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Sex differences in acromegaly at diagnosis: A nationwide cohort study and meta-analysis of the literature

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Abstract

Objective: Data on sex differences in acromegaly at the time of diagnosis vary considerably between studies.

Design: A nationwide cohort study including all incident cases of acromegaly (1978–2010, n = 596) and a meta-analysis on sex differences in active acromegaly (40 studies) were performed.

Method: Sex-dependent differences in prevalence, age at diagnosis, diagnostic delay, pituitary adenoma size, insulin-like growth factor 1 (IGF-I) and growth hormone (GH) concentrations were estimated.

Results: The cohort study identified a balanced gender distribution (49.6% females) and a comparable age (years) at diagnosis (48.2 CI95% 46.5–49.8 (males) vs. 47.2 CI95% 45.5–48.9 (females), p = 0.4). The incidence rate significantly increased during the study period (R^2 = 0.42, p < 0.01) and the gender ratio (F/M) changed from female predominance to an even ratio (SR: 1.4 vs. 0.9, p = 0.03). IGF-I_{SDS} was significantly lower in females compared to males, whereas neither nadir GH nor pituitary adenoma size differed between males and females.

In the meta-analysis, the weighted percentage female was 53.3% (CI95% 51.5–55.2) with considerable heterogeneity (I^2 = 85%) among the studies. The mean age difference at diagnosis between genders was 3.1 years (CI95% 1.9–4.4), and the diagnostic delay was longer in females by 0.9 years (CI95% −0.4 to 2.1). Serum IGF-I levels were significantly lower in female patients, whereas nadir GH, and pituitary adenoma size were comparable.

Conclusion: There are only a minor sex differences in the epidemiology of acromegaly at the time of diagnosis except that female patients are slightly older and exhibit lower IGF-I concentrations and a longer diagnostic delay.

KEYWORDS
acromegaly, age, diagnostic delay, gender, GH, IGF-I, sex

1 | INTRODUCTION

Acromegaly is a rare disorder caused by chronic hypersecretion of growth hormone (GH) from a pituitary adenoma. Recent data from population-based studies suggest a prevalence of 85–137 cases per million inhabitants and an annual incidence of approximately four cases per million person years.[1–5] The natural history of GH-secreting pituitary adenomas is subject to inter-individual variation with distinct clinical, radiological and histopathological subtypes.[6,7] The onset of acromegaly is insidious and a diagnostic delay of 5–10 years is common,[8] although this period may have shortened within recent years.[7,9]

As opposed to other hormone-secreting pituitary tumours where a female preponderance is present, it is less clear if the incidence and prevalence of acromegaly differ between men and women.[10] Two recent reviews conclude that acromegaly is more prevalent in women but the gender distribution differs considerably between cohorts.[11,12] Female predominance has indeed been reported,[13–17] and females are often older at the time of diagnosis.[13,16–18] Most of the observations on sex differences derive from registries reporting a low disease prevalence, which could indicate underdiagnosis of a subgroup of patients including older males with mild acromegaly.[13–17] A more even gender distribution has been reported in recent population-based surveys with overall higher disease prevalence.[1,3,19,20]

Serum insulin-like growth factor I (IGF-I) concentrations at the time of diagnosis are lower in females,[21,22] but it is less clear whether GH concentrations and pituitary tumour size also display a gender difference.[22,23] Such data are relevant for understanding the natural history of the condition and for providing gender-based reference values, where appropriate.[24]

The inconclusive data on gender differences in acromegaly highlight the need for population-based studies with complete coverage and follow-up. We therefore conducted a population-based cohort study in Denmark and a meta-analysis of the literature to examine sex differences in active acromegaly.

2 | MATERIALS AND METHODS

2.1 | Population-based Danish cohort study

The source population comprised the cumulative population of Denmark during the period 1977–2010. The Danish National Health Service provides (tax-supported) public health care, with free access to hospital-based and primary medical care. To ensure unambiguous data linkage, we used the Danish Civil Registration System, which assigns a unique personal identifier, the civil personal registration number, to each Danish resident at time of birth or upon immigration. We identified members of the acromegaly cohort from the Danish National Patient Registry, which contains records on all hospitalizations since 1 January 1977, together with primary and secondary diagnoses coded according to the International Classification of Diseases (ICD).[25] The Eighth Revision (ICD-8) was used until 1993 and then replaced by the Tenth Revision (ICD-10).[25]

We validated each individual acromegaly diagnosis, as previously described.[25] All patients with a validated acromegaly diagnosis residing in Denmark between 1978 and 2010 were eligible for the study. Disease-specific clinical variables were retrieved from patient records, including pituitary tumour size (maximal diameter), serum GH and IGF-1 levels at the time of diagnosis which were only available for patients diagnosed after 1991. IGF-I standard deviation scores (SDS) were calculated *post hoc* based on IGF-I data from each patient record using the gender and age-related cut-off levels provided for the particular assay, at the time of measurement.

