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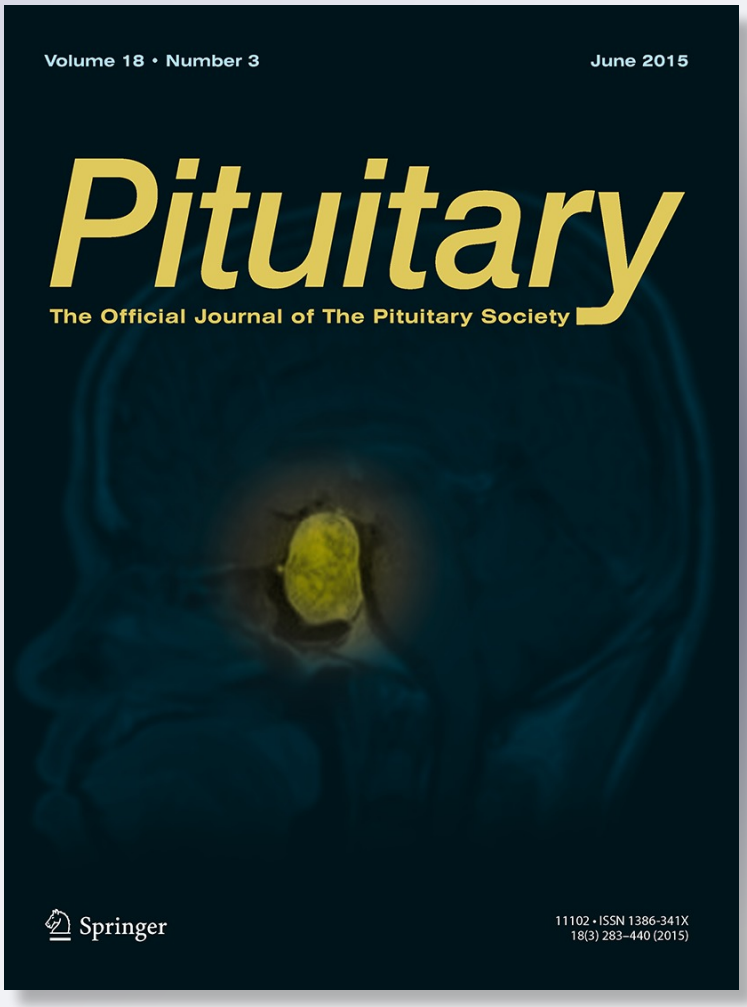

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Incidence of Cushing's syndrome and Cushing's disease in commercially-insured patients <65 years old in the United States

Michael S. Broder · Maureen P. Neary · Eunice Chang · Dasha Cherepanov · William H. Ludlam

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Abstract
Purpose To estimate the incidence of Cushing's syndrome (CS) and Cushing's disease (CD) in the US.
Methods MarketScan Commercial database 2007–2010 (age <65 years) was used. CS patients were defined with ≥2 claims of CS diagnosis, while CD patients were defined with CS plus a benign pituitary adenoma diagnosis or hypophysectomy in the same calendar year. Annual incidence was calculated by dividing the number of CS or CD cases by the total number of members with the same enrollment requirement during the calendar years.
Results CS incidence rates per million person-years were 48.6 in 2009 and 39.5 in 2010. The lowest rates of CS were in ≤17-year-olds and highest rates were in 35 to 44-year-olds. CD incidence rates were 7.6 in 2009 and 6.2 in 2010. The lowest rates of CD were in ≤17-year-olds and highest rates were in 18 to 24-year-olds. The rates varied by sex (2.3–2.7 in males, 9.8–12.1 in females). In females, lowest rates ranged 2.5–4.0 in ≤17-year-olds and highest 16.7–27.2 in 18–24 year olds. In males, there were too few cases to report estimates by age.
Conclusions In the first large US-based study, the annual incidence of CS in individuals <65 years old was nearly 49 cases per million, substantially higher than previous estimates, which were based primarily on European data. Using similar methods, we estimated the incidence of CD at nearly 8 cases per million US population. These estimates, if confirmed in other epidemiologic databases, represent a new data reference in these rare conditions.

