"Time to Diagnosis in Cushing's Syndrome: A Meta-Analysis Based on 5367 Patients."

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ABSTRACT

CONTEXT: Signs and symptoms of Cushing's syndrome (CS) overlap with common diseases, such as the metabolic syndrome, obesity, osteoporosis, and depression. Therefore, it can take years to finally diagnose CS, although early diagnosis is important for prevention of complications. OBJECTIVE: The aim of this study was to assess the time span between first symptoms and diagnosis of CS in different populations to identify factors associated with an early diagnosis. DATA SOURCES: A systematic literature search via PubMed was performed to identify studies reporting on time to diagnosis in CS. In addition, unpublished data from patients of our tertiary care center and 4 other centers were included. STUDY SELECTION: Clinical studies reporting on the time to diagnosis of CS were eligible. Corresponding authors were contacted to obtain additional information relevant to the research question. DATA EXTRACTION: Data were extracted from the text of the retrieved articles and from additional information provided by authors contacted successfully. From initially 3326 screened studies 44 were included. DATA SYNTHESIS: Mean time to diagnosis for patients with CS was 34 months (ectopic CS: 14 months; adrenal CS: 30 months; and pituitary CS: 38 months; P < .001). No difference was found for gender, age (<18 and ≥18 years), and year of diagnosis (before and after 2000). Patients with pituitary CS had a longer time to diagnosis in Germany than elsewhere. CONCLUSIONS: Time to diagnosis differs for subtypes of CS but not for gender and age. Time to diagnosis remains to be long and requires to

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Time to diagnosis in Cushing's syndrome: A meta-analysis based on 5367 patients

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Precis: A systematic literature and meta-analysis was performed to assess the time to diagnosis in Cushing's syndrome (CS). Significant differences for different subtypes of Cushing's syndrome were found.

Declaration of interest: The authors have nothing to disclose.

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Abstract

Context: Signs and symptoms of Cushing's syndrome (CS) overlap with common diseases, such as the metabolic syndrome, obesity, osteoporosis, and depression. Therefore, it can take years to finally diagnose CS, though early diagnosis is important for prevention of complications.

Objective: The aim of this study was to assess the time span between first symptoms and diagnosis of CS in different populations in order to identify factors associated with an early diagnosis.

Data Sources: A systematic literature search via PubMed was performed to identify studies reporting on time to diagnosis in CS. In addition, unpublished data from patients of our tertiary care center and 4 other centers were included.

Study Selection: Clinical studies reporting on the time to diagnosis of CS were eligible. Corresponding authors were contacted to obtain additional information relevant to the research question.

Data Extraction: Data were extracted from the text of the retrieved articles and from additional information provided by authors contacted successfully. From initially 3326 screened studies 44 were included.

Data Synthesis: Mean time to diagnosis for patients with CS was 34 months (ectopic CS: 14 months; adrenal CS: 30 months; and pituitary CS: 38 months; $p<0.001$). No difference was found for gender, age (</≥ 18 years), and year of diagnosis (before/after 2000). Patients with pituitary CS had a longer time to diagnosis in Germany than elsewhere.

Conclusions: Time to diagnosis differs for subtypes of CS but not for gender and age. Time to diagnosis remains to be long and requires to be improved.

Key words: Hypercortisolism; ACTH; cortisol; symptoms; meta-analysis

Outline

Cushing's syndrome (CS) is a rare, potentially life-threatening endocrine disease causing, among others, metabolic, psychiatric, musculoskeletal and cardiovascular comorbidities [1]. If left untreated it is associated with increased mortality, mainly due to cardiovascular and infectious complications, but even in appropriately treated CS mortality remains elevated [2]. CS is mostly ACTH dependent, the consequence of corticotroph pituitary adenoma or ectopic ACTH secretion from neuroendocrine tumors. Approximately 20% of cases are ACTH independent due to autonomous cortisol production from adrenal sources. Chronically elevated glucocorticoid concentrations cause the characteristic phenotype, such as weight gain, moon face, buffalo hump, muscle weakness, bruisability, skin atrophy, striae rubrae, menstrual irregularities, hirsutism, acne and co-morbidities like diabetes mellitus, hypertension, hypercholesterolemia and osteoporosis [3]. Due to the rareness of CS and because these symptoms overlap with other non CS conditions it can take many years to diagnose CS in a given patient [4]. The recent obesity 'epidemic' causes additional challenges to distinguish the few patients with true CS from those with a metabolic syndrome. As the duration of hypercortisolism appears to be the most relevant determinant for the degree of morbidity and preterm mortality, it is important to establish the diagnosis as early as possible [5]. Also, there is increasing evidence that restitution of symptoms and body changes after surgery depends on the duration of CS [6]. Duration of CS is an important factor influencing patient's recovery after successful surgery, especially regarding psychiatric morbidity [7], which coincides with changes in brain structure and function sustained during exposure to glucocorticoid excess [8]. We hypothesized, that the time span from first symptoms to final diagnosis of CS could have changed to the better over time. This could be due to either