2.2 | Statistical analysis

Histogram and qq-plot were used to test continuous variables for normal distribution. If data were not normally distributed, log transformation was applied. Data are expressed as mean CI95% or as geometric mean ± CI95% for log-transformed data. Unpaired *t* tests were used to compare continuous variables between groups. Chi-square test was used to test differences in cross-tables. Correlation analyses were performed using Pearson's correlation coefficient. A p-value < 0.05 was considered statistically significant.

2.3 | Meta-analysis

To identify published studies containing gender-specific data on patients with acromegaly, we searched the PubMed and Scopus databases in February 2019. Based on two separate search strings including index search terms as MeSH (PubMed) or Emtree (Embase) but also free text search, using the search terms: 'acromegaly' or 'pituitary tumor size' or 'biomarkers' or 'GH' or 'IGF-I' or 'age' combined with either (a) 'incidence' or 'prevalence' or (b) 'sex' or 'gender'. Studies that provided data on gender distribution and gender-specific variables at the time of acromegaly diagnosis including age, random GH, nadir GH, IGF-I, IGF-I SDS and pituitary adenoma size were all included. For estimates on sex distribution and age at diagnosis only studies with >50 patients from a well-defined source population were selected. The following exclusion criteria were used to avoid bias. (1) Duplicate data, only the largest or most recent publication from a specific study setting was included.[26] (2) Selected patient population, for example, cohorts including only surgically treated patients or cohorts excluding acromegaly patients with prolactin co-secretion. (3) Non-population-based registries, such as insurance databases and small local registries.

Standardized incidence rations (SIRs) were computed by dividing the number of observed events by the number of expected events in the selected studies. Random-effects model was used by default given the expected heterogeneity; heterogeneity was assessed using the chi^2-test and I^2-statistics. Regression analyses were performed using meta-regression. Funnel plots were used when at least

10 studies were available for analysis. All statistical analyses were performed using STATA 16.

3 | RESULTS

3.1 | Nationwide cohort study

569 patients with acromegaly were included in the study, of whom 49.6% were females (F = 282 cases, M = 287 cases). The mean annual incidence rate (IR) of acromegaly was 3.3 cases/10^6 person-years (py) (CI95% 2.9–3.7), which increased during the observation period (β = 0.07, R^2 = 0.42, p < 0.01, Figure 1A). An increase in incidence appeared during the initial period, after which the incidence rate reached a plateau (1977–1988, IR: 2.2 cases/10^6 py (CI95% 1.5–2.9) vs. 1989–2010, IR: 3.8 cases /10^6 py (CI95% 3.5–4.1), p < 0.01, Figure 1A). The IR was higher in female patients only in the first period (F: 2.5 (CI95% 1.6–3.5) vs. M: 1.8 (CI95% 1.2–2.4), p = 0.05) and the sex ratio (female/male) changed from a female predominance to an even ratio (SR: 1.4 vs. 0.9, p = 0.03).

The mean age at diagnosis was comparable for males and females (M: 48.2 years, CI95% 46.5–49.8; F: 47.2 years, CI95% 45.5–48.9, p = 0.4, Figure 1B) and remained unchanged during the observation period. The sex ratio in patients ≤ 25 years (F: 15 cases vs. M: 10 cases, NS) and ≤ 18 years (F: 3 cases vs. M:2 cases) was also comparable.

IGF-I_{SDS} was significantly lower in females compared with males (M: 5.5 SDS (CI95%: 5.3–5.7) vs. F: 5.0 SDS (CI95%: 4.7–5.1), p < 0.01), whereas neither nadir GH nor pituitary adenoma size differed between males and females (Table 1). IGF-I_{SDS} was comparable for males and females older than 50 years at the time of diagnoses (M: 5.0 SDS (CI95%: 4.7–5.3) vs. F: 4.9 SDS (CI95%: 4.5–5.1), p = 0.55).

3.2 | Meta-analysis and literature review

The search yielded 1,525 unique publications, of which 128 were retrieved for further evaluation based on title or abstract reviewed but two individuals (Figure 2). In total, 40 publications were included in the meta-analysis (Tables 2 and 3). For the analysis of sex distribution and age at diagnosis, a total of 33 publications were included. (Figure 2, Table 2). For the analysis of sex-specific data on GH, IGF-I or adenoma size, all available studies including gender-segregated data were included (n = 12, Figure 2, Table 3).

The weighted percentage female was 53.3% (CI95% 51.5–55.2) based on 31 studies including 25,043 cases (Figure 3). There was considerable heterogeneity (I^2 = 85%) among the studies and the funnel plot was symmetric providing no firm evidence of small study effects (data not shown). The mean weighted age at diagnosis was 47.0 years (CI95% 45.7–48.3) and 43.6 years (CI95% 41.6–45.5) for females and males, respectively. The mean weighted age difference at diagnosis between males and females was 3.1 years (CI95% 1.9–4.4, n = 15 studies, 11,787 cases, Figure 4). There was considerable heterogeneity (I^2 = 84%) among the studies and the funnel plot was symmetric (data not shown). The diagnostic delay was significantly longer in females by 0.9 years (CI95% −0.4 to 2.1, n = 5 studies, 5432 cases, Figure 5). The mean weighted diagnostic delay was 6.3 years (CI95% 4.3–8.3) and 5.2 years (CI95% 3.4–6.9) for females and males, respectively.