Keywords Cushing's syndrome · Cushing's disease · Incidence · Population study · Insurance claims · Secondary data analysis

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Introduction

Cushing's syndrome (CS) is an uncommon endocrine disorder resulting from excessive exposure to glucocorticoids [1, 2]. When Cushing's syndrome is caused specifically by an adrenocorticotropic hormone (ACTH, also called corticotrophin) secreting pituitary tumor, the condition is termed Cushing's disease (CD) [3].

The diagnosis of CS may be missed initially because the condition can manifest with a variety of nonspecific clinical symptoms [4]. After CS has been identified, the diagnostic workup typically includes tests of pituitary and adrenal function [2]. CS in the presence of a pituitary neoplasm on imaging generally confirms the diagnosis of CD, although definitive diagnosis requires surgical excision [3]. Treatment usually involves transsphenoidal surgery to remove the neoplasm. Disease recurrence can be treated by repeat operation, radioablation, or medical treatment [2, 5].

The incidence (annual rate of newly identified cases) and the prevalence (proportion of the population having the condition at a given time) of CS and CD has not been well characterized, particularly in the US population. Several epidemiological studies were conducted in Europe, and estimates of CD incidence are typically reported to range from 1.2 to 2.4 cases per million annually [2, 3, 6–9]. In the United States, the incidence of CS is historically estimated

at 10–15 new cases per million annually, though Guaraldi et al. state that this figure is not supported by substantial published evidence [10]. However, CD is estimated to account for approximately 70 % of all cases of CS, occurring at a 3.5:1 female:male ratio [11]. Given the lack of up-to-date US data, this study sought to examine US health insurance claims in order to estimate the incidence of CS and CD.

Methods

Study design and data sources

We conducted a retrospective cross-sectional multiple cohort study to estimate the incidence of CS and CD, using data for 2007, 2008, 2009, and 2010 in the Thomson Reuters MarketScan® Commercial Claims and Encounters (Truven Health Analytics, Ann Arbor, MI) database. MarketScan is a Health Insurance Portability and Accountability Act-compliant commercial administrative claims database that contains de-identified adjudicated pharmacy claims (e.g., outpatient prescriptions) and medical claims (e.g., inpatient and outpatient services) submitted for payment by providers, healthcare facilities, and pharmacies, as well as member enrollment and benefit, patient, provider, and hospital demographic information. MarketScan contains claims data on approximately 16 million insured lives per year from all regions of the United States. Medicare plans are not included in the database; therefore, the analysis focused only on patients <65 years old.

Study population and study timeframe

CS and CD patients were identified in each calendar year (2007, 2008, 2009, and 2010) during the study timeframe (1/1/2007 to 12/31/2010). Patients with CS were defined as those with ≥2 claims of CS diagnosis (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code: 255.0) in the calendar year. We used a previously published strategy [12] to identify patients with CD since it has no ICD-9-CM code. CD patients were defined as those with a claim of CS and either benign pituitary adenoma diagnosis (ICD-9-CM: 227.3) or hypophysectomy (ICD-9-CM: 07.6x, Current Procedural Terminology [CPT]: 61546, 61548, 62165) in the calendar year.

Cohorts

There are known limitations of using claims data to estimate disease incidence—primarily the inability to know with certainty that the first diagnosis seen in the data represents that first clinical diagnosis of the condition [13]. To address this issue, we created multiple patient cohorts and conducted sensitivity analyses with them. For each condition, CS and CD, we identified 2 groups of patients. The first group, used in the main analysis, (which we called the 3-year continuous enrollment cohort) must have been enrolled for the calendar year in which their disease was first noted and the 2 prior years. During these 2 prior years they could not have had any evidence of disease (2 year disease-free period). The second group, used in the sensitivity analysis, (which we called the 2-year continuous enrollment cohort) had only 2 years of continuous enrollment: one in the year of diagnosis and one in the year before the diagnosis. Patients in the sensitivity analysis must have been enrolled for the calendar year in which their disease was first noted and the prior year, and during this prior 1 year they must have had no evidence of disease (1 year disease-free period) (Fig. 1).