improved biochemical screening tools for CS or also increasing awareness for rare diseases [9]. The aim of this study was to assess the time between first symptoms and diagnosis of CS in different populations and geographic backgrounds and from different decades by performing a systematic literature review and meta-analysis including additional results from the German Cushing's Registry. By that we wanted to identify factors, which are associated with early or late diagnosis.

METHODS and PATIENTS

Study selection

We performed a systematic literature search in PubMed database and Cochrane library according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines [10]. We used the term "Cushing's syndrome, Cushing syndrome, Cushing's disease, Cushing disease, pituitary ACTH hypersecretion" in the title or abstract to identify published articles reporting on Cushing's syndrome/disease in general. The literature search was performed in the last week of July 2018.

Inclusion and exclusion criteria

Studies were eligible for analysis, when data reporting on time to diagnosis was available as mean time +/- standard deviation. Reviews, case reports, guidelines, non-English literature and non-human studies were excluded.

Data extraction

Abstracts were screened carefully by one of the authors (GR) for clinical / patient-based studies. If this was the case, the full-text manuscript was screened for content reporting on time to diagnosis in CS. To obtain data on mean time +/- standard deviation for all studies, we contacted the respective corresponding authors of the

studies to retrieve missing data. Furthermore, we asked authors to perform additional analysis of their data for different subtypes and gender (if available and possible). Authors of studies published before 2000 were not contacted because of a decreased likelihood to contact successfully.

Munich cohort

We analyzed the data of 172 patients (140 women and 32 men) with all subtypes of CS diagnosed and followed-up at Ludwig-Maximilian-University hospital tertiary care center between 1986 and 2018. Of all patients, 122 had pituitary CS (103 patients diagnosed after 2000), 18 ectopic CS and 32 adrenal CS. The study was performed accordingly to the Declaration of Helsinki. Written consent was given by all study participants.

Definition of the time to diagnosis (onset between first symptom and diagnosis of CS/diagnostic delay)

As in most studies this information was reported rather as a side information, the exact definitions of how the first symptom was defined was mostly not available. In studies with available definition on the first symptom, in general two different methods were used: either retrospective definition by the patient alone (e.g. in a questionnaire) or by defining the first symptoms in a clinical assessment by an endocrinologists.

Definition of variables

We analyzed subtype of CS (pituitary, ectopic and adrenal (excluding adrenal carcinoma, primary bilateral macronodular adrenal hyperplasia and primary pigmented nodular adrenocortical disease)), sex (female, male), age (children and teenagers <18 years, adults ≥18 years), year of publication (before and after the year

2000). Analysis of different geographic regions was performed for countries with at least four studies available. The analysis for age, year of publication and geographic regions was done only in patients with pituitary CS due to the imbalance in the number of studies for different subtypes.

Statistical analysis

For statistical analysis of the Munich cohort IBM SPSS Statistics (version 21.0, IBM North America) was used. Metric variables are reported as mean ± standard deviation. Due to the low sample number non-parametric tests were used: Mann-Whitney-U test for two unpaired groups and the Kruskal-Wallis test with subsequent Post-hoc analysis for more than two unpaired groups. P-values ≤0.05 were considered statistically significant.