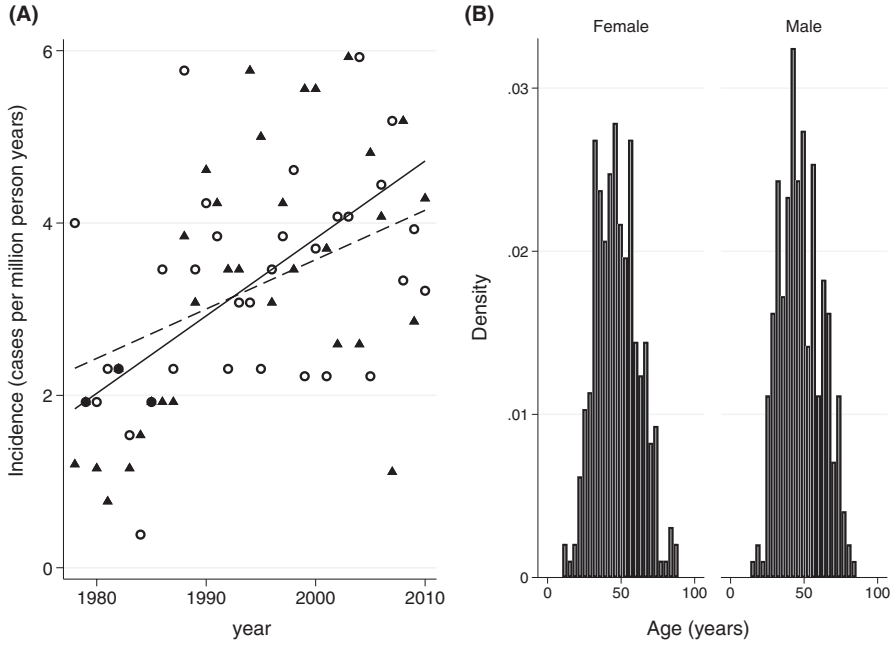

FIGURE 1 Panel (A) Incidence of acromegaly during the time period 1977 to 2010 segregated by gender (○ = females, **Δ** = males). Regression lines for female (- -) and male are shown (–). Panel (B) Age at the time of acromegaly diagnosis segregated by gender

TABLE 1 Descriptive characteristics of the Danish acromegaly cohort

	All (CI95%)	Female (CI95%)	Male (CI95%)	*p*-value
Number of patients	569	282	287	
Age (years)	48 (47-49)	47 (46-50)	48 (46-50)	0.62
IGF-I (SDS)	5.3 (5.1-5.4)	5 (4.7-5.2)	5.5 (5.3-5.7)	<0.01
GH nadir (ug/L)	10.3 (8.9-12.1)	9.1 (7.2-11.6)	11.5 (9.4-14.0)	0.16
Adenoma size (mm)	16.2 (14.8-17.5)	16.5 (14.7-18.3)	15.8 (13.9-17.8)	0.31
Micro-/Macro-/Giant pituitary adenoma (%)	31/67/2	27/71/2	35/63/2	0.31

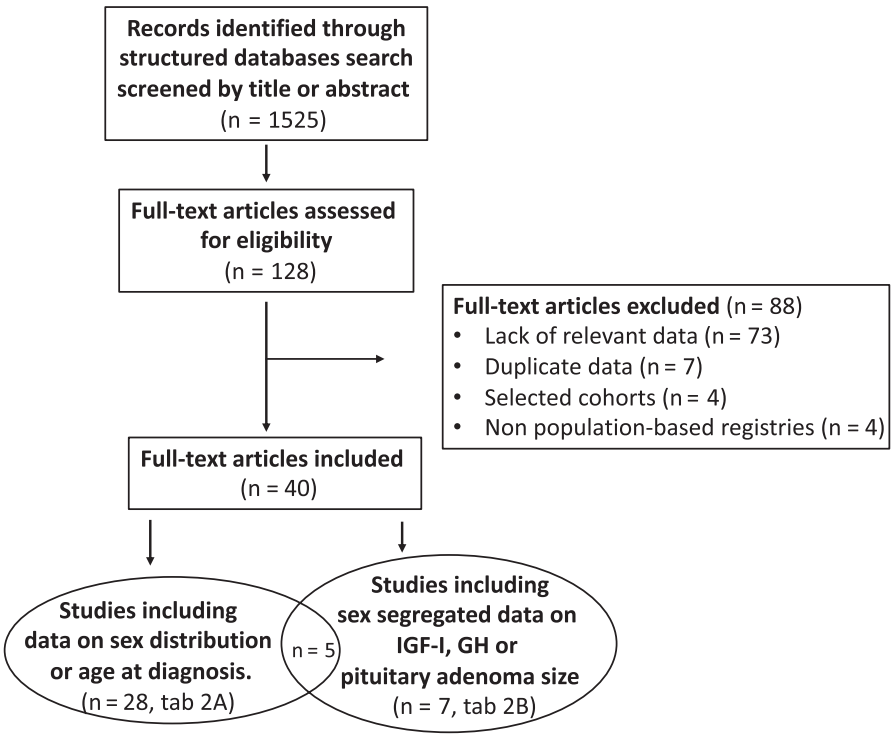

FIGURE 2 Selection of articles included in the meta-analysis

Serum IGF-I levels were significantly lower in female patients at the time of diagnosis (6 studies pooled, 3567 cases, mean difference −106.6 ug/L (95% CI −128.4, −84.8, Figure 6)), whereas nadir GH (6 studies, 2512 cases), and pituitary adenoma size (3 studies, 1019 cases) were comparable.

4 | DISCUSSION

The overall findings from our population-based cohort study and meta-analysis suggest the presence of an almost even sex distribution in acromegaly. Female patients at the time of diagnosis are older with a lower age-adjusted IGF-I level and a more prolonged diagnostic delay as compared to males.

In the Danish cohort study, we observed a balanced sex distribution, which contrasts somewhat with the meta-analysis, where we observed a small female predominance. A significant time-dependent shift in sex distribution from initial female predominance to a more even sex balance was observed in the cohort study (Figure 1). This pattern has been reported in several recent studies that include sex distribution as a function of calendar year.[4,7,8,27–30] At the same time, most of these studies report an increasing age at diagnosis,[4,7,8,29,30] which is ascribed to both a later onset, and a milder phenotype.[7,17,31,32] This could indicate that milder cases of acromegaly were previously undiagnosed. In the Danish study, the increase in incidence mainly occurred from 1985 to 1995 (Figure 1) during which IGF-I assays and pituitary MRI gradually became part of routine clinical practice. It is plausible that these diagnostic improvements contribute to the observed increase in the incidence of milder cases of acromegaly and a shift towards a balanced sex distribution.

Similar to the Danish cohort, an even sex distribution was reported in all cohorts with a high prevalence (≥80/million) and/or incidence (≥4/million) in the meta-analysis.[2,19,33,34] A recent review on

TABLE 2 Characteristics of studies included in the Meta-Analysis: sex and age at diagnosis

Author (reference no)	Country	Patients (N)	Females (%)	Age at acromegaly diagnosis, y	Study period
Agustsson, T. T. et al[33]	Iceland	53	40	F: 44, M: 45	1955–2012
Anagnostis, P. et al[46]	Greece	115	61		1987–2009
Bex, M. et al[47]	Belgium/ Luxembourg	418	49	F: 46, M: 42	2000–2004
Cannavo, S. et al[34]	Italy	64	50		–2008
Ciresi, A. et al[23]	Italy	307	51	F: 49, M: 48	2000–2010
Dagdelen et al[48]	Turkey	160	49	F: 44, M: 40	1990–2012
Dal, J. et al[1]	Denmark	405	47	F: 48, M: 49	1991–2010
Drange, M. et al[49]	United States	176	49		1982–1999
Esposito, D. et al[20]	Sweden	603	54	F: 52, M: 52	2001–2013
Etxabe, S. et al[18]	Spain	74	65	F: 46, M: 40	1970–1989
Gruppetta, M. et al[2]	Malta	52	58	F: 50, M: 37	2000–2011
Holdaway, I. M. et al[50]	New Zealand	208	40		1964–2000
Holdaway, I. M. et al[51]	World wide	2649	50		1940–1999
Howlett, T. A. et al[52]	United Kingdom	2572	50		1943–2011
Khamesh, M. et al[53]	Iran	85	45		2014–2016
Kwon, O. et al[4]	Korean	1350	54		2003–2007
Varadhan, L. et al[27]	United Kingdom	167	54		1960–2012
Maione, L. et al[13]	France	999	54	F: 49, M: 43	1980–2012
Nachtigall, L. et al[9]	United States	100	55		1985–2005
Park, J. et al[54]	Korea	215	49		1994–2008
Petersenn, D. et al[17]	Germany	1485	54	F: 41, M: 47	–2005
Petrossians, P. et al[7]	European	3173	54	F: 46, M: 44	2012–2016
Popovic, V. et al[55]	Serbia	220	62		1992–1989
Portocarrero, L. A. et al[15]	Mexico	2057	59		1990–2012
Reid, T. J. et al[8]	United States	324	48		1981–2006
Reincke, M. et al[56]	Germany	1543	54		–2005
Ritvonen, E. et al[19]	Finland	333	52	F: 50, M: 45	1980–1999
Scaroni, C. et al[57]	Italy	496	55		1990–2016
Sesmilo, G. et al[14]	Spain	1658	61		1970–2010
Terzolo, M. et al[16]	Italy	1512	59	F: 47, M: 43	1980–2012
Vallette, S. et al[29]	Canada	329	49	F: 47, M: 44	1980–2010
Vandevan, S. et al[58]	Bulgaria	534	65	F: 42, M: 42	1980–2012
Vila, G. et al[59]	Austria	607	54		–2013