For the main analysis, the diagnosis of CS or CD could have been made in 1 of the last 2 years (2009 or 2010) and still allow the identification of a 2 year disease-free period, as the study database spanned 5 years in total. For the sensitivity analysis, the diagnosis could have been made in 2008, 2009, or 2010. (Fig. 1). For each condition, this resulted in 5 distinct cohorts: 2 different 3-year continuous enrollment cohorts, with disease identification in either 2009 or 2010; and 3 different 2-year continuous enrollment cohorts, with disease identification in either 2008, 2009, or 2010.

Measures

Annual incidence rates were calculated by using the number of patients in each cohort as the numerator and the number of all continuously enrolled patients during the respective 2-year or 3-year timeframe as the denominator. Rates were calculated separately for each calendar year of disease identification as shown in Table 1.

Analyses

Annual incidence rates were calculated for both CS and CD patients for years 2009 and 2010 based in the main analyses and for years 2008, 2009, and 2010 for the sensitivity analyses. For each condition, overall rates combining all relevant years were reported. Rates were stratified by age and gender. Data transformations and statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC).

Results

Cushing's syndrome

In the main analysis, there were 522 new cases of CS identified in 2009 (out of 10,734,671 continuously enrolled

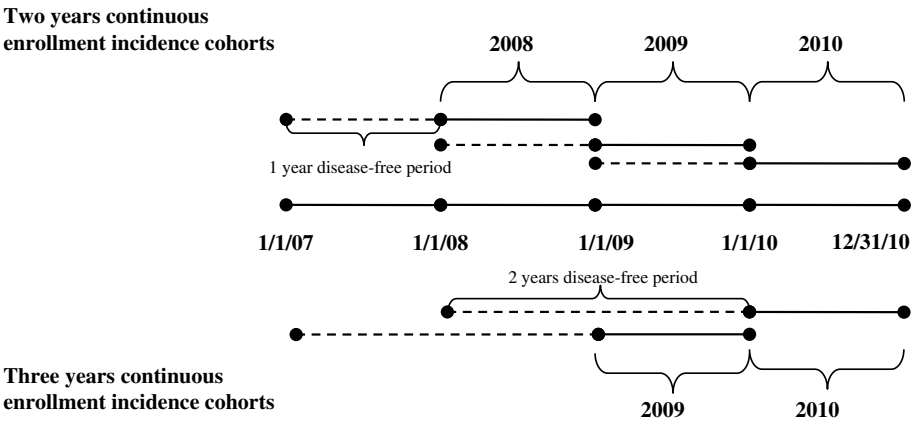

Fig. 1 Incidence cohort selection

Table 1 Disease incidence calculations

Main analysis (3 year continuous enrollment requirement; 2 year disease-free period):

(Number of patients meeting definition of incident CS[a] or CD[b] in 2009 or 2010)/(Number continuously enrolled in that year and 2 years prior)

Sensitivity analysis (2 year continuous enrollment requirement; 1 year disease-free period):

(Number of patients meeting definition of incident CS[a] or CD[b] in 2008, 2009, or 2010)/(Number continuously enrolled in that year and 1 year prior)

[a] ≥2 claims of Cushing's syndrome in the calendar year

[b] ≥1 claim of Cushing's syndrome in the calendar year and either benign pituitary adenoma or hypophysectomy

individuals) and 537 in 2010 (out of 13,593,774 continuously enrolled individuals), an annual incidence rate of 48.6 per million person-years (PMPY) in 2009 and 39.5 PMPY in 2010. Disease incidence was higher in women than men, with rates of 77.4 PMPY in 2009 and 61.5 PMPY in 2010 for women, compared to 17.2 PMPY and 15.6 PMPY for men. Incidence varied by age, with the highest rates in 35–44 year olds (65.8 PMPY in 2009 and 51.8 PMPY in 2010) and the lowest in those aged ≤17 years old (13.7 PMPY in 2009 and 12.9 PMPY in 2010). In women, the highest incidence rate was among 35–44 year-olds (111.2 PMPY in 2009 and 82.2 PMPY in 2010) while in men incidence was highest in 55–64 year-olds (25.4 and 26.1 PMPY) (Table 2).