For the meta-analysis forest plots were generated to show mean time to diagnosis along with 95% confidence intervals (CI) for the different studies. To combine data from different studies for meta-analysis, random-effects models were fitted with inverse variance weighting. Mixed-effects models were used to investigate potential effects of different moderators like subtype of CS on time to diagnosis. P-values ≤0.05 were considered statistically significant. Statistical analysis was performed using the rma (robust multi-array average) and forest functions of the package metafor (version 2.0) with R version 3.5.0 (www.r-project.org).

RESULTS

Time to diagnosis in the Munich cohort

Time to diagnosis in the Munich cohort was in total 48 +/- 51 months. Considering the differential diagnosis, time to diagnosis in patients with adrenal CS was 50 +/- 48 months, with ectopic CS 34 +/- 52 months and with pituitary CS 49 +/- 52 months

(p=0.022). Post-hoc analysis showed a significant difference for the mean time to diagnosis for ectopic and adrenal CS (p=0.039, ectopic and pituitary (p=0,024) and a non-significant difference for adrenal and pituitary CS (p=1). Time to diagnosis in women with CS was 47 +/- 49 months, in men with CS 53 +/- 61 months (p=0.892). Time to diagnosis in 103 patients with pituitary CS diagnosed after 2000 was 52 +/- 53 months, in 19 patients with pituitary CS diagnosed before 2000 38 +/- 47 months (p=0.121). Data is given in mean +/- SD.

Included studies

We identified a total of 3325 studies. 71 of these studies contained information on time to diagnosis/duration of symptoms in CS. 6 studies were removed due to overlapping or identical patient cohorts. 34 studies presented data as mean time +/- standard deviation. 11 lead authors of these already eligible studies were contacted to get additional information (e.g. gender/subtype-related data). The other 31 studies expressed data not as mean time +/- standard deviation (e.g. median and range or other) and were therefore not eligible. 6 of them were published before the year 2000. We contacted 25 lead authors of these initially not eligible studies to obtain data presented as mean time +/- standard deviation. Of all 36 contacted authors, 13 did not respond, 6 responded but could not provide data, and 17 provided additional data. Four of these 17 authors provided us with unpublished data of 1336 patients from their centers (Marco Losa from San Raffaele, University Vita-Salute, Milan, Italy; Atanaska Elenkova from Medical University, Sofia, Bulgaria, Márcio Carlos Machado from Universidade de São Paulo, Brasil; Felicia Alexandra Hanzu from Hospital Clinic Barcelona, Spain).

In total, data from 44 studies (including our patient cohort) collected between 1969 and 2018 and containing appropriate data on time to diagnosis of 5367 patients were analyzed in this meta-analysis. Studies were heterogeneous regarding subtype of CS, gender, age and time of recruitment (Table 1; Figure 1).

Time to diagnosis according to subtype

Meta-analysis of all included studies showed a mean time to diagnosis of 34 months (95% CI 30-38) without stratifying for subtypes, gender, age, recruitment time and geographical background (Figure 1 in [11]). Among the studies stratifying for CS subtypes, mean time to diagnosis was 30 months (95% CI 24-36) in adrenal CS, 14 months (95% CI 11-17) in ectopic CS and 38 months (95% CI 33-43) in pituitary CS ($p<0.001$). Post-hoc analysis showed a significant difference for the mean time to diagnosis for ectopic and adrenal CS ($p=0.0025$), ectopic and pituitary ($p<0.0001$) and a non-significant trend for adrenal and pituitary CS ($p=0.098$) (Figure 2). The majority of patients with ectopic CS had bronchial or thymic carcinoids, some gastroenteropancreatic neuroendocrine tumors. Small cell lung carcinomas (SCLC) were present in 0-27% of the series, with the largest series compromising 110 of which 4% had SCLC.

Impact of sex

Overall, mean time to diagnosis in female patients with CS (all subtypes) was 33 months (95% CI 27-38) compared to 31 months (95% CI 26-36) in males ($p=0.66$) (Figure 2 in [11]), with similar distribution according to subtypes in both sexes.

Time to diagnosis according to age in pituitary CS

We hypothesized that mean time to diagnosis might be shorter in pediatric CD (age below 18) than in adults because of the typical growth retardation observed in the

former. However, in the nine pediatric studies mean time was 33 months (95% CI 29-38) versus 39 months (95% CI 33-45) in adult patients (p=0.37) (Figure 3 in [11]).

