Journal of the Endocrine Society, 2023, **7**, 1–10
https://doi.org/10.1210/jendso/bvad050
Advance access publication 18 April 2023
Research Article

Recent Trends in Hypoparathyroidism-Related Inpatient and Emergency Department Admissions and Costs in the United States

Sanjiv Kaul,[1] Elvira O. Gosmanova,[2] Felicia Castriota,[3] Abby Hitchens,[4] Sean Candrilli,[4] Rohan Parikh,[4] Elizabeth Esterberg,[4] and Olulade Ayodele[5]

[1]Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR 97239, USA
[2]Albany Medical College, Albany, NY 12208, USA
[3]Takeda Pharmaceuticals U.S.A., Inc., Cambridge, MA 02139, USA
[4]RTI Health Solutions, Research Triangle Park, NC 27709, USA
[5]Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA 02420, USA

Correspondence: Olulade Ayodele, PhD, Takeda Pharmaceuticals U.S.A, Inc., 55 Hayden Ave, Lexington, MA 02420, USA. Email: Lade.Ayodele@takeda.com.

Abstract

Hypoparathyroidism (HypoPT) is a rare disease associated with high morbidity. Its economic impact is not well understood. This retrospective, cross-sectional study used data from the United States-based National Inpatient Sample and the Nationwide Emergency Department Sample from 2010 to 2018 to quantify overall trends in number, cost, charges, and length of stay (LOS) for inpatient hospitalizations and number and charges for emergency department (ED) visits for HypoPT-related and for non-HypoPT-related causes. Additionally, the study estimated the marginal effect of HypoPT on total inpatient hospitalization costs and LOS as well as ED visit charges. Over the observed period, a mean of 56.8–66.6 HypoPT-related hospitalizations and 14.6–19.5 HypoPT-related ED visits were recorded per 100 000 visits per year. Over this period, the rate of HypoPT-related inpatient hospitalizations and ED visits increased by 13.5% and 33.6%, respectively. The mean LOS for HypoPT-related hospitalizations was consistently higher than for non-HypoPT-related causes. Total annual HypoPT-related inpatient hospitalization costs increased by 33.6%, and ED visit charges increased by 96.3%. During the same period, the annual costs for non-HypoPT-related hospitalizations and charges for ED visits increased by 5.2% and 80.3%, respectively. In all years, HypoPT-related hospital encounters resulted in higher charges and costs per individual visit than non-HypoPT-related encounters. The marginal effect of HypoPT on inpatient hospitalization costs and LOS, and on ED charges, increased over the period of observation. This study demonstrated that HypoPT was associated with substantial and increasing healthcare utilization in the United States between 2010 and 2018.

Key Words: hypoparathyroidism, economic burden, emergency department, inpatient hospitalization

Hypoparathyroidism (HypoPT) is a rare disease with an estimated prevalence of 37 per 100 000 person-years in the United States [1, 2]. HypoPT is characterized by absent or insufficient levels of parathyroid hormone (PTH) caused most commonly by parathyroid gland injury or removal during neck surgery or by genetic or autoimmune diseases [3, 4]. A lack of PTH is associated with hypocalcemia and hyperphosphatemia [4]. Decreased serum calcium levels can cause neuromuscular manifestations such as muscle cramps, paresthesia, and seizures [4].

While HypoPT was traditionally thought of as a disorder of mineral homeostasis and bone remodeling, a paradigm shift has occurred in recent years, recognizing HypoPT as a systemic disease affecting the central nervous system [5], kidneys [6], and cardiovascular system [7]. The morbidity of HypoPT is reflected in the high number of hospitalizations among patients with the condition compared with healthy individuals, especially due to hypocalcemia, hypercalcemia, and cardiovascular diseases [8].

The yearly costs of medical care for patients with HypoPT in the United States have been estimated to be about 3 times those of age- and sex-matched controls [9]. Additionally, in the United Kingdom, a study using the Hospital Episode Statistics (HES) database highlighted the clinical and economic burden of chronic HypoPT on secondary care [10]. The study reported a significantly higher occurrence of comorbidities such as renal complications and infections among patients with chronic HypoPT (both post- and nonsurgical) than patients with hypothyroidism and those who underwent thyroid surgery but did not have HypoPT [10].

Short-term studies have reported the impact of HypoPT on the use of hospital facilities in the United States [11, 12]; however, there are limited real-world data on the long-term burden of HypoPT attributable to specific areas of the healthcare system. This study evaluated real-world data on HypoPT-related and non-HypoPT-related inpatient hospitalizations and emergency department (ED) visits in the United States between 2010 and 2018 from 2 large national databases.

Received: 20 December 2022. **Editorial Decision:** 9 April 2023. **Corrected and Typeset:** 4 May 2023

Methods

Objectives

This study aimed to report the rates of HypoPT-related and non-HypoPT-related inpatient hospitalizations and ED visits and to describe the demographic, clinical, and facility-level characteristics of these visits. In addition, the study aimed to estimate the marginal effect of HypoPT on costs, charges, and length of stay (LOS) related to inpatient stays and charges related to ED visits. Marginal effect refers to the association between a change in a regressor (ie, HypoPT) and a change in the response variable (eg, cost), while all other covariates are held constant.

Study Design

This was a retrospective, observational, cross-sectional study using existing deidentified and publicly available data from 2 large US Healthcare Cost and Utilization Project databases between 2010 and 2018. No formal calculation was carried out to establish the size of the study. The data presented represent individual hospitalization and ED visit events and not unique patients. It is possible the individual patients may have had multiple hospitalizations and/or ED visits throughout the study period.

Data Sources

Data were obtained from the National Inpatient Sample (NIS) and the Nationwide Emergency Department Sample (NEDS) databases, which document charge information for all patients. The NIS is the largest all-payer inpatient care database in the United States. It is sampled from the State Inpatient Database and covers more than 97% of the US population, containing data on more than 7 million inpatient hospitalizations each year [13]. The NEDS is the largest all-payer ED database in the United States. It is sampled from the State Inpatient Database and the State Emergency Department Database, which record information on ED visits that do and do not result in hospitalization, respectively, covering more than 30 million unweighted ED visits each year [14].

The NIS and the NEDS contain information about charges for inpatient hospitalizations and ED visits for all individuals, regardless of health insurance presence or payer type, such as commercial, private, and government payers. The databases contain clinical and resource use information in a typical discharge abstract, including details of primary and secondary diagnoses and procedures, as well as LOS (NIS only). Diagnoses and procedures were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes before and after October 1, 2015, respectively. The NIS and the NEDS contain information about patient demographics, including age, sex, race, and median household income for the patients' reported ZIP code, as well as details about hospital characteristics, such as ownership, size, and location/teaching status (ie, rural, urban teaching, urban non-teaching). Financial data in the NIS and the NEDS are presented as charges that can be converted to costs through hospital-specific cost-to-charge ratios.

Survey sampling weights provided by the Healthcare Cost and Utilization Project were applied to data from these databases to produce nationally representative estimates of the number of inpatient hospitalizations and ED visits. These weights were computed by dividing the total number of discharges in the sampling universe for each stratum by the total number of discharges selected for inclusion in the stratum. The NIS strata are characterized by the following hospital characteristics: census division, rural/urban location, number of beds, teaching status, and hospital ownership. The NEDS strata are characterized by the following hospital characteristics: geographic region, teaching status, hospital ownership, rural/urban location, and ED trauma-level designation. The computed discharge weights are the same for all discharges in a given stratum. Each discharge weight, therefore, accounts for the number of discharges of the sample universe that the sampled discharge represents. Additional details on the sampling procedure and weights are described on the Agency for Healthcare Research and Quality website [13, 14].

For this study, the 9 most recent years (from 2010 to 2018 inclusive) of the NIS and the NEDS data available at the time of study initiation were used, allowing recent trends to be highlighted with respect to the approval of recombinant human PTH (1–84) in 2015 [15].

Identification of Events

The case selection approach was based on a previously published study [16] and reviewed by clinical experts in HypoPT. Primary and secondary ICD diagnosis codes were used to identify HypoPT-related inpatient hospitalizations and ED visits for inclusion in the study. Both ICD-9-CM and ICD-10-CM codes were used to identify relevant conditions in the 2015 data sets due to a change in the coding system from ICD-9-CM to ICD-10-CM in 2015. The diagnoses codes included: hypoparathyroidism [ICD-9-CM: 252.1; ICD-10-CM: E20.0 (idiopathic hypoparathyroidism), E20.8 (other hypoparathyroidism), E20.9 (hypoparathyroidism, unspecified)], postprocedural hypoparathyroidism (ICD-10-CM: E89.2), autoimmune polyglandular syndrome (ICD-9-CM: 258.1; ICD-10-CM: E31.0), DiGeorge's syndrome (ICD-9-CM: 279.11; ICD-10-CM: D82.1), and mitochondrial disorders associated with hypoparathyroidism (ICD-9-CM: 277.87; ICD-10-CM: E88.41, H49.8). Non-HypoPT-related inpatient hospitalizations and ED visits were characterized by the absence of HypoPT-associated diagnosis codes.

Hospital and Hospitalization Characteristics

Demographic, clinical, and facility-level characteristics of HypoPT-related and non-HypoPT-related inpatient hospitalizations and ED visits were reported. The number of HypoPT-related vs non-HypoPT-related inpatient hospitalizations and ED visits was evaluated. Total charges were calculated for both inpatient hospitalizations and ED visits, while total costs and LOS were analyzed for inpatient hospitalizations only. Charges represent the amount that hospitals billed for services, while costs represent the actual expenses incurred in the provision of hospital services including wages, supplies, and utility [17]. Total costs were calculated by multiplying total charge by a facility-specific cost-to-charge ratio included within the NIS database. All financial data were converted to 2020 US dollars using the medical care component of the consumer price index [18].

Statistical Methods

All study variables are presented separately for inpatient hospitalizations (NIS) and ED visits (NEDS) by year. Counts and

Table 1. Demographic, clinical, and facility-level characteristics of inpatient hospitalizations from the NIS database by year before and after switch from using ICD-9-CM codes to ICD-10-CM codes

	2010		2011		2012		2013		2014		2015		2016		2017		2018	
Characteristic	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related
Number of hospitalizations	**21 908**	**37 330 105**	**20 999**	**36 941 416**	**22 465**	**36 462 381**	**22 520**	**35 575 272**	**22 475**	**35 336 343**	**22 305**	**35 747 637**	**23 150**	**35 652 271**	**22 980**	**35 775 473**	**23 660**	**35 503 821**
Age, years, mean (SD)	43.7 (28.7)	48.2 (27.6)	46.6 (27.8)	49.4 (27.4)	43.6 (28.5)	48.6 (27.6)	42.8 (28.6)	48.7 (27.6)	42.6 (28.0)	48.6 (27.6)	44.4 (27.7)	48.8 (27.6)	48.9 (26.4)	49.0 (27.4)	49.2 (26.7)	49.6 (27.4)	49.1 (26.2)	49.9 (27.3)
Sex, female, %	63.9	57.5	63.2	57.9	62.7	57.7	61.4	57.4	63.1	57.3	63.3	57.0	63.2	56.7	65.2	56.4	65.8	56.1
Race, %																		
White	57.8	57.9	57.1	59.5	60.9	62.4	61.7	61.9	59.0	62.0	59.9	61.4	58.6	62.0	58.5	62.1	60.5	62.5
Black	16.0	14.1	15.5	13.5	14.1	13.9	13.2	13.9	14.1	14.0	15.2	14.5	17.2	14.4	17.5	14.7	16.7	14.7
Hispanic	11.5	10.9	11.0	11.3	11.6	11.2	12.4	11.5	12.7	11.4	12.0	11.5	13.0	11.6	12.2	12.0	13.1	12.4
Geographic region, %																		
Northeast	15.0	19.3	16.7	19.3	18.8	19.1	18.8	18.9	19.4	18.7	19.5	18.5	18.8	18.5	18.5	18.4	18.2	18.2
Midwest	23.7	22.7	27.8	22.7	23.9	22.6	24.8	22.5	24.4	22.5	23.8	22.3	23.8	22.2	25.3	22.3	23.7	22.3
South	40.5	38.2	37.9	38.3	35.8	38.7	35.5	38.8	35.1	39.0	36.5	39.4	37.8	39.3	36.2	39.3	39.0	39.5
West	20.8	19.8	17.6	19.8	21.5	19.6	20.8	19.8	21.1	19.8	20.3	19.8	19.6	20.0	20.0	20.1	19.1	20.1
Comorbidity, %																		
Hypertension	23.6	33.0	25.5	34.1	23.3	33.9	24.1	34.0	23.9	33.9	26.9	34.5	31.1	36.0	41.0	41.0	41.8	42.0
Cardiac dysrhythmias	16.7	14.6	18.4	15.9	17.9	16.0	19.5	16.5	19.5	16.9	20.4	17.3	20.6	16.9	20.5	17.7	22.0	18.5
Cerebrovascular disease	5.3	5.6	5.5	5.9	4.6	5.8	5.3	5.8	5.5	5.8	5.0	5.8	5.4	5.7	5.4	5.8	6.3	6.0
Coronary artery disease	15.1	17.3	17.8	18.3	15.6	18.1	15.5	17.9	14.9	17.7	15.2	17.8	18.7	17.6	17.8	18.0	16.7	18.4
Heart failure	14.7	10.9	16.0	11.7	14.6	11.5	14.8	11.9	14.6	12.3	15.2	12.9	17.4	13.3	18.8	14.2	18.3	15.1
Peripheral vascular disease	5.3	4.8	6.6	5.5	5.3	5.3	5.3	5.4	5.4	5.6	6.4	5.9	8.2	6.5	7.6	6.1	6.9	6.0
Chronic kidney disease	36.3	17.2	37.2	18.6	34.3	18.7	35.9	19.6	34.4	20.5	36.5	21.6	42.8	23.4	42.3	24.5	42.3	25.6
Hypercalciuria	7.0	1.0	6.7	1.1	8.7	1.2	8.1	1.3	8.0	1.3	6.5	1.0	0.0	0.0	0.0	0.0	0.0	0.0
Hypocalcemia	6.0	0.6	5.5	0.7	6.8	0.7	6.7	0.8	6.4	0.8	10.7	0.9	21.8	1.0	21.3	1.0	21.4	1.0
Osteoporosis	6.0	4.3	6.8	4.4	6.9	4.1	5.8	4.0	6.3	4.1	5.8	3.7	4.8	2.5	5.2	2.5	5.4	2.5
Type 2 diabetes	20.2	18.6	21.6	19.8	20.0	19.7	19.4	20.0	19.1	20.2	20.1	20.5	24.3	20.7	23.7	21.5	23.0	22.2
Hypothyroidism	26.3	8.7	30.3	9.6	28.5	9.7	30.1	9.9	29.4	10.1	33.3	10.3	34.9	10.5	34.6	10.7	35.1	10.9
Any acute HypoPT event	25.1	16.2	26.9	17.6	27.5	17.7	28.5	18.3	29.1	18.7	33.2	19.2	42.4	18.8	42.7	19.6	43.3	20.5

Abbreviations: HypoPT, hypoparathyroidism; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; NIS, National Inpatient Sample.

Table 2. Demographic, clinical, and facility-level characteristics of ED visits from the NEDS database by year before and after switch from using ICD-9-CM codes to ICD-10-CM codes

	2010		2011		2012		2013		2014		2015		2016		2017		2018	
Characteristic	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related	HypoPT-related	Non-HypoPT-related
Number of visits	18 791	128 951 573	19 784	131 028 821	20 256	134 378 923	21 163	134 847 852	22 462	137 785 439	24 225	143 445 445	25 070	144 817 672	26 447	144 788 356	27 916	143 426 514
Age, years, mean (SD)	41.8 (28.5)	38.8 (24.1)	39.9 (28.3)	38.8 (24.4)	40.5 (28.0)	38.7 (24.3)	41.4 (27.6)	39.5 (24.4)	42.6 (27.7)	39.8 (24.2)	45.0 (26.9)	40.0 (24.5)	48.3 (26.0)	39.9 (24.5)	49.4 (25.2)	41.2 (24.5)	48.0 (26.7)	40.7 (24.8)
Sex, female, %	67.6	55.4	61.7	55.4	64.4	55.4	65.1	55.5	62.4	55.5	65.0	55.2	65.9	55.5	66.1	55.4	65.1	55.3
Died in the hospital, %	1.4	0.4	1.3	0.4	1.1	0.4	0.7	0.4	1.1	0.4	1.3	0.4	0.9	0.3	1.3	0.4	1.1	0.4
Disposition of patient at discharge from ED, %																		
Routine	27.9	80.4	33.1	80.4	37.0	81.1	37.5	81.2	36.5	81.2	32.6	74.4	36.2	82.2	37.7	80.9	38.4	81.0
Transfer to short-term hospital	2.6	1.5	2.2	1.5	2.0	1.6	1.9	1.5	1.8	1.5	1.6	1.4	1.4	1.6	1.6	1.6	1.8	1.6
Admitted as an inpatient to this hospital	68.0	15.3	62.5	15.0	58.9	14.2	58.4	14.3	59.5	14.1	59.2	13.6	60.4	13.1	58.6	14.0	57.7	14.0
Comorbidity, %																		
Hypertension	21.9	17.6	21.0	18.0	21.0	17.9	21.2	18.6	23.7	19.3	25.1	20.1	30.6	20.7	38.0	23.4	37.6	23.2
Cardiac dysrhythmias	13.2	5.6	13.5	5.8	11.9	5.7	13.8	6.1	16.3	6.3	17.5	6.6	16.3	6.2	17.7	6.9	19.0	7.4
Cerebrovascular disease	3.9	1.6	3.9	1.6	3.5	1.5	3.4	1.6	4.8	1.7	3.8	1.6	4.0	1.5	3.9	1.7	5.2	1.7
Coronary artery disease	11.9	5.7	11.8	5.8	10.7	5.5	11.5	5.8	13.5	5.9	14.2	6.1	14.3	5.8	15.2	6.3	15.9	6.5
Heart failure	11.5	3.4	10.2	3.5	9.5	3.3	10.3	3.6	12.2	3.7	14.3	4.0	13.7	4.0	14.5	4.5	15.5	4.7
Peripheral vascular disease	4.1	1.3	3.3	1.4	3.2	1.3	3.4	1.5	5.3	1.7	5.8	1.7	6.7	1.8	6.0	1.8	5.6	1.8
Chronic kidney disease	29.2	5.4	28.0	5.5	27.0	5.5	27.3	5.9	30.8	6.1	32.4	6.6	36.2	7.0	36.8	7.9	36.7	8.2
Hypercalciuria	7.1	0.2	6.1	0.2	6.5	0.2	7.3	0.3	6.7	0.3	5.6	0.2	0.0	0.0	0.0	0.0	0.0	0.0
Hypocalcemia	6.0	0.1	5.2	0.1	5.5	0.1	5.6	0.1	5.2	0.2	9.9	0.2	19.6	0.2	19.0	0.2	16.9	0.2
Osteoporosis	5.3	1.3	4.7	1.3	4.0	1.3	4.3	1.3	5.2	1.4	5.1	1.2	4.4	0.7	4.5	0.8	4.6	0.8
Type 2 diabetes	17.1	9.1	15.8	9.2	17.9	9.2	16.7	9.6	19.9	10.1	19.1	10.5	21.4	10.5	21.7	11.4	22.7	11.5
Hypothyroidism	21.6	2.7	21.5	2.9	22.1	2.9	23.4	3.1	25.7	3.2	27.5	3.5	30.3	3.5	30.3	3.7	30.5	3.8
Any acute HypoPT event	22.8	6.8	22.8	7.0	20.7	6.9	23.2	7.3	24.7	7.6	30.2	7.8	37.4	7.5	38.1	8.3	36.8	8.7

Abbreviations: ED, emergency department; HypoPT, hypoparathyroidism; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; NEDS, Nationwide Emergency Department Sample.

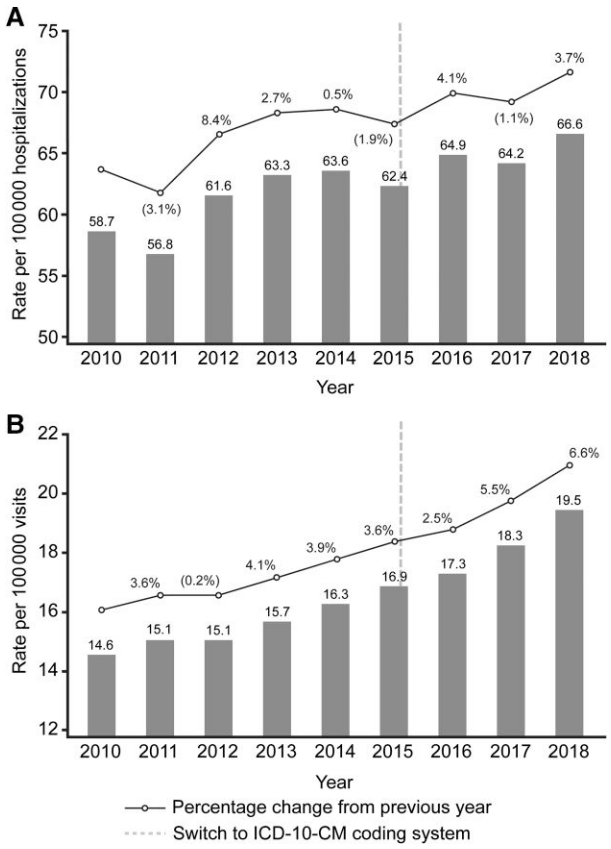

Figure 1. Rate of (A) HypoPT-related inpatient hospitalizations and (B) ED visits. Overall percentage change from 2010 to 2018: (A) 13.5%; (B) 33.6%. Percentages were calculated based on raw values. Brackets indicate decrease in percentage.

Abbreviations: ED, emergency department; HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

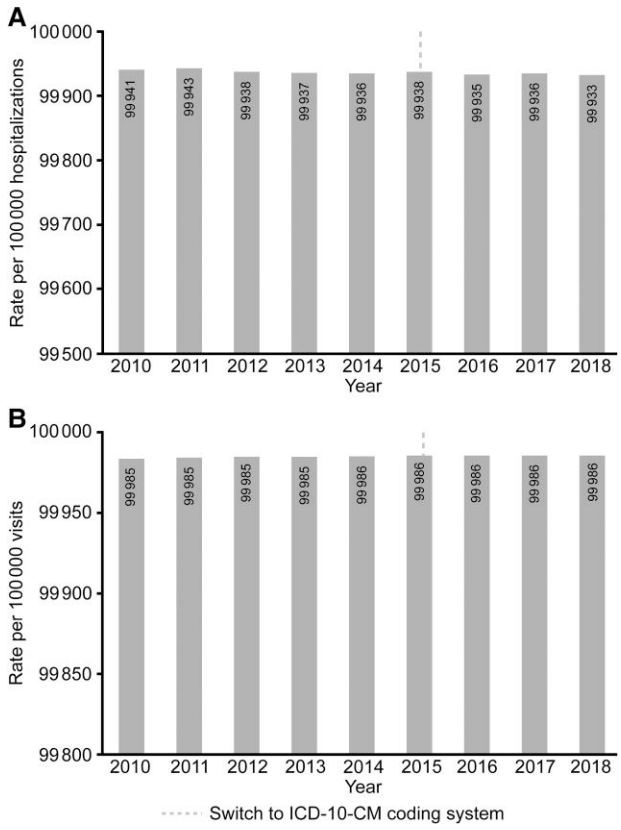

Figure 2. Rate of non-HypoPT-related (A) inpatient hospitalizations and (B) ED visits. Overall percentage change from 2010 to 2018: <0.01% for (A) and (B).

Abbreviations: ED, emergency department; HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

percentages were provided for categorical variables; means and standard deviations were provided for continuous variables. Total numbers of HypoPT-related inpatient hospitalizations and ED visits and non-HypoPT-related hospitalizations and ED visits were summed for each year.

No formal statistical analyses were planned. Post hoc statistical analyses using an F test were conducted to compare differences in the rates of increase of costs/charges between the HypoPT-related and non-HypoPT-related cohorts over time.

Each case of HypoPT-related inpatient hospitalization and ED visit was matched to 3 non-HypoPT-related controls using direct covariate matching based on age, sex, race, elective vs nonelective admission (NIS only), whether a patient was dead or alive, primary expected payer, median household income, national quartile for patient ZIP code, hospital region, hospital size based on bed numbers (NIS only), control/ownership of hospital, and location and teaching status of the hospital. Multivariable generalized linear models with a log-link function and gamma distribution for the error term were used to account for covariates not included during matched cohort selection and to address the skewed cost distribution that is common to claims data [19].

For the NEDS, total charges included those incurred for ED services only. Total costs could not be calculated because cost-to-charge ratios were not available for all data years included in this study.

The study aimed to estimate the marginal effect of HypoPT on total inpatient cost and LOS and ED visit charges. The marginal effect is the measure of association between a change in a regressor (in this case, HypoPT) and a change in the response variable (eg, total cost), while all other covariates are held constant.

Analyses were conducted using SAS Studio, version 3.8 (SAS Institute, Cary, NC, USA) and STATA, version 16 (StataCorp LLC, College Station, TX, USA).

Results

Hospital and Hospitalization Characteristics

Demographic, clinical, and facility-level characteristics of 202 462 HypoPT-related and 324 324 719 non-HypoPT-related inpatient hospitalizations and 206 114 HypoPT-related and 1 243 470 595 non-HypoPT-related ED visits are summarized in Tables 1 and 2, respectively. Across all years, HypoPT-related hospitalizations involved a higher proportion of women (range 61.4–65.8% and 61.7–67.6% for inpatient hospitalizations and ED visits, respectively) than non-HypoPT-related hospitalizations (range 56.1–57.9% and 55.2–55.5% for inpatient hospitalization and ED visits, respectively). Although HypoPT-related inpatient hospitalizations involved patients who were younger than those involved in non-HypoPT-related inpatient hospitalizations, the reverse was observed for ED visits. Race was recorded only for

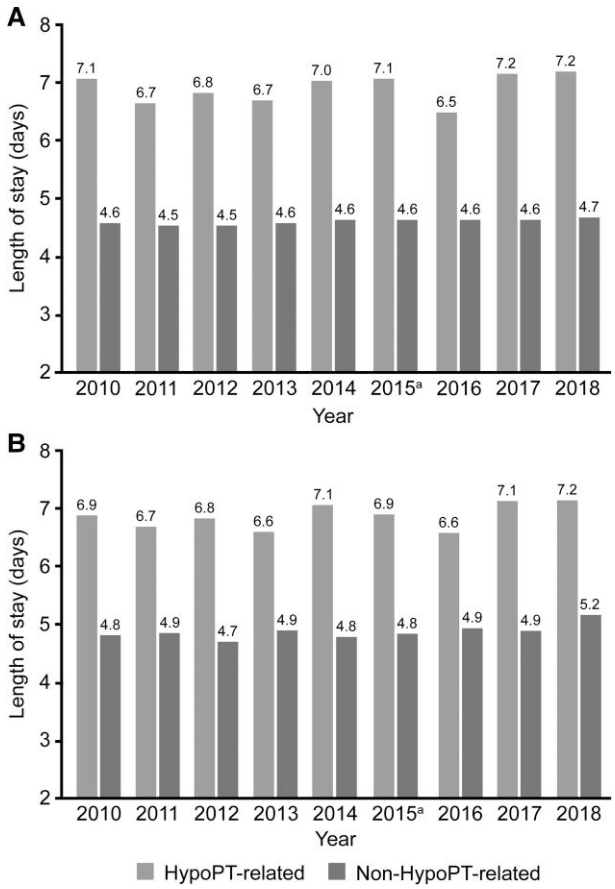

Figure 3. Mean length of HypoPT-related and non-HypoPT-related inpatient hospitalization per visit in (A) unmatched and (B) matched cohorts. Matching was performed based on age, sex, race, elective vs non-elective admission (NIS only), vital status at discharge, primary expected payer, median household income, national quartile for patient ZIP code, hospital region, hospital size based on bed numbers (NIS only), control/ownership of hospital, and location and teaching status of the hospital. [a]Switch to ICD-10-CM coding system. Abbreviations: HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; NIS, National Inpatient Sample.

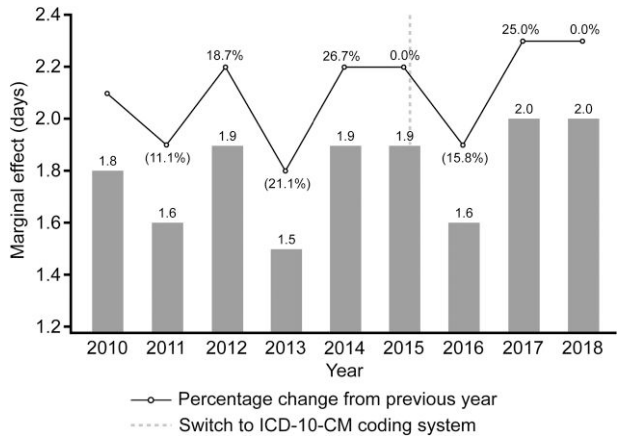

Figure 4. Marginal effect of HypoPT on length of stay for inpatient hospitalization, compared with no HypoPT, by year. Overall percentage change from 2010 to 2018: 11.1%. Percentages were calculated based on raw values. Brackets indicate decrease in percentage. Abbreviations: HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

inpatient hospitalizations; there were similar proportions of patients within each race group involved in HypoPT-related and non-HypoPT-related inpatient hospitalizations.

Chronic kidney disease was more common among individuals with HypoPT-related than with non-HypoPT-related inpatient hospitalizations and ED visits (range for HypoPT-related vs non-HypoPT-related means during the observation period were 34.3–42.8% vs 17.2–25.6% for inpatient hospitalizations and 27.0–36.8% vs 5.4–8.2% for ED visits) (Tables 1 and 2).

Cardiovascular comorbidities recorded during inpatient hospitalizations included hypertension, cardiac dysrhythmias, cerebrovascular disease, coronary artery disease, heart failure, and peripheral vascular disease. Overall, cardiac dysrhythmia, heart failure, and peripheral vascular disease were more common among HypoPT-related than non-HypoPT-related inpatient hospitalizations, with the exception of peripheral vascular disease: in 2013 and 2014, peripheral vascular disease was more common in non-HypoPT-related inpatient hospitalizations (HypoPT: 5.3%, non-HypoPT: 5.4%, and HypoPT: 5.4%, non-HypoPT: 5.6%, respectively), and in 2012, equal proportