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The prevalence of acromegaly is higher than previously reported: Changes over a three-decade period

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Abstract

Objective: To study time-related changes in the prevalence and patient characteristics of acromegaly, as well as to assess the impact of changes in treatment on disease control.

Methods: A total of 107 patients with acromegaly were identified by healthcare registries and subsequently validated by patient chart review over a three-decade period (1992–2021). A systematic literature review focusing on the incidence and prevalence of acromegaly was performed identifying 31 studies.

Results: The prevalence of acromegaly significantly increased throughout the study period ($R^2 = 0.94$, $p < .001$) and was 122 cases/10^6 persons in 2021 whereas the annual incidence remained constant at 4.6 cases/10^6 persons. The age at the first sign of acromegaly and the age at diagnosis significantly increased during the study period, whereas growth hormone and insulin-like growth factor I decreased. Incidentalomas constituted 32% of all cases diagnosed with acromegaly in the last decade. Primary surgery was used in 93% of all cases, and repeated surgery decreased from 24% to 10% during the three decades. The use of first-generation somatostatin analogues (21%–48%) and second-line medical treatment (4%–20%) increased with a concomitant improvement of biochemical disease control (58%–91%).

Conclusion: The prevalence of acromegaly is higher than previously reported and the clinical presentation has shifted towards a milder phenotype. Modern treatment of acromegaly enables individualized treatment and disease control in the majority of patients.

KEYWORDS
acromegaly, growth hormone, pituitary adenoma, pituitary endocrinology

Charlotte Aagaard and Amanda Skjervedal Christophersen are joint first co-authors.

1 | INTRODUCTION

Acromegaly is a rare and systemic disease characterized by hypersecretion of growth hormone (GH) and insulin-like growth factor I (IGF-I).[1,2] Due to an insidious disease onset, a diagnostic delay of 5–10 years is common,[3,4] although, this period has been reported to be decreasing.[4] Classic signs of acromegaly include the growth of hands, feet, and facial changes, together with less specific symptoms like joint and muscular pain, excessive sweating, snoring, and headache.[5] Before the 1990s the prevalence of acromegaly was reported to be 40–60/10^6 persons,[6–8] however, in more recent reports the prevalence has increased to 70–90/10^6 persons.[1,9–14] This increase has been ascribed to improved disease awareness and more incidental findings due to increased use of cerebral computed tomography (CT) and magnetic resonance imaging (MRI) scans.[4,15] At the same time a shift towards a milder phenotype of acromegaly has been suggested.[4,15] The annual incidence of acromegaly, on the other hand, is more constantly reported to be 3–5 cases/10^6 individuals.[1,9,11,16]

During recent decades, several diagnostic improvements have evolved such as new imaging techniques, (MRI, PET), additional biochemistry (IGF-I), and more accurate GH assays. The treatment of acromegaly has gradually changed with the introduction of modern medical treatment modalities and the continuous development of increasingly advanced and refined surgery techniques. In Denmark, first-generation somatostatin analogues were introduced in the late 1990s, whereas GH receptor antagonist (GHRA), treatment followed in the early 2000s, and second-generation SSAs in the late 2000s. Such progress presumably allows a more individualized treatment with better chances of achieving biochemical disease control.[17,18]

The aim of this study was to investigate time-dependent changes in incidence, prevalence, and patient characteristics in acromegaly during a three-decade period (1992–2021) in the North Denmark Region (NDR). Furthermore, we aim to explore changes in treatment strategies and the effect of such changes on biochemical disease control.

2 | METHODS

2.1 | Study population and clinical variables

The source population comprised the cumulative entire population of the NDR with ~600,000 inhabitants (2021) during the period 1992–2021. The Danish National Health Service provides public health care, with free access to hospital-based and primary medical care.[19] Each Danish citizen is identified by a unique personal ID (CPR-number) in the Danish Central Person Registry. We identified patients with a diagnosis of acromegaly from the Danish National Patient Registry, which contains records on all hospitalizations since 1 January 1977, together with primary diagnoses coded according to the International Classification of Diseases (ICD). This method of identifying individuals with acromegaly was previously validated.[20] ICD-8 (codes 25300 + 253001) was used to identify cases with acromegaly until 1993 and then replaced by the ICD-10 (code E22.0).[1] Among a total of 155 patients registered with a relevant code in ICD-8 or ICD-10, the acromegaly diagnosis could be confirmed in 107, based on elevated GH and IGF-I measurement. Forty-eight patients were registered with ICD codes indicating acromegaly, only due to a suspicion of acromegaly, which had subsequently been dismissed after hormonal examination.

A number of disease-specific clinical variables were retrieved from patient records, including pituitary tumour size (maximal diameter), serum GH, IGF-I, and prolactin levels at the time of diagnosis, after 3–5 years of follow-up, and at the latest follow-up. The fasting GH level ($GH_{fasting}$) was calculated as the mean value of two measurements and the nadir GH (GH_{nadir}) was defined as the lowest GH measurement after overnight fasting before a 180 min glucose suppression test. Biochemical disease control was defined as normalization of either $GH_{fasting}$, GH_{nadir}, or IGF-I < 1.2 times the upper limit of normal (×ULN).[2] During the period 1992–2011 the cut-off values of $GH_{fasting}$ and GH_{nadir} were ≤2.5 and ≤1 μg/L, respectively. In 2011 the assay changed from hGH RIA to hGH IDS-iSYS, thus changing the cut-off values for $GH_{fasting}$ and GH_{nadir} to ≤1 and ≤0.4 μg/L, respectively.[21] The IGF-I assay changed several times during the study period; however, each assay used age- and gender-specific reference values. Data on treatment (primary surgery, repeated surgery, medical therapy, radiotherapy), genetic screening (AIP, MEN1), signs and symptoms of acromegaly at the time of diagnosis, as well as estimated diagnostic delay, were retrieved from relevant medical files. Signs of acromegaly included the growth of hands or feet and facial changes. Symptoms included headache, joint or muscular pain, excessive sweating and snoring.

In the analysis regarding prevalent cases, 107 patients were included, among whom 32 patients had died during follow-up, thus resulting in 75 prevalent cases in 2021. Six patients had subsequently moved to other regions of Denmark, whereas three newcomers had arrived to the NDR. In the analysis describing changes in incidence over the three-decade period, a total of 80 patients were included and grouped as follows: 1992–2001 (n = 31), 2002–2011 (n = 24) and 2012–2021 (n = 25). The remaining patients had all been diagnosed before 1992. Two children at the age of 9 and 11 years diagnosed during the period 2002–2011 were excluded from data on patient characteristics (Table 1) due to their age and a diagnosis of (potential) gigantism rather than acromegaly.

When describing changes in treatment modality, all patients who received at least one type of treatment for acromegaly were included, with the treatment inclusion date being defined as the starting date for each given treatment. Since several patients received more than one type of treatment and often in different decades, a patient could be included in more than one decade and even several times in one decade. In all, 127 treatments were performed during the three decades: 1992–2001 (n = 42), 2002–2011 (n = 37) and 2012–2021 (n = 48), and the number of patients given at least one type of treatment varied as follows: 1992–2001 (n = 33), 2002–2011 (n = 28), and 2012–2021 (n = 29 patients).

TABLE 1 Patient characteristics at time of diagnosis

	Total	1992–2001	2002–2011	2012–2021	*p* Value
Number of patients, *n* (F/M)	80 (46/34)	31 (13/18)	24 (17/7)	25 (16/9)	-
Age at diagnosis (years, mean [±SD])	51.3 (±14.6)	45.4 (±14.0)	52.6 (±15.3)	57.4 (±12.3)	.001[a]
Diagnostic delay (years, median [IQR])	5 (2–10)	4 (2–10)	6 (3–19)	5 (2–15)	.56[a]
Age at symptom debut (years, mean ±SD])	45.6 (±14.2)	41.8 (±12.8)	45.1 (±16.1)	51.3 (±12.9)	.003[a]
Incidentalomas *n*, (%)	16/80 (20%)	1/31 (3%)	7/24 (29%)	8/25 (32%)	-
Adenoma size (mm, median [IQR])	17 (10–25)	15 (8–22)	18 (11.5–25)	17 (10–26)	-
Micro-/macro pituitary adenoma, *n*, (% macro)	13/54 (81%)	6/17 (74%)	3/20 (87%)	4/17 (81%)	-
Chiasma opticus compression	14/80 (18%)	7/31 (23%)	5/31 (16%)	2/25 (8%)	-
GH fasting (μg/L, median [IQR])	7 (3.8–22.1)	17.6 (6–48.9)	7.9 (4–18.7)	3.7 (1.7–6.6)	.002[b]
GH nadir (μg/L, median [IQR])	5.5 (3–21.2)	13 (4.4–22.5)	5.8 (3.3–22.1)	2.8 (1.2–12)	.01[b]
IGF-I (times ULN, median [IQR])	2.3 (1.5–3.5)	3.4 (1.5–5)	1.8 (1.1–3.1)	2.3 (1.8–3.1)	.03[b]
Prolactin (times ULN, median of prolactinomas [IQR])	2.55 (1.3–7.6)	1.7 (1.2–7.6)	1.4 (1.3–49.2)	3.2 (1.6–18.8)	-
Prolactin (times ULN > 1 at diagnosis), *n* (%)	20 (25%)	8 (26%)	5 (21%)	7 (28%)	-
Growth changes (facial changes and growth of hands and feet), *n* (%)	64 (86%)	25 (86%)	18 (82%)	21 (91%)	-
Symptoms (headache, fatigue, joint pain and excessive sweating), *n* (%)	52 (70%)	18 (62%)	15 (68%)	19 (83%)	-

Abbreviations: SD, standard deviation; ULN, Upper Limit of Normal.

[a]Regression analysis in changes during the entire follow-up period.

[b]Differences between the period 1992–2001 and 2002–2021.

2.2 | Statistical analysis

Histograms and qq-plots were used to examine continuous variables for normal distribution. If data was not normally distributed, log transformation was applied to obtain a normal distribution. Data was expressed as mean ± standard deviation or as median (interquartile range) for log-transformed data. Student's unpaired *t*-tests were used to compare variables between groups. Correlation analyses were performed using Pearson's correlation coefficient. Wilcoxon rank-sum tests were used to compare nonparametric data between groups. Fischer's exact test was used to test differences in cross tables. A $p < .05$ was considered statistically significant.

The study protocol was approved by the Danish Patient Safety Authority (ID 2021-004763) and the Danish Data Protection Agency (ID 2021-173).

2.3 | Literature review

To identify published studies containing data on the incidence and prevalence of acromegaly, we searched the PubMed and Scopus databases in January 2022. Based on search strings including index search terms as MeSH (PubMed) or Emtree (Embase) but also free text search, using the search terms: 'acromegaly' OR 'growth hormone secreting adenoma' AND 'incidence' OR 'prevalence'.

3 | RESULTS

3.1 | Prevalence and incidence

The mean prevalence of acromegaly increased throughout the study period from 69 (±11.9) to 96 (±9.0) and 116 (±2.9) cases/10^6 persons, respectively, in the three decades ($p < .000$, $R^2 = 0.94$) (Figure 1A). In the last year of follow-up (2021) the point prevalence was 127 cases/10^6 persons (75 patients diagnosed with acromegaly among 590.388 inhabitants in the NDR). If excluding three newcomers, the point prevalence decreased to 122 cases/10^6 person. Based on the mean annual incidence rate (cf. below), the mean age at the time of diagnosis (51.3 years in 1992–2021) and a life expectancy comparable to the general population in the NDR (81.4 years in 2020), the maximum theoretical prevalence can be estimated to 138 acromegaly cases/10^6 persons ([51.3–81.4] × 4.6 = 138).

The mean annual incidence of acromegaly was 4.6 cases/10^6 persons (±2.7) for the entire period from 1992 to 2021 (Figure 1B). A particularly high incidence was observed during the initial 5 years including an annual incidence of 8.7 cases/10^6 persons in 1993 and