Impact of the year of publication on the time to diagnosis in pituitary CS

We further wondered whether the publication year of the study might have impact on time to diagnosis. Based on the assumption that secular trends in disease awareness, improved diagnostic tools and phenotypic presentation might influence the speed in identifying CS we chose the year 2000 as a cut-off. Surprisingly, studies published before 2000 had an identical latency (37 months, 95% CI 29-46) than studies published after 2000 (37 months, 95% CI 31-44) (p=0.92) (Figure 4 in [11]).

Time to diagnosis in pituitary CS according to geographic regions

Due to the fact that studies from all over the world were included, we wondered whether differences in the mean time to diagnosis in the largest subgroup of patients with pituitary CS could be identified. Countries with at least 4 studies available were Germany, Italy, United Kingdom (UK) and the United States of America (USA).

Mean time to diagnosis was 34 months (95% CI 29-40) for USA, 35 months (95% CI 26-45) for Italy, 39 months (95% CI 27-51) for UK and 56 months (95% CI 43-68) for Germany (p=0.02). Post-hoc analysis showed significant differences for the mean time to diagnosis between Germany and USA (0.0038), Italy (p=0.0052) and UK (p=0.039) and non-significant differences for other comparison (Figure 3; Table 2).

DISCUSSION

We report here the meta-analysis of the time to diagnosis from 44 studies, to which our own unpublished series was added. The results of our own cohort is in line with the results after statistical analysis of all the pooled studies.

We herein demonstrate that the mean time to diagnosis of CS in general is 34 months. Patients with ectopic CS had a significantly shorter time to diagnosis than patients with adrenal and pituitary CS. Patients with adrenal CS have a trend to shorter time to diagnosis than patients with pituitary CS without reaching statistical significance. It seems reasonable to speculate that ectopic CS due to aggressive ACTH-producing tumors is associated with a more severe clinical phenotype developing much more rapidly and causing more life-threatening complications (including severe hypokalemia and hyperglycemia)[12], even though only a minority of patients in our meta-analysis had small cell lung cancer, an entity with a particular aggressive clinical phenotype.

The non-significant difference in the time to diagnosis between adrenal and pituitary CS is not fully understood. This finding contrasts with the significantly faster recovery of adrenal insufficiency in pituitary CS compared to adrenal CS [13], which would rather imply a longer duration of hypercortisolism and time to diagnosis in adrenal CS. The more complicated biochemical testing and tumor localization (e.g. sinus petrosus catheterization) in pituitary CS compared to the usually rather straight forward diagnostic work-up in adrenal CS might be a possible explanation to this fact.

On the other hand the longer exposure to high glucocorticoid levels in pituitary CS could contribute to the fact, that patients with pituitary CS have significantly lower disease-specific quality of life (CushingQoL) scores compared to patients with adrenal CS [14]. Together with the risk of recurrence and pituitary deficiency it can explain the increased long-term emotional instability observed in this subtype. This underscores the necessity of careful screening for psychiatric comorbidities in every Cushing patient. In addition, psychological counseling by health care professionals should be part of every Cushing clinic [15].

Gender does not seem to have a relevant impact on the time to diagnosis. It confirms the results of Kreitschmann-Andermahr and colleagues, who did not find a difference in the overall diagnostic delay between females and males. These authors, however, showed that females contacted physicians earlier than males whereas in male patients the physician was the one recognizing symptoms of CS [16].

Surprisingly, we did not identify significant differences in time to diagnosis according to age in pediatric CD versus adult CD (33 versus 39 months, p=0.37). This is unexpected since hypercortisolism in children comes with severe growth retardation, a feature, which is difficult to overlook. In addition, children with CD gain weight, which makes CD the only condition in pediatrics, where curves for height and weight on the growth chart deviate in different directions.