In the sensitivity analysis, there were 641 patients identified as new cases of CS in 2008, 859 in 2009, and 830 in 2010. The incidence rates of CS were higher than those seen in the main analysis, ranging from 41.3 PMPY in 2010 to 46.7 in 2008. In women, the rates ranged from 64.9 to 72 PMPY compared to from 15.7 to 19.2 PMPY in men. The highest rates were observed in patients 35–44 years

Table 2 Cushing's syndrome incidence rates, main analysis (3 year continuous enrollment requirement, 2 year disease-free period)

Gender	Age, years	Cushing's syndrome incidence rate per million patient year (PMPY)			
		2009		2010	
		Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]	Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]
Female	≤17	18.4	23/1,250,367	16.9	27/1,596,557
	18–24	95.1	35/368,059	70.8	34/480,273
	25–34	80.3	46/572,713	70.9	54/761,546
	35–44	111.2	108/971,077	82.2	101/1,228,675
	45–54	93.4	123/1,316,216	73.0	118/1,616,544
	55–64	87.8	99/1,127,218	72.5	101/1,392,433
	All	**77.4**	**434/5,605,650**	**61.5**	**435/7,076,028**
Male	≤17	9.2	12/1,302,233	9.0	15/1,670,918
	18–24	10.9	4/365,929	14.7	7/477,567
	25–34	16.6	8/482,112	7.7	5/645,526
	35–44	14.1	12/851,493	17.5	19/1,087,041
	45–54	23.6	27/1,143,803	17.0	24/1,409,559
	55–64	25.4	25/983,451	26.1	32/1,227,135
	All	**17.2**	**88/5,129,021**	**15.7**	**102/6,517,746**
All	≤17	13.7	35/2,552,600	12.9	42/3,267,475
	18–24	53.1	39/733,988	42.8	41/957,840
	25–34	51.2	54/1,054,825	41.9	59/1,407,072
	35–44	65.8	120/1,822,570	51.8	120/2,315,716
	45–54	61.0	150/2,460,019	46.9	142/3,026,103
	55–64	58.7	124/2,110,669	50.8	133/2,619,568
	All	**48.6**	**522/ 10,734,671**	**39.5**	**537/ 13,593,774**

[a] Number of members with continuous enrollment in that year and 2 years prior

Table 3 Annual Cushing's syndrome incidence rates, sensitivity analysis (2 year continuous enrollment requirement; 1 year disease-free period)

Gender	Age, years	Cushing's syndrome incidence rate per million patient year (PMPY)					
		2008		2009		2010	
		Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]	Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]	Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]
Female	≤17	17.8	30/1,689,028	15.8	37/2,347,239	16.7	41/2,461,208
	18–24	99.9	49/490,260	87.0	61/701,317	74.1	56/755,674
	25–34	93.1	75/805,968	77.4	93/1,202,121	81.5	104/1,275,458
	35–44	102.9	129/1,254,179	96.5	168/1,741,154	86.5	157/1,816,083
	45–54	88.6	142/1,602,371	89.0	193/2,169,445	76.1	173/2,272,141
	55–64	68.7	89/1,295,370	82.1	142/1,728,767	78.8	147/1,866,492
	All	**72.0**	**514/7,137,176**	**70.2**	**694/9,890,043**	**64.9**	**678/10,447,056**
Male	≤17	9.7	17/1,759,663	9.0	22/2,454,103	8.2	21/2,575,186
	18–24	25.0	12/479,657	16.1	11/683,763	16.2	12/740,342
	25–34	14.4	10/692,925	16.4	17/1,035,771	11.0	12/1,091,478
	35–44	21.5	24/1,114,920	18.0	28/1,559,445	17.3	28/1,621,064
	45–54	17.1	24/1,404,927	25.1	48/1,911,914	18.6	37/1,989,130
	55–64	34.9	40/1,147,216	25.2	39/1,549,127	25.4	42/1,653,016
	All	**19.2**	**127/6,599,308**	**17.9**	**165/9,194,123**	**15.7**	**152/9,670,216**
All	≤17	13.6	47/3,448,691	12.3	59/4,801,342	12.3	62/5,036,394
	18–24	62.9	61/969,917	52.0	72/1,385,080	45.5	68/1,496,016
	25–34	56.7	85/1,498,893	49.2	110/2,237,892	49.0	116/2,366,936
	35–44	64.6	153/2,369,099	59.4	196/3,300,599	53.8	185/3,437,147
	45–54	55.2	166/3,007,298	59.0	241/4,081,359	49.3	210/4,261,271
	55–64	52.8	129/2,442,586	55.2	181/3,277,894	53.7	189/3,519,508
	All	**46.7**	**641/13,736,484**	**45.0**	**859/19,084,166**	**41.3**	**830/20,117,272**

[a] Number of members with full year enrollment in that year and the year before

old (ranging from 53.8 to 64.6) and the lowest in patients ≤17 years old (12.3–13.6 PMPY) (Table 3).

Cushing's disease

In the main analysis, there were 82 new cases of CD identified in 2009 and 84 in 2010. Incidence rates ranged from 6.2 to 7.6 PMPY. As in CS, the incidence was higher in women (ranging from 9.8 to 12.1 PMPY) than men (range 2.3–2.7 PMPY). Age-specific rates may be imprecise since patient counts in the various age groups were in the single digits (Table 4). In the sensitivity analysis there were 102 cases identified in 2008, 150 in 2009, and 126 in 2010. Incidence rates were similar to those in the main analysis, ranging from 6.3 to 7.9 PMPY (Table 5).

Discussion

Using a commercial healthcare claims database, we found that the incidence of CS in US patients <65 years of age was 39.5–48.6 per million patient years, and the incidence of CD was 6.2–7.6 PMPY. The CS figures are substantially higher than previous reports. However, the most commonly cited statistics were derived from two studies of European based populations from 20 to 40 years ago [7, 8]. Lindholm et al. [8] estimated CS incidence at 2.3 per million population per year. The study used data collected in Denmark, a country of approximately 5.5 million people, of whom 90 % are White and of Danish descent (www.denmark.de accessed 2-28-14), potentially limiting the relevance of the estimates to other countries. Etxabe and Vazquez [7] reported an annual Cushing's Disease incidence of 2.4 per million population per year. These results were based on data collected from a province of just over 1 million inhabitants in the Spanish Basque region, the residents of which form a highly distinct population, genetically dissimilar in many respects to other Europeans [14]. In addition to these potential genetic differences between the populations studied previously, the passage of time may make these prior estimates less accurate. Lindholm et al. [8] used data from 1985 to 1995, and Etxabe and Vazquez [7] from 1975 to 1992. Since that time, obesity and diabetes mellitus type 2 have developed

Table 4 Annual Cushing's disease incidence rates, main analysis (3 year continuous enrollment requirement, 2 year disease-free period)

Gender	Age, years	Cushing's disease incidence rate per million patient year (PMPY)			
		2009		2010	
		Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]	Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]
Female	≤17	4.0	5/1,250,367	2.5	4/1,596,557
	18–24	27.2	10/368,059	16.7	8/480,273
	25–34	24.4	14/572,713	11.8	9/761,546
	35–44	12.4	12/971,077	13.0	16/1,228,675
	45–54	12.2	16/1,316,216	14.2	23/1,616,544
	55–64	9.8	11/1,127,218	6.5	9/1,392,433
	All	**12.1**	**68/5,605,650**	**9.8**	**69/7,076,028**
Male	≤17	0.8	1/1,302,233	3.0	5/1,670,918
	18–24	8.2	3/365,929	2.1	1/477,567
	25–34	2.1	1/482,112	1.5	1/645,526
	35–44	2.3	2/851,493	2.8	3/1,087,041
	45–54	2.6	3/1,143,803	1.4	2/1,409,559
	55–64	4.1	4/983,451	2.4	3/1,227,135
	All	**2.7**	**14/5,129,021**	**2.3**	**15/6,517,746**
All	≤17	2.4	6/2,552,600	2.8	9/3,267,475
	18–24	17.7	13/733,988	9.4	9/957,840
	25–34	14.2	15/1,054,825	7.1	10/1,407,072
	35–44	7.7	14/1,822,570	8.2	19/2,315,716
	45–54	7.7	19/2,460,019	8.3	25/3,026,103
	55–64	7.1	15/2,110,669	4.6	12/2,619,568
	All	**7.6**	**82/10,734,671**	**6.2**	**84/13,593,774**

[a] Number of members with full year enrollment in that year and 2 years before

into major public health concerns in the US, and CS may occur in patients with these disorders at a higher rate than in the general population [15–17]. Etxabe and Vazquez [7] also found a rising incidence of CD over the years studied (increasing from 1.5 to 3.9 per million over the period studied), lending support to the need for estimates based on more recent data. More recently, Arnardóttir and Sigurjonsdóttir [6] reported overall incidence of CD in Iceland over the past 54 years (1955–2009) at 1.5 per million population per year, with higher incidence over the past 5 years (2.6 per million population per year). However, as with the other two studies, the study conducted in the small Icelandic nation may not be generalizable to the US population.

We found the incidence rate of CS in women was about three times that found in men and the incidence of CD was about four times that found in men. In addition, CS was most common in women aged 35–44, but in men aged 55–64. The significance of this finding is unknown as it has not been previously reported. Further research is warranted to examine potential pathophysiologic or demographic reasons for why CS appears at a younger age in women compared to men.

Interestingly, the number of new cases of CD per year represented less than 20 % of new cases of CS; Newell-Price et al. reported that CD represents 70 % of all cases of CS [1]. One likely explanation is that the 70 % figure cited by Newell-Price represents prevalence, while our calculations reflect incidence. High-prevalence, low-incidence figures are characteristic of low-mortality, chronic illnesses, such as CD. Another possible explanation is that a proportion of CD cases were not identified in our analysis because of their age, as the >65-year-old population was not included in our study. Finally, because CD does not have its own ICD-9-CM code, it is plausible that many cases of CD were not detected in this analysis.

Our results also indicated that in both CS and CD females outnumber males by approximately three- to four-fold, and these figures appear consistent with published literature [1]. The results also demonstrated that patients 17 years of age or younger had the lowest rates of either CS or CD, consistent with an epidemiological study of CD incidence in Denmark by Lindholm et al. [8]. We recognize that claims analyses such as the current study are at risk of overestimating incidence. Shorter disease-free periods have been demonstrated to significantly increase the estimated incidence of a condition [13]. This was reflected in our sensitivity analysis for CS, which found that the calculated incidence was higher with a shorter disease-free period (1 vs. 2 year in the primary analyses).

Major strengths of this study include the use of a well-published, large national claims database to calculate incidence, and the use of US-specific data. Results from this type of epidemiological study are more generalizable than estimates derived from single-institution studies or case series. We used an accepted ICD-9-CM code to identify CS patients and previously published definitions to isolate cases that would be most consistent with CD [12]. We also used rigorous methodology to produce best estimates of incidence by establishing adequately long enrollment periods. Notwithstanding these strengths, the study should be confirmed, using different data if possible, to increase the rigor of the findings.

This study does have several limitations. First, this study only examined patients under age 65, and thus the results may not be generalizable to elderly populations. In addition, the age limitation likely excluded cases of CD that contributed to the low incidence of CD in this study. Next, we used a database that lacks granular clinical information that could permit diagnostic confirmation. In particular, CD

Table 5 Annual Cushing's disease incidence rate, sensitivity analysis (2 year continuous enrollment requirement; 1 year disease-free period)

Gender	Age, years	Cushing's disease incidence rate per million patient year (PMPY)					
		2008		2009		2010	
		Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]	Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]	Rate PMPY	No. of patients in cohort/No. of continuously enrolled[a]
Female	≤17	3.0	5/1,689,028	3.4	8/2,347,239	1.6	4/2,461,208
	18–24	10.2	5/490,260	20.0	14/701,317	18.5	14/755,674
	25–34	21.1	17/805,968	19.1	23/1,202,121	12.5	16/1,275,458
	35–44	11.2	14/1,254,179	15.5	27/1,741,154	13.8	25/1,816,083
	45–54	17.5	28/1,602,371	12.4	27/2,169,445	14.5	33/2,272,141
	55–64	10.0	13/1,295,370	11.6	20/1,728,767	8.0	15/1,866,492
	All	**11.5**	**82/7,137,176**	**12.0**	**119/9,890,043**	**10.2**	**107/10,447,056**
Male	≤17	0.6	1/1,759,663	0.8	2/2,454,103	2.3	6/2,575,186
	18–24	12.5	6/479,657	7.3	5/683,763	1.4	1/740,342
	25–34	0.0	0/692,925	1.0	1/1,035,771	1.8	2/1,091,478
	35–44	3.6	4/1,114,920	5.8	9/1,559,445	1.9	3/1,621,064
	45–54	1.4	2/1,404,927	3.7	7/1,911,914	1.5	3/1,989,130
	55–64	6.1	7/1,147,216	4.5	7/1,549,127	2.4	4/1,653,016
	All	**3.0**	**20/6,599,308**	**3.4**	**31/9,194,123**	**2.0**	**19/9,670,216**
All	≤17	1.7	6/3,448,691	2.1	10/4,801,342	2.0	10/5,036,394
	18–24	11.3	11/969,917	13.7	19/1,385,080	10.0	15/1,496,016
	25–34	11.3	17/1,498,893	10.7	24/2,237,892	7.6	18/2,366,936
	35–44	7.6	18/2,369,099	10.9	36/3,300,599	8.1	28/3,437,147
	45–54	10.0	30/3,007,298	8.3	34/4,081,359	8.4	36/4,261,271
	55–64	8.2	20/2,442,586	8.2	27/3,277,894	5.4	19/3,519,508
	All	**7.4**	**102/13,736,484**	**7.9**	**150/19,084,166**	**6.3**	**126/20,117,272**

[a] Number of members with full year enrollment in that year and the year before

does not carry its own ICD-9-CM diagnostic code, and thus some cases may have been missed. Claims databases are characterized by limited duration of continuous patient enrollment and follow-up periods, and the structure of claims databases does not permit review of diagnoses that may have been established under different health plans either before or after the included period of observation [18]. Finally, our study only included patients with commercial insurance, and so the results may not necessarily represent the general CS or CD populations. The MarketScan database represents a convenience sample, despite its size and national distribution. Because the sample is non-random, it may be prone to selection biases and lack of generalizability to uninsured populations or patients covered by policies not included in MarketScan. We could not accurately estimate prevalence in this study since our identification algorithm used hypophysectomy as one of the possible inclusion criteria. Since surgery is most commonly performed shortly after diagnosis, the inclusion of this criterion in the algorithm means that we are likely identifying newly diagnosed (incident) patients only. Future research assessing prevalence of these conditions may be warranted.

Conclusion

Our study indicates that the annual incidence of CS in US individuals <65 years old may be as high as 49 cases per million, and the annual incidence of CD in the same population approaches 8 cases per million. Even our conservative estimates of 39.5 and 6.2 cases per million population are substantially higher than frequently cited prior estimates. However, those data were collected 20–40 years ago and were derived from two distinct and potentially non-representative populations: Danes and residents of the Basque region in Spain. Accurate epidemiologic data are critical to understanding the implications and burden of a condition to society. The current study fills a notable lack in the literature of these rare, and often difficult to diagnose, conditions. The methods we used to estimate incidence rates using commercial claims data may

be useful as a model for future research in variety of indications.

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