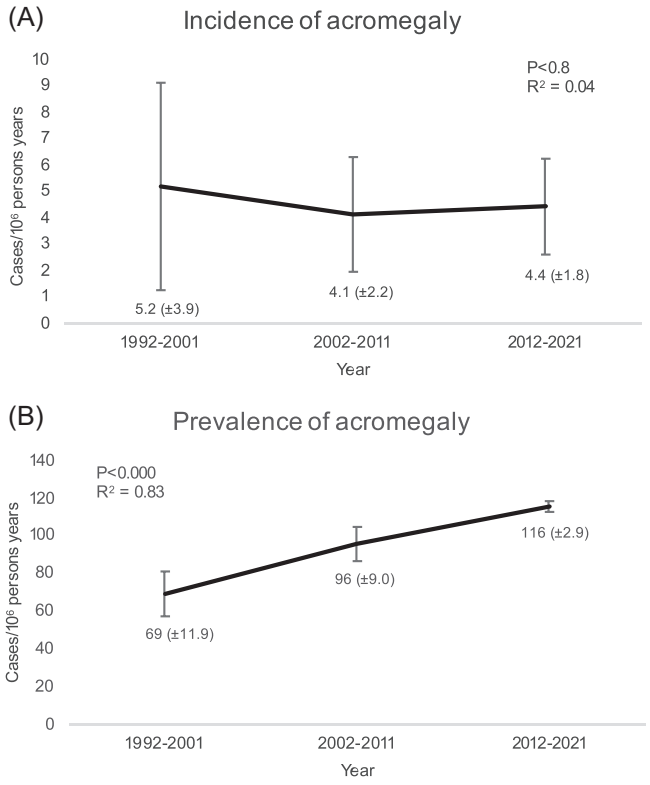


FIGURE 1 Mean prevalence of acromegaly per 10^6 persons (A) and annual incidence rate of acromegaly per 10^6 persons over calendar time with standard deviations (B). R^2, R-squared.

13.9 cases/10^6 persons in 1994, during which period the IGF-I assay became available for clinical use in the NDR.

3.2 | Changes in patient characteristics

Eighty patients with acromegaly diagnosed during the period 1992–2021 were included in the analysis of changes in patient characteristics (Table 1). The mean age at the time of diagnosis increased from 45.4 (±14) years in 1992–2001 to 57.4 (±12.3) years in 2012–2021 (Table 1). The age at the time of diagnosis (p = .001, R^2 = 0.14) and the age at the first symptom or sign of acromegaly (p = .001, R^2 = 0.13) significantly increased during the follow-up period. The diagnostic delay on the other hand was constant with a median delay of 5 years (2-10). Females and males had comparable age at the time of diagnosis (F: 51.3 [±14] years vs. M: 51.6 [±15] years, p = .88) and the diagnostic delay (F: 6 (3–11) years vs. M: 4 (2–10) years, p = .35) was similar in the two groups.

The mean adenoma size (15–18 mm remained unchanged throughout the three decades; the majority of all the adenomas being macroadenomas (89.5%) (Table 1). As compared to the decade 1992–2001, GH and IGF-I levels significantly decreased in the following two decades (2002–2021). The changes in hormone levels included $GH_{fasting}$ (18 μg/L (6–31) vs. 5 μg/L (3–13), p = .002), GH_{nadir} (14 μg/L(5–27) vs. 4 μg/L (2–18), p = .01) and IGF-I (3.2 × ULN [1.6–4.8] vs. 2.1 × ULN [1.6–3.1], p = .03). However, regression analysis revealed a possible tendency toward a time-dependent decrease in hormone levels (IGF-I: p = .08, $GH_{fasting}$: p = .06, GH_{nadir}: p = .54). In addition, females presented with significantly lower IGF-I levels than males (F: 2.0 × ULN (1.2–3.0) vs. M: 3.0 × ULN (2.0–4.2), p = .005), but with comparable $GH_{fasting}$ (p = .45), GH_{nadir} (p = .48) and prolactin (p = .70) levels as compared to males. The prevalence of hyperprolactinemia (p = .63) did not differ between male and female patients.

Growth changes such as facial changes and growth of hands or feet were common features in all three decades and reported in more than 80% of patients (Table 1). Male patients were more prone than female patients to exhibit facial growth changes. In general, though, female patients were significantly more symptomatic at the time of diagnosis as compared to males (79% vs. 53%, p = .02). The most frequent symptoms were excessive sweating (F:50%, M:28%), joint and muscular pain (F:45%, M:25%), headache (F:32%, M:25%) whereas snoring (F21%, M6%) was less commonly reported. There were no cases of familial acromegaly. Among 13 patients who were diagnosed before the age of 30 years, 12 were genetically screened without positive findings of MEN-1 or AIP gene mutations.

Sixteen cases were incidentally diagnosed i.e., without a prior suspicion of acromegaly but as a result of diagnostic imaging due to neurologic symptoms or head trauma. Most of those patients were females (F:11, M:5), and only three incidentalomas were diagnosed before the year 2009. Patients with incidentalomas presented with lower IGF-I × ULN (1.8 × ULN (1.1–2.6) vs. 2.3 × ULN (1.7–3.6), p = .03) and $GH_{fasting}$ (5 ug/L (2–23) vs. 10 ug/L (4–23), p = .03) but at the same time, larger pituitary adenomas (20 mm (16–26) vs. 16 mm (9–25), p = .047) as compared to other cases with acromegaly. There was an overall tendency towards fewer symptoms of active acromegaly in the group of incidentalomas (p = .11), although only the frequency of severe snoring was significantly lower (p = .04) as compared to non-incidentaloma cases. Age at diagnosis (p = .61) and age at first symptom or sign of acromegaly (when specifically questioned) (p = .94) were comparable between incidentalomas and other cases.

3.3 | Changes in treatment

Among the prevalent cases (2021) most patients had received transsphenoidal surgery as first-line treatment (97%), and less frequently repeated surgery (18%, Figure 2). Successful surgery with normalization of GH or IGF-I measurements was achieved in 64% of patients being operated. The proportion of patients that received repeated surgery decreased from initially 24% in the first decade to 10% in the last decade. Correspondingly, the proportion of patients receiving first-generation SSAs increased from the first decade (21%) to the last decade (48%, Figure 2). The use of second- or third-line medical treatment, including GHRAs, second-generation SSAs or Das, also increased from 3% in the first decade to 21% in the period 2012-2021. In most cases second- or third-line medical treatment

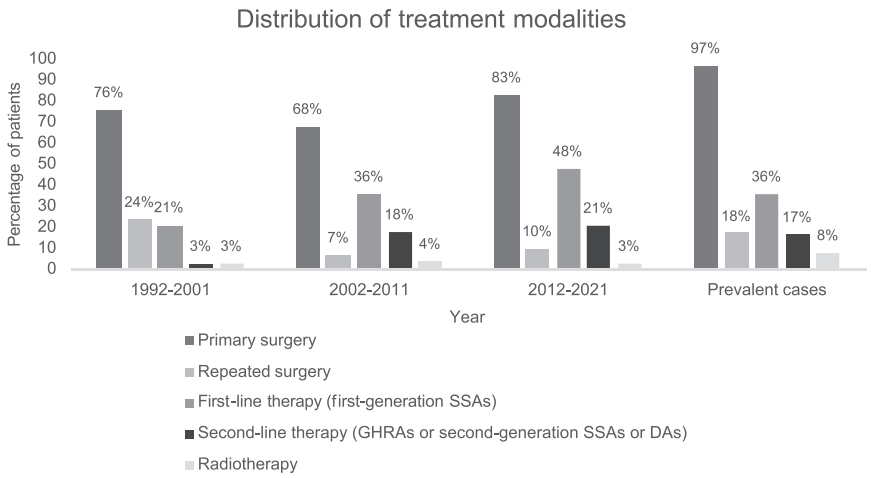
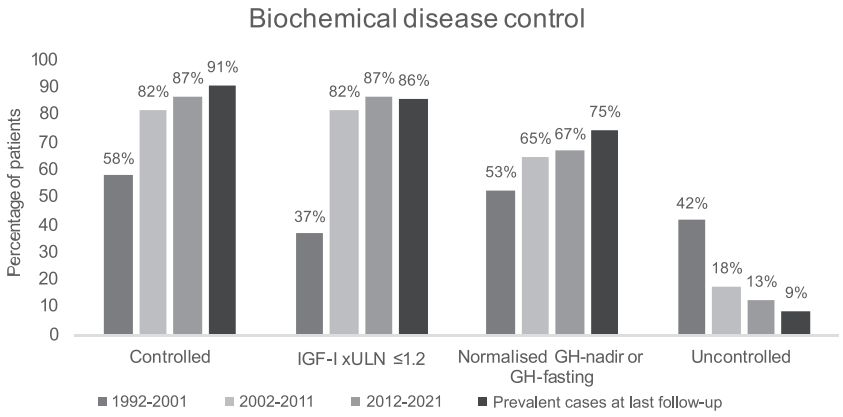


FIGURE 2 Treatment of acromegaly in the period 1992–2021. The bars indicate the percentage of patients commencing a type of treatment at a given decade. Treatment modalities incudes; Primary surgery, repeated surgery, first-line medical therapy including first-generation SSAs, second- and third-line therapy including GHRAs and second-generation SSA, DAs and radiotherapy. DAs, Dopamine agonists; GHRAs, growth hormone receptor antagonists; SSA, somatostatin analogues.

FIGURE 3 Changes in biochemical disease control after 3–5 years of at follow-up. Data presented as decades according to the year at diagnosis and at last follow-up for all prevalent cases in year 2021. Controlled disease was defined as IGF-I × ULN ≤ 1.2 or normalization of $GH_{fasting}$ or GH_{nadir}. according to the respective assay used. IGF-I, insulin-like growth factor I; ULN, Upper Limit of Normal.



was given in combination with first-generation SSA (14%). Less than five per cent of patients received radiotherapy in each decade (Figure 2). There were no sex differences in the frequency of surgery or use of SSAs (including dosage, data not shown). Twenty per cent ($n = 15$) of patients underwent long-term pituitary hormone replacement therapy during the period 1992–2021, the exact number of patients with hypopituitarism varying from 17% to 24% over the three decades. One fourth of all prevalent cases developed hypopituitarism. In approximately half of this subgroup more than one axis was affected, as a constant finding over the whole study period. Diabetes Mellitus ($n = 24$, 30%) and hypertension ($n = 50$, 63%) were common co-morbidities.

3.4 | Biochemical disease control

Biochemical disease control was assessed after 3–5 years (mean 3.3 years ±0.9) of treatment. The proportion of patients achieving biochemical disease control increased markedly from 58% among patients diagnosed between 1992 and 2001 to 87% between 2012 and 2021 (Figure 3). Additionally, 91% of all prevalent cases showed biochemical disease control, whereas 9% had uncontrolled acromegaly at the latest visit to the hospital. Approximately half of uncontrolled patients were recently diagnosed and still undergoing treatment adjustments directed at a persisting GH hypersecretion. There were no sex differences in the proportion of patients achieving biochemical disease control ($GH_{fasting}$, GH_{nadir}, or IGF-I, data not shown).

3.5 | Literature review

The search yielded 1959 unique publications, of which 214 were retrieved for further evaluation based on title or abstract reviewed by two individuals. Publication including <20 cases ($n = 6$) or data from insurance databases ($n = 3$) were excluded. In total, 31 publications contained data on the incidence and/or prevalence of acromegaly (Table 2).

TABLE 2 Characteristics of studies identified by a literature review: incidence and prevalence of acromegaly

Author	Country	Study period	Incidence Cases/100,000/year (95% CI or ± SD)	Prevalence Cases/100,000 persons (95% CI or ± SD)	Patients Number
Aagaard et al. (the present study)	Denmak	1992–2021	0.46 (±2.7)	12.2	72
Arnardóttir et al.[27]	Sweden	1991–2011	0.37	-	698
Yun et al.[32]	Korea	2013–2017	0.42	3.2	1093
Dal et al.[3]	Denmark	1978–2010	0.22 (1.5–2.9)–0.38 (3.5–4.1)	-	569
Matsubayashi et al.[9]	Japan	2013–2017	0.49	9.2	28.936
Park et al.[33]	Korea	2010–2013	0.36 (0.33–0.38)	-	718
AlMalki et al.[34]	Saudi Arabia	2017–2019	-	0.59	195
Wu et al.[35]	Taiwan	1997–2013	0.28 (0.26–0.29)	4.3 (4.0–4.6)	1195
Caputo et al.[36]	Italy	2012–2016	0.53 (0.42–0.67)	8.3 (7.5–9.2)	369
Gatto et al.[10]	Italy	2000–2014	0.31	6.9 (5.4–8.5)	74
Portocarrero-Ortiz et al.[37]	Mexico	1990–2012	-	1.8	2057
Dal et al.[1]	Denmark	1991–2010	0.38 (0.37–0.40)	8.5 (7.7–9.3)	405
Gruppetta et al.[38]	Malta	2000–2014	0.40 (0.27–0.60)	13.6 (10.5–17.6)	58
López Gavilanez et al.[39]	Ecuador	2000–2014	0.13	1.9 (1.4–2.5)	48
Al Dahmani et al.[40]	Canada	2000–2013	0.38	6.9 (5.4–8.8)	65
Hoskuldsdottir et al.[22]	Iceland	1955–2013	0.12–0.77	13.3	53
Agustsson et al.[41]	Iceland	1955–2012	0.8 males, 0.4 females	13.7 (10.2–18.4)	53
Tjörnstrand et al.[42]	Sweden	2001–2011	0.35 (0.25–0.45)	-	53
Dal et al.[20]	Denmark	1991–2009	0.45 (0.36–0.55)	-	110
Kwon et al.[43]	South Korea	2003–2007	0.39	2.8 (2.6–2.9)	1350
Almalki et al.[44]	Canada	2009–2011	-	2.9	130
Cannavó et al.[45]	Italy	2008	-	9.8 (7.7–12.5)	64
Raappana et al.[46]	Finland	1992–2007	0.34 (0.23–0.44)	-	54
Carlsen et al.[47]	Norway	1999–2004	0.36	-	83
Bex et al.[28]	Luxembourg, Belgium	2003–2004	0.19	4.0 (3.5–4.2)	418
Kauppinen-Mäkelin et al.[48]	Finland	1980–2002	0.40	-	334
Mestrón et al.[49]	Spain	1997–2004	-	3.4	1219
Ko et al.[50]	China	1984–1992	0.38	-	34
Etxabe et al.[8]	Spain	1970–1989	0.31	6.0 (4.8–7.6)	74
Ritchie et al.[7]	Northern Ireland	1959–1984	0.41	6.3 (5.2–7.8)	131
Bengtsson et al.[51]	Sweden	1955–1984	0.33	6.9	166
Alexander et al.[52]	UK	1960–1971	0.28	5.3 (4.6–6.2)	164

Abbreviations: CI, confidence interval; SD, standard deviation.

4 | DISCUSSION

In this retrospective single-center study, we observed a time-dependent increase in the prevalence of acromegaly to a higher level than generally reported. At the same time, the clinical presentation changed toward a milder phenotype and the frequency of incidentalomas increased. We used an almost ideal setting to conduct this type of study since all health care contacts are registered in the Danish health care registries.[19] Each case of acromegaly was subsequently validated by patient chart review, where elevated GH and IGF-I levels confirmed the diagnosis. The completeness of data is high and data quality is rather uniform since all patients with documented or suspected acromegaly in NDR are referred to our Neuro-Endocrine Center at Aalborg University Hospital. Finally, we use a well-defined catch-up area (NDR) and background population to make robust estimates on the incidence and prevalence.

In 2021 the point prevalence of acromegaly was approximately 127 cases/10^6 persons in the NDR or 122 cases/10^6 persons when excluding three newcomers. An increasing prevalence and incidence have been reported over the last decades which have been ascribed to factors such as improved diagnostics, incidental findings, and increased awareness of acromegaly.[4] In line with this, we observed an increase of incidentalomas with acromegaly due to increased use of high resolution cerebral CT scans and MRI (after year 2009). As shown in Table 2, the prevalence estimates obtained from cohorts during the periods 1970s and 1980s are typically 30–60 cases/10^6 persons[6–8] whereas an increase in prevalence to 70–90 cases/10^6 persons is reported for the period 2010–2015.[1,9–12] A similar increase in incidence has been reported from 2 to 4 cases/10^6 to 4–5 cases/10^6 (Table 2). These figures are in line with our findings during these respective periods. Two other studies can be identified that reported comparable high prevalence estimates (Table 2). One study from Iceland reported a prevalence of 133 cases/10^6 persons based on 52 cases,[22] and one study from Malta reported a similar prevalence of 136/10^6 persons based on 58 cases.[16] Both cohorts arise from relatively small populations with well-defined catch-up areas and centralized treatment, which like NDR make them ideal for estimating the prevalence. The study from Iceland reports a particular time-dependent increase in incidence from 2.6 to 7.7 cases/10^6 cases together with increasing age. This increase was predominantly among male cases who showed a comparable risk of co-morbidities such as hypertension and diabetes as our cohort. A suspicion of familiar cases was raised in the two cohort which could overestimate the prevalence, especially in small cohorts. In contrast, we did not observe cases of familial acromegaly in the NDR, and most persons with early-onset acromegaly were genetically screened without the finding of MEN-1 or AIP mutations. Interestingly, a particularly high prevalence and incidence are reported in the Nordic countries (Table 2). These countries are characterized by having a universal healthcare system with central patient registries making patients easy to identify. However, another important similarity is that these countries have relatively old populations and a rather genetic homogeneous population, which could explain these high figures.

A shift in the clinical presentation of acromegaly was observed with decreasing GH and IGF-I levels as well as increasing age at the time of symptoms onset and diagnosis. This suggests that mild cases of acromegaly are more frequently being diagnosed and thereby increasing the prevalence. This observation is in line with other reports describing a similar trend.[4,15,17] Changes in hormone levels should nevertheless be interpreted with some caution since several assays were used over the study period. The incidental diagnostic of acromegaly increased during the study period and accounted for ~30% of all cases in the last decades. Incidentaloma cases showed even lower IGF-I and GH levels together with fewer symptoms of acromegaly, but interestingly the pituitary adenomas were larger. A shift in histological subtypes of somatropinomas could give rise to the change in clinical presentations.[23] The densely granulated adenoma subtype is more frequently observed in older patients, with a relatively lower GH secretion, which could be the case in our cohort.[23] Of note, the densely granulated subtype is more responsive to medical treatment with SSA and hence easier to treat.[23] Surprisingly, symptoms related to active acromegaly and growth changes did not decrease during the three decades. This could reflect, that we only registered whether a given symptom was present rather than the severity of a symptom. We observed some sex differences in the presentation of acromegaly. Females presented with fewer classic growth-related signs of acromegaly and lower IGF-I levels as compared to males. On the other hand, females presented with more less specific symptoms as musculoskeletal pain, excess sweating, and headache compared to male patients. This sex difference in the clinical presentation have previously been associated with a particular prolonged diagnostic delay[4,21] together with an impaired socioeconomic status observed in females with acromegaly.[24] We observed a sex-independent diagnostic delay of 5 years, which is lower than in most other studies. This could be due to the high frequency of female cases being diagnosed as incidentaloma, thereby reducing the diagnostic delay.

In general, transsphenoidal surgery was applied as first-line treatment in our cohort and, unless contraindicated for medical or surgical reasons or disregarded because of patient's preference for medical treatment, performed in 97% of all prevalent cases (2021). The surgical remission rate was high (58%), which also includes intended debulking surgery. In previously published studies, remission rates after neurosurgical treatment of acromegaly vary considerably from 34% to 85%. A high remission rate was reported from patients with microadenoma and among experienced surgeons.[25] The treatment strategies seem to have changed over the three decades, with a decrease in repeated surgery from 24% to 10%. In parallel, the use of first and second or third line medical treatment increased, which is in line with other studies.[17,26] The use of first-generation SSAs (first-line medical treatment) increased from 21% to 48% of patients receiving treatment corresponding to 36% of all prevalent cases in 2021. Second and third-line medical treatments include DAs, GHRAs, and second-generation SSAs, the use of which increased from 3% to 21% of medically treated patients. In most cases, second-line treatment was

applied as an add-on of either GHRA or with DA (14%). Concomitantly with the proposed changes in treatment strategy, we observed an improvement in biochemical disease control. This is similar to some[17,18,27] but not all other studies.[28] Based on the normalization of either GH or IGF-I, the disease control increased to 91% among prevalent cases. Discordance where only GH (5%) or IGF-I (16%) reached the predefined cut-off level was observed in 21% of all prevalent cases, similar to previously reported figures.[29,30] The clinical relevance of such discordance is unclear, as the risk of co-morbidities seems to be similar to patients achieving concordant control of GH and IGF-I.[31] The largest improvement in disease control was observed from the period 1992–2001 to 2002–2011. This could be because of the introduction of SSAs in 1999, before which only surgery and DAs were available. Our data suggest that disease control may be reached within the first 4 years after diagnosis. This is in accordance with another study where disease control is achieved after an average of just 14 months.[18] The proportion of disease control varies considerably between studies ranging from 56% to 93.2%.[17,28,53] In nine per cent of our prevalent cases, biochemical control was not obtained. This emphasizes the need for further development of potent yet well tolerated treatment options.

There are some inborn limitations to this study, mainly due to its retrospective nature. Varying data quality, including some missing data and (possibly) recall bias, primarily affecting data on symptoms and diagnostic delay, is inevitable in a study of this nature. However, all patients were followed by a small team of dedicated pituitary endocrinologists and experienced neurosurgeons aiming at uniformity in data registration, interpretation as well as uniformity in treatment. Another point of weakness was the change of GH and IGF-I assays during the study period, thus making comparison difficult. To overcome this issue, IGF-I measurements were recalculated and expressed as multiples of 'Upper Limit of Normal' (ULN), based on assay-specific age and sex-specific reference levels. GH measurements were even more challenging since both the type of GH assay and the definition of disease remission changed during the study period.

In summary, this study shows that the prevalence of acromegaly is increasing to higher levels than previously suggested. Changes in patient characteristics suggest that the increase in prevalence can be ascribed to factors such as an increase in incident findings, the diagnosis of milder cases of acromegaly, and a longer life expectancy. By using a multi-disciplinary approach in a centralized setting, biochemical disease control can be achieved in most patients.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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