In addition, we did not identify a trend towards earlier diagnosis in more recently treated patients in comparison to studies published before the year 2000. We explain this by a higher prevalence of advanced obesity nowadays, which besides the obvious weight gain is the condition with the most overlapping symptoms with CS (moon facies, diabetes mellitus, hypertension, menstrual irregularities). In our experience, patients with confirmed CS in fact have a lower BMI compared to patients with suspected, but biochemically not confirmed CS (~30kg/m^2 vs. 33 kg/m^2; unpublished data). Therefore, it is good clinical practice that primarily not obesity, but the presence of unusual features for age (such as osteoporosis or hypertension), multiple progressive features, and signs and symptoms of protein catabolism (i.e. myopathy) should rise the suspicion for CS [3,4]. A diagnostic score of clinical variables predicting diagnosis of CS could be useful in this clinical situation [17].

Novel diagnostic approaches such as automatic face recognition using computerized techniques were thought to be useful in early recognition of body changes, but have lately turned out to be of limited value [18].

Strengths and limitations: We were able to include a large body of studies and obtain additional data for those studies in which the data format was not appropriate. This makes this study the largest ever published on this subject. Most of the limitations are inherent to this type of meta-analysis. A relevant limitation is the fact, that in most of the included publications the information about time to diagnosis / diagnostic delay was not the primary endpoint of the study. In such a scenario, there is almost always a lack of a definition of how the first symptom was defined. Moreover, when it was described, different methods and definitions were used to assess the first symptoms: Some authors used questionnaires in order to retrospectively assess first symptoms, whereas other authors defined first symptom related to CS by clinical assessment by an endocrinologist. As cognitive deficits and emotional disturbances may be present in patients with CS their definitions might not be accurate. In summary, different definitions and perspectives (patients/physicians) were used to assess the time from first symptom to final diagnosis, which might have led to rather strict (with a shorter time to diagnosis) or permissive (longer time to diagnosis) definitions. We nevertheless think that this is applying to all studies and did not change over time. In addition, as estimates for time to diagnosis were not the primary endpoints of the studies, publication bias seems rather unlikely for this meta-analysis.

Different definitions of first symptom of CS might be also an explanation why time to diagnosis varied in different geographic regions. For example, the estimation of the first symptom related to CS in 3 of the 4 studies conducted in Germany were made

by the patients themselves, which could explain the rather long time to diagnosis due to the cognitive and emotional impairment.

In summary, the main finding of our study is twofold: first, there is a clear difference in the time to diagnosis depending on the subtype of CS, being shortest in ectopic CS; second, despite a multitude of improvements in the care of patients, we did not detect secular trends towards earlier diagnosis in pediatric patients or patients with more recent diagnosis. Although there may be methodical limitations to our meta-analysis, this is clearly disappointing from both patients and physicians perspectives.

It remains unclear how to shorten the time to diagnosis in CS. Patients with rare diseases in general and CS in particular face the problem of a delayed diagnosis. At the same time, CS is often wrongly suspected in cohorts with a low pre-test probability (such as obesity).

On the other hand, published data and our own experience have shown that the prevalence of Cushing's syndrome is significantly higher among patients with uncontrolled diabetes mellitus and arterial hypertension, adrenal incidentalomas and osteoporosis [4]. Consequently, these common diseases, especially when occurring together, may be subject to a preselection in the process of targeted search for this rare pathology especially in young patients.

In our opinion it seems unlikely to educate non-endocrinologists on symptoms of CS. More effective measures could be to educate non-endocrine-specialists and general practitioners in pattern recognition: unusual presentations and dynamic developments (multiple progressive features especially of catabolic effects from hypercortisolism such as myopathy and skin atrophy) apply to many rare diseases and might be better discriminants for diagnosis.

In addition, there is a high need for simple and effective biochemical screening approaches [19]. Current tests have significant sensitivity and specificity issues. Recently we showed that a seven steroid finger print from baseline plasma samples could nicely separate CS from rule-out CS. This study stokes the hope, that such a test (if validated) could be superior to currently used standard Cushing screening tests [20].

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Tables:

Table 1: Characteristics of the 44 included studies. Adr: Adrenal. Ect: Ectopic. N.a: not avalaible. Pit: Pituitary.

Table 2: Post-hoc analysis with p-values for the time to diagnosis in pituitary CS according to geographic regions.