Note: F = female, M = male, Y = years, N = amount, No = number.

acromegaly registries found a female predominance with an overall sex-ration on 1.26 (female/male).[12] These registries often cover several decades including the period in which a female predominance also occurred in the Danish cohort. Moreover, male patients are often much younger than females in these cohorts (up to 7 years), which could suggest under-reporting of older males patients.[12] In addition, these registries are characterized by a relatively low estimated prevalence, which also suggest underdiagnosis.[13–17]

Females were older at the time of diagnosis and exhibited a longer diagnostic delay[7,11,17,35–37] according to the meta-analysis. However, this age difference seemed to narrow as a function of calendar year.[7] In contrast to the meta-analysis, studies from Denmark,[1] Sweden,[37]

TABLE 3 Characteristics of studies included in the Meta-Analysis: pituitary adenoma size, GH and IGF1

	Patients	Adenoma size (mm)	GH nadir (ug/L)	GH random (ug/L)	IGF1 (ug/L)	IGF1 SDS,
Author	N	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Tanaka, S. et al[60]	F: 47			F: 8.7 ± 33.1	F: 679 ± 224	F: 7.3 ± 2.0
	M: 27			M: 6.1 ± 10.4	M: 769 ± 281	M: 9.2 ± 2.8
Markkanen, H. et al[61]	F: 4		F: 11.2 ± 2.1	F: 19.2 ± 5.8		
	M: 3		M: 9.4 ± 7.5	M: 13.7 ± 7.5		
Arafat, A. M. et al[62]	F: 9		F: 7.4 ± 10.6	F: 10.3 ± 10.6		
	M: 19		M: 3.8 ± 4.7	M: 4.9 ± 6.2		
Freda, P. U. et al[63]	F: 11		F: 1.2 ± 0.7	F: 2.2 ± 1.8		
	M: 18		M: 1.4 ± 1.4	M: 1.8 ± 1.6		
Park, S. H. et al[64]	F: 260	F: 18.0 ± 8.2			F: 667 ± 197	
	M: 203	M: 15.7 ± 7			M: 782 ± 255	
Colao, A. et al[22]	F: 79	F: 12.9 ± 5.3	F: 27.5 ± 33.8	F: 33.8 ± 31.1	F: 665 ± 221	
	M: 72	M: 14.6 ± 5.9	M: 18.5 ± 19.5	M: 39.5 ± 28	M: 756 ± 279	
Dal, J. et al[1]	F: 191	F: 15.0 ± 10.7	F: 7.9 ± 19			F: 4.9 ± 1.7
	M: 214	M: 15.8 ± 12	M: 10.1 ± 22			M: 5.5 ± 1.7
Petersenn, S. et al[17]	F: 808		F: 10.0 ± 52.8	F: 21.0 ± 103.3	F: 679 ± 328	
	M: 677		M: 13.2 ± 75.3	M: 14 ± 92.7	M: 773 ± 314	
Ciresi, A. et al[23]	F: 150		F: 18.0 ± 17.8	F: 26.8 ± 22.3		F: 2.43 ± 0.89
	M: 157		M: 21.7 ± 17.9	M: 31.4 ± 24.2		M: 2.31 ± 0.8
Terzolo, M. et al[16]	F: 888					F: 8.3 ± 4.7
	M: 624					M: 8.8 ± 4.7
Higuchi, Y. et al[65]	F: 19			F: 85 ± 118	F: 988 ± 432	
	M:25			M: 78 ± 123	M: 995 ± 379	
Kwon, O. et al[4]	F: 723			F: 42.1 ± 80.3	F: 920 ± 468	
	M: 627			M: 42.7 ± 68.4	M: 1062 ± 535	

Note: F = female, M = male, SD = standard derivation, N = amount, No = number.

Iceland[3,33] and Finland[19,38] did not record an age-related sex difference at diagnosis. The underlying explanation for this discrepancy is unclear but could involve a difference in the sex-dependent diagnostic delay. Of note, the Scandinavian studies are population-based with virtually complete follow-up. The incidence and prevalence of acromegaly in these countries are relatively high, and the same is true for the age at diagnosis.

The reason why female patients are older and experience a longer diagnostic delay according to the meta-analysis is unclear. The initial diagnosis is more often made by the patient's family physician or a specialist in internal medicine[9,36] and the changes in physical appearance are more likely noticed by others than the patients.[8] The most common symptoms leading to the initial diagnosis of acromegaly are growth changes and headaches.[3,9,36,39,40] However, signs and symptoms of acromegaly may differ between sexes. Males seem prone to classical physical changes as prognathism and growth of hands and feet, whereas, females are more likely to show symptoms such as headache.[36,41] Moreover, symptoms such as sweating and amenorrhoea could be interpreted as menopausal in female patients,[36] which could delay the diagnosis. In line with this, female patients are known to have consulted more doctors before being diagnosed with acromegaly,[36] and it has been suggested that an implicit physician bias could contribute to this sex-specific healthcare disparity[42] as seen with other medical conditions.[36,43,44] A diagnostic delay and a prolonged GH exposure in females is supported by an increased burden of co-morbidities during this pre-diagnostic period.[37] Metabolic changes induced by GH excess as metabolic syndrome is also more prevalent in females at the time of diagnosis[23] and females have increased risk of type 2 diabetes and hypertension.[1,11]

At the time of diagnosis, we observed comparable tumour size and GH levels but lower IGF-I levels in female patients in virtually all studies. A sex-specific difference in the relationship between GH and IGF-I in patients with active acromegaly in terms of lower IGF-I concentrations in female patients has previously been reported.[21] The low IGF-I level in female patients has been ascribed to a suppressive effect of oestrogen on the hepatic IGF-I production, although additional underlying mechanisms may exist.[21,22]

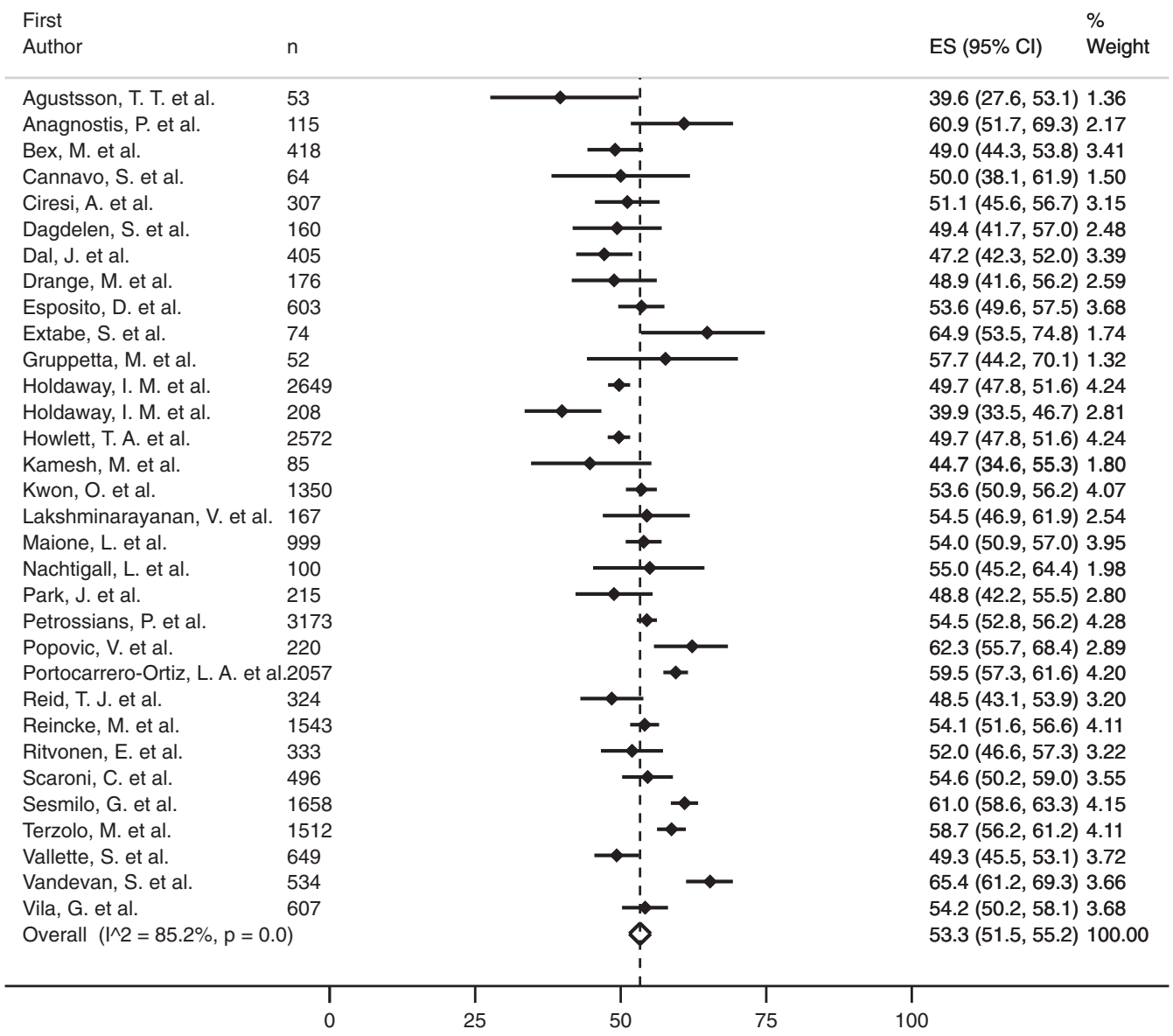

FIGURE 3 Percentage females in patients with acromegaly

This could be associated with less pronounced physical changes found in females[41] including IGF-I mediated effects on bone growth[45] and hence contribute to a slightly older age at time of diagnosis. Sex differences in GH levels in patients with acromegaly are less consistent. Recently, comprehensive BMI- and sex-specific GH reference values have become available from which it appears that sex differences only apply to premenopausal women and patients on oral oestradiol treatment, both of whom exhibit elevated GH levels relative to male counterparts.[24] Larger adenomas have been reported in some female cohorts,[11] and a negative correlation between tumour size and age has also been reported.[1,11,30] In our cohort study and meta-analysis, however, we did not record a sex difference in adenoma size.

Our Danish study benefits from the population-based nationwide data with virtually complete follow-up. This minimizes the risk of selection bias, which is reinforced by free public health care access in Denmark. Moreover, the diagnosis of each patient in our study was validated, as previously reported.[25] There could be cultural differences across the included countries with different sex-specific thresholds for seeking medical attention or differences in the diagnostic process that also could also be affected by the degree of self-payment of medical costs. The meta-analysis on GH, IGF-I, adenoma size and diagnostic delay is limited by the low number of publications reporting sex segregated data.

In summary, the results from our cohort study and the meta-analysis suggest that there is only a minor sex difference in the epidemiology of acromegaly at the time of diagnosis except that female patients are slightly older and exhibit lower IGF-I concentrations and a longer diagnostic delay.

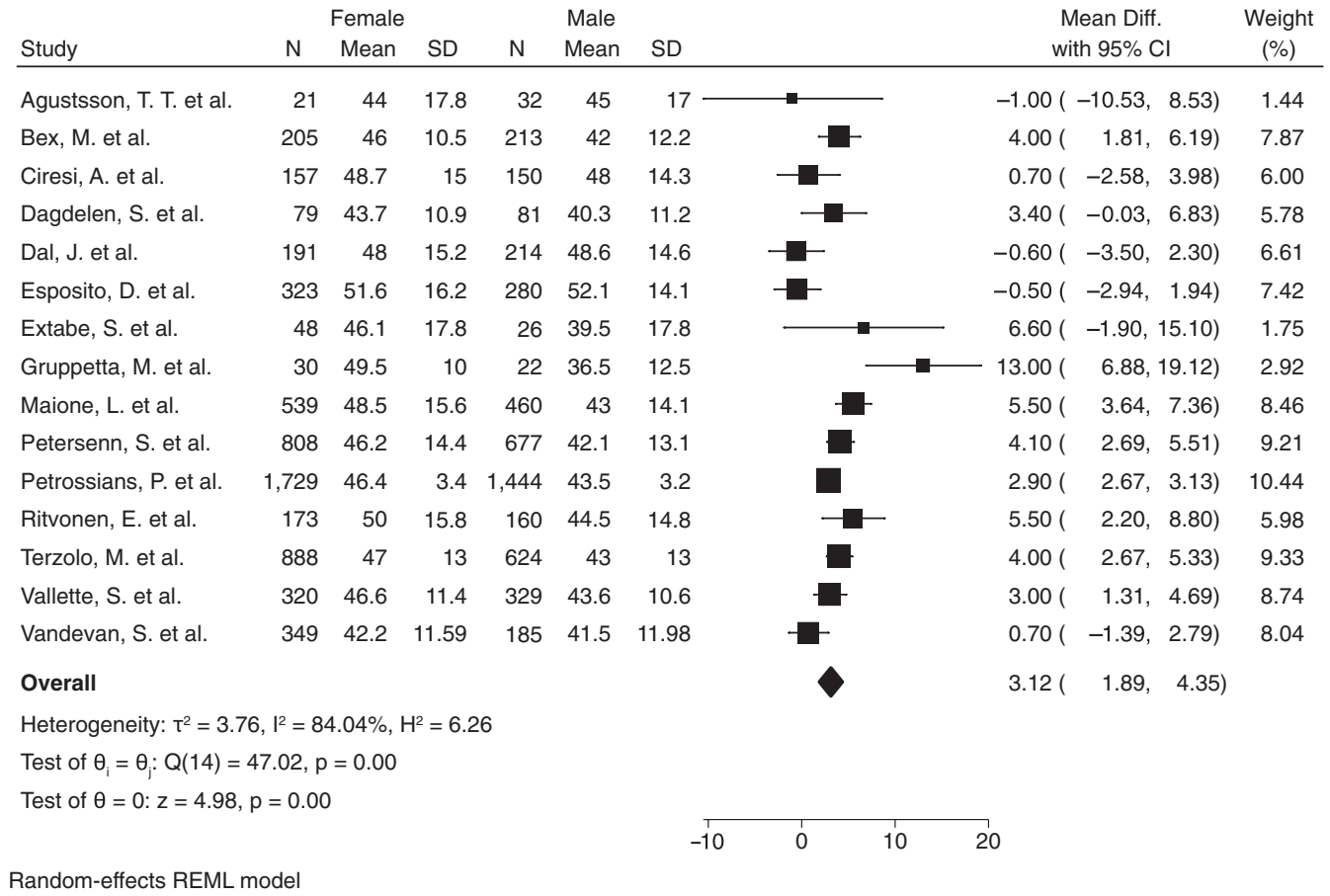

FIGURE 4 Age at time of acromegaly diagnosis

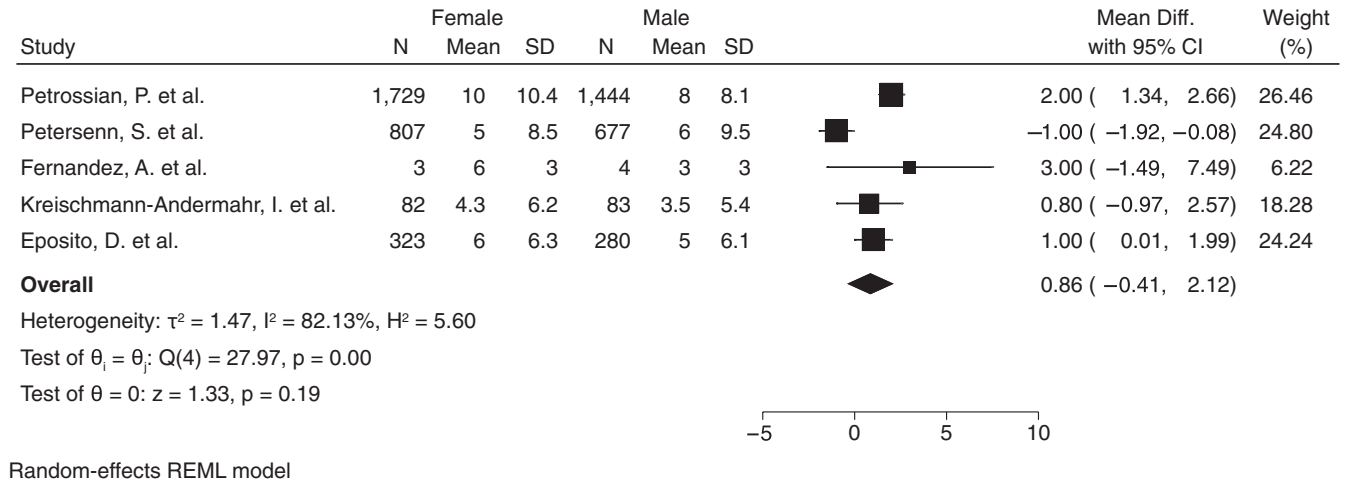

FIGURE 5 Diagnostic delay in acromegaly

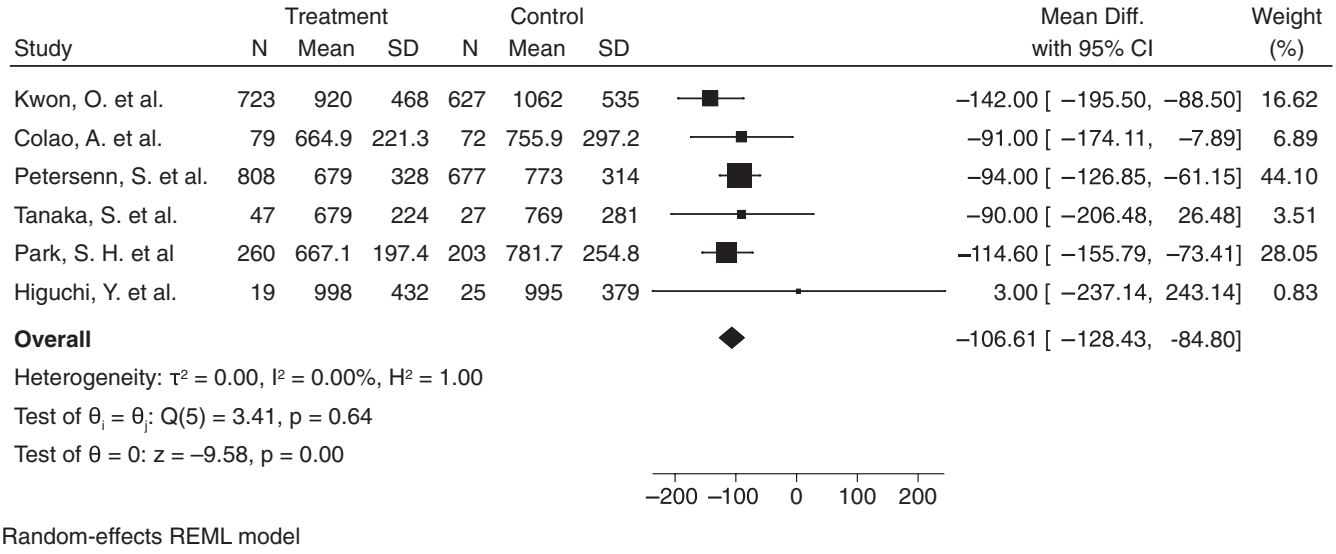

FIGURE 6 IGF-I levels at time of acromegaly diagnosis

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CONFLICT OF INTEREST

JD: unrestricted research grants and lecture fee from Pfizer, JOJ: Grants and lecture fees from Pfizer, IPSEN and Novartis, CF: Lecture fee from Bristol Myers Squibb.

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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