role of endocrine-disrupting chemicals (EDCs) present in industrial pollution that, as reported by Cannavò *et al.*, led to an increased incidence and prevalence of acromegaly in areas with a high concentration of industrial plants (35). Moreover, other factors potentially explaining the differences reported might also include the lifestyle of the reference population and the different ability of the healthcare providers in managing the comorbidity (56).

In the last decades, an increase in acromegaly prevalence, to a larger extent than for incidence, has been reported (from less than seven cases per 100 000 people to 11–13 case for 100 000 in some studies). This could be explained by a significantly improved management, mainly related to early detection as well as treatment of complications leading to increased patients' survival. Currently, the mortality risk of acromegalic patients may be reduced by controlling GH and IGF-1 levels in the context of long-term follow-up (57). Furthermore, the improved physicians' awareness and education on this endocrinology disease, especially among general practitioners, have contributed to detect many cases of previously undiagnosed acromegaly (4). Accordingly, data from national registries show that, in the last decade, the percentage of cured or controlled disease significantly increased in most countries (58). However, the variable access of the healthcare providers to the different treatment options (in different countries or periods) might affect the morbidity and mortality rates in acromegaly, thus, at least in part, potentially explaining the variability in the prevalence reported by different studies (56).

Studies conducted on larger populations reported lower acromegaly prevalence than studies conducted on smaller populations. This could probably be due to the characteristics of the total reference population or data collection (e.g. registries or EMRs). In general, the identification of acromegalic patients through secondary use of healthcare data based on diagnostic code, which is not directly associated with a biochemical test, is likely to be less accurate as compared to identification based primarily on biochemical testing. However, a more accurate identification of true acromegaly cases does not translate into more accurate epidemiological estimates of this disease. Both basal and OGTT-suppressed GH levels are the mainstay of biochemical evaluation in suspected patients. However, independently from the variation of the GH nadir toward more sensible values (from ≤ 1 to ≤ 0.4 ng/mL in recent years), the association with IGF1 is mandatory (59). The diagnostic criteria and the assays used for GH and IGF1 have changed over time, and this issue might be one of the factors potentially affecting the different incidence rates of the studies included in the meta-analysis, since they refer to a very long period of time (1980–2020). Particularly, although the Consensus Statement on acromegaly management published in 2000 already suggested a GH nadir <1 µg/L as one of the main criteria to define the diagnosis of acromegaly, the assays used to measure GH levels changed significantly over the years (60, 61).

The largest share of included studies concerning the epidemiology of acromegaly was published in Europe, where research in the context of rare diseases is a priority in the field of public health (62). The evaluation of rare diseases global epidemiology by pooling the estimates of different studies is very important to investigate the impact of such diseases in the general population and to provide useful data for public health decision-makers (63).

Up to 70% of all identified studies used real-world data (i.e. data collected from routine clinical practice) and almost half of them used healthcare claims databases, while the others used EMRs and clinical registries. The main added value of using real-world data compared to other sources is that they cover a large population size, and this is particularly relevant for research in the field of rare diseases, where the number of affected persons is very small (64). However, this also comes with limitations. One of the most critical limitations in the use of real-world data sources in

this field lies in the accurate identification of the disease under study based on the availability of specific diagnostic codes (i.e. ICD-9 or ICD-10 codes). In fact, there is no specific code for most rare diseases (65). In the case of acromegaly, for example, the ICD-9 code 253.0 and ICD-10 code E22.0 is rather specific, despite it also refers to gigantism that is due to GH overproduction in the period of rapid linear growth during childhood and adolescence, specifically. On the contrary, the ICD codes for acromegaly are less specific, since they may not capture patients that did not undergo surgical therapy. In general, to capture rare diseases using claims databases, coding algorithms based on the combination of diagnostic codes as well as exemption codes and other proxies have to be developed and validated. To address this issue, whenever possible, it might be useful to link individual patients level data from claims databases to corresponding EMRs/clinical registries from the same catchment area (65).

The quality of study reporting was assessed using an adaptation of the STROBE checklist for rare diseases, resulting in overall medium to low quality. Specifically, no study reported an adequate characterization of the study participants. This finding was consistent even when restricting the analysis to those studies based on secondary use of existing healthcare databases, which were judged to be of medium quality in approximately 80% of cases. A similar finding was observed in a systematic review and meta-analysis of the epidemiologic studies of Duchenne muscular dystrophy (66).

The main strength of our study is that it is a systematic review and, as such, it involved an extensive literature search up to 2020 and a review process carried out by two reviewers independently in parallel, with a study reporting quality assessment. However, there are also limitations to consider. Since most of the included studies did not report age-related and ethnicity-related disease epidemiology, we were not able to distinguish gigantism from acromegaly and to stratify our analysis by ethnicity. Another potential limitation of this study is that excluding those studies not written in English, we may not have identified potentially relevant data on the epidemiology of acromegaly. Moreover, the quality of this study is affected by the limitations of each included study. Finally, although we did not find publication bias, between-study heterogeneity was very high.

Conclusion

This meta-analysis of global epidemiologic studies documented a pooled prevalence of 5.9 (95% CI: 4.4–7.9) per 100 000 persons and a pooled IR was 0.38 (95% CI: 0.32–0.44) per 100 000 person-years. Although a high heterogeneity of the epidemiology estimates across different studies was observed, the data source and the geographic area could represent relevant study-level factors which could explain about 50% of the total between-study variability.

It is necessary to develop an algorithm based on data that are available almost everywhere (e.g. claims databases) so that the various countries can conduct epidemiological studies in a standardized way and produce comparable results.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-21-0216.

Declaration of interest

Gianluca Trifirò has served on advisory boards for Sandoz, Hospira, Sanofi, Biogen, Ipsen, and Shire and is a consultant for Otsuka. Gianluca Trifirò is the principal investigator of observational studies funded by several pharmaceutical companies (e.g. Amgen, AstraZeneca, Daiichi Sankyo and IBSA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contribution statement

Gianluca Trifirò was responsible for the conception and design of the study and reviewed the manuscript. Salvatore Crisafulli, Nicoletta Luxi, Federica Spagnolo and Giuseppe Giuffrida reviewed the articles. Salvatore Crisafulli, Nicoletta Luxi and Janet Sultana conducted the systematic review and drafted the manuscript. Andrea Fontana performed the statistical analyses. Francesco Ferraù, Daniele Gianfrilli, Alessia Cozzolino, Maria Cristina De Martino, Federico Gatto, Francesco Barone-Adesi and Salvatore Cannavò reviewed and revised the draft manuscript. All authors have read and approved the final version of the manuscript.

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