Reference	Year published	Study type	Period of time	Number of patients	Subtype of CS (Number of patients with subtype)	Country	Adults/ children	Re-Analysis
Welbourn[21]	1969	Retrospective, double-center	1953-1968	45	Adrenal: 8; Pituitary: 37	UK	Adults	No
McArthur[22]	1979	Retrospective, single center	1947-1977	27	Pituitary	USA	Children	No
Bertagna[23]	1981	Retrospective, single center	1951-1978	22	Adrenal	USA	Adults	No
Hotta[24]	1985	Single-Center	N.a.	8	Adrenal: 3; Pituitary: 5	Japan	Adults	No
Sandler[25]	1987	Retrospective, single center	1959-1982	51	Pituitary	UK	Adults	No
Magiakou[26]	1994	Retrospective, single center	After 1954	10	Ectopic: 1; Pituitary 9	USA	Children	No
Bochicchio[27]	1995	Retrospective, Multi-Center	1975-1990	668	Pituitary	Europe	Adults	No
Magiakou[28]	1997	Single-Center	N.a.	31	All (Adr: 5; Ect: 3; Pit: 23)	USA	Children	No
Massoud[29]	1997	Retrospective, single center	Since 1982	12	Pituitary	UK	Children	No
Robyn[30]	1997	Retrospective, single center	1976-1996	6	Pituitary	Australia	Children	No
Invitti[31]	1998	Retrospective, multicentric	Since 1978	393	All (Adr: 80; Ect: 25; Pit: 288)	Italy	Adults	No
Selvais[32]	1998	Retrospective, single center	1990-1996	21	Pituitary	Belgium	Adults	No
Flitsch[33]	2000	Prospective, Single-Center	N.a.	19	Pituitary	Germany	Adults	No
Vella[34]	2001	Retrospective, single center	1996-2001	16	Ectopic: 4; Pituitary: 12	USA	Adults	No
Faggiano[35]	2003	Prospective, single-center	N.a.	25	Pituitary	Italy	Adults	No
Giraldi[36]	2003	Retrospective, multicentric	N.a.	280	Pituitary	Italy	Adults	No
Johansson[37]	2004	Retrospective, single center	Since 1964	15	Pituitary	Sweden	Adults	No
Salgado[38]	2006	Retrospective, single-center	1975-2005	25	Ectopic	Brazil	Adults	No
Bhansali[39]	2007	Retrospective,	1985-	12	Ectopic	India	Adults	No

		single-center	2006					
Barahona[40]	2009	Retrospective, single-center	Since 1982	55	Adrenal: 11; Pituitary: 44)	Spain	Adults	Yes
Oliveira[41]	2010	Retrospective, single-center	1982-2006	15	Pituitary	Brazil	Children	Yes
Bolland[42]	2011	Retrospective, multicentric	1960-2005	253	All (Adr: 45; Ect: 15; Pit: 167; 26 with missing data)	New Zealand	Adults	Yes
Psaras[43]	2011	Retrospective, single-center	1998-2007	33	Pituitary	Germany	Adults	No
Valassi[44]	2011	Retrospective, from 2008 prospective, multicentric	Since 2000	420	All (Adr: 107; Ect: 22; Pit: 291)	Europe	Adults	Yes
Lodish[45]	2012	Retrospective, Single-center	1997-2007	57	Pituitary	USA	Children	No
Lonser[46]	2013	Prospective, single-center	1982-2010	200	Pituitary	USA	Children	No
Van der Werff[47]	2014	Single-center	N.a.	22	Pituitary	Netherlands	Adults	Yes
Zilio[48]	2014	Retrospective, single-center	2002-2010	84	Pituitary	Italy	Adults	Yes
Aranda[49]	2015 (and unpublished data)	Retrospective, Single-center	1974-2011	67	All (Adr: 8; Ect: 2; Pit: 57)	Spain	Adults	Yes
Ghazi[50]	2015	Retrospective, single-center	Since 1985	15	Ectopic	Iran	Adults	No
Kreitschmann-Andermahr[16]	2015	Retrospective, multicentric	Since 2005	176	Pituitary	Germany	Adults	Yes
Zielinski[51]	2015	Retrospective, single-center	2000-2005	10	Pituitary	Poland	Adults	No
Geer[52]	2016	Prospective, Single-center	N.a.	30	Pituitary	USA	Adults	No
Machado[53]	2016 (and unpublished data)	Retrospective, single-center	1990-2014	421	Ectopic: 49; Pituitary: 37	Brazil	Adults	Yes
Shapiro[54]	2016	Retrospective, single-center	1982-2014	39	Pituitary	UK	Children	Yes
Bansal[55]	2017	Retrospective, single-center	1987-2015	230	Pituitary	India	Adults	Yes
Davi[56]	2017	Retrospective, multicentric	1986-2014	110	Ectopic	Italy	Adults	Yes
Johnston[57]	2017	Retrospective, single-center	2004-2013	101	Pituitary	USA	Adults	Yes
Sathyakumar[58]	2017	Retrospective	2006-2015	21	Ectopic	India	Adults	No

Brichard[59]	2018	Retrospective, single-center	1997-2017	71	Pituitary	Belgium	Adults	Yes
Dogansen[60]	2018	Retrospective, single-center	Since 2007	35	All (Adr: 15; Ect: 3; Pit: 17)	Turkey	Adults	Yes
Elenkova	Unpublished, contact based on [61]	Retrospective, single-center	1968-2018	520	All (Adr: 159; Ect: 13; Pit: 348)	Bulgaria	Adults	Yes
Losa	Unpublished, contact based on [62]	Retrospective, single-center	1990-2017	624	Pituitary	Italy	Adults	Yes
Rubinstein	Unpublished (own data)	Retrospective, single-center	1986-2018	172	All (Adr: 32; Ect: 18; Pit: 122)	Germany	Adults	

Table 2:

	Germany	Italy	UK	USA
Germany	X	0.0052	0.039	0.0038
Italy	0.0052	X	0.61	0.96
UK	0.039	0.61	X	0.57
USA	0.0038	0.96	0.57	X

Figures:

Figure 1: Study flow.

Figure 2: Mean time to diagnosis according to subtype (adrenal, ectopic, pituitary).

Figure 3: Mean time to diagnosis according to region in pituitary CS (Germany, Italy, UK, USA).

Figure 1:

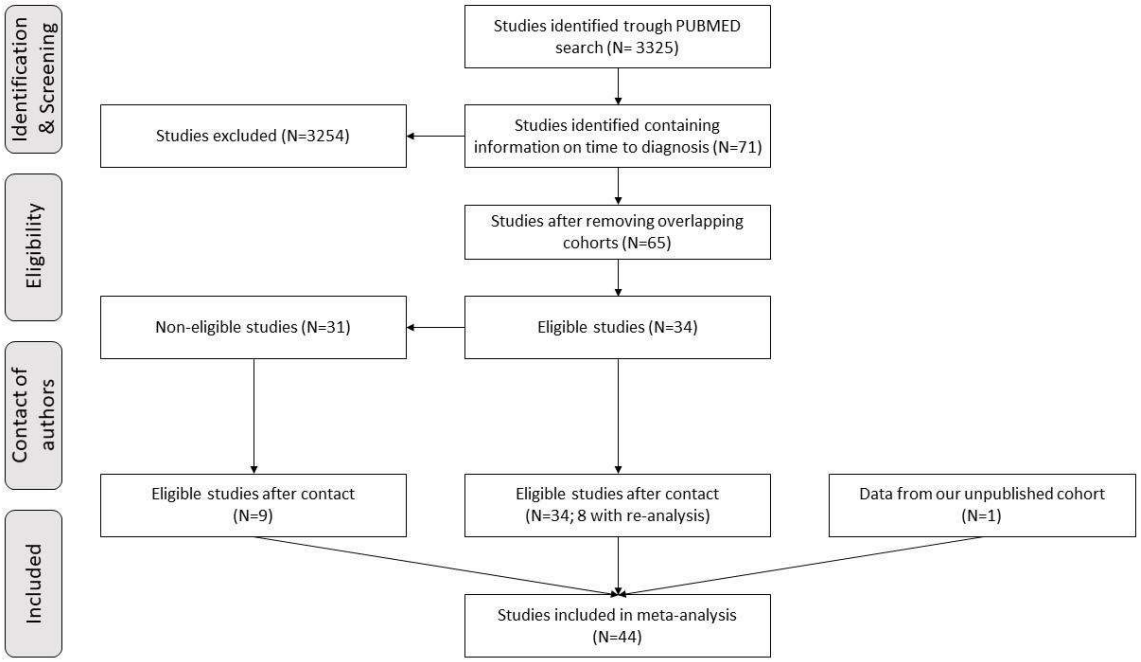

Figure 2:

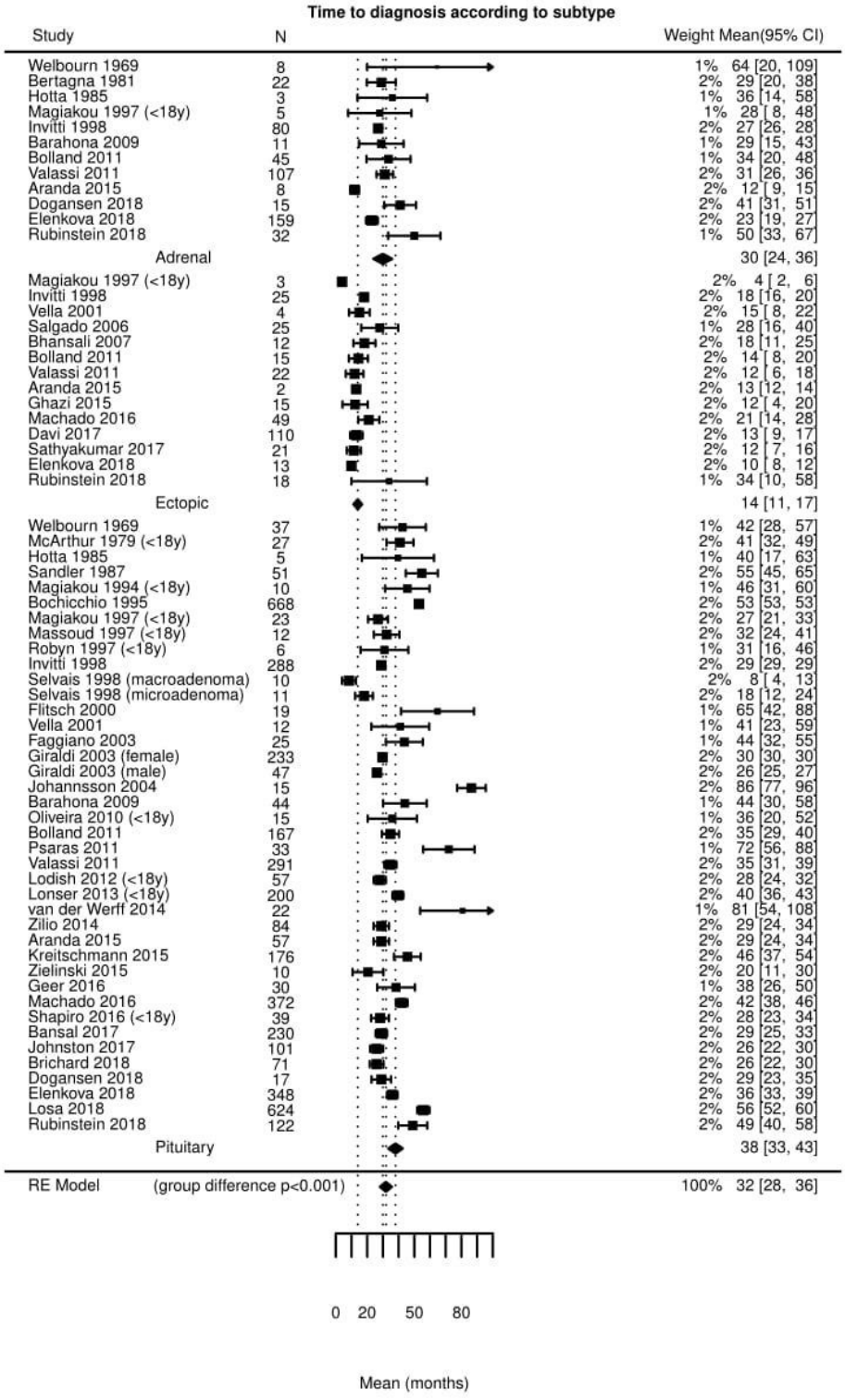

Figure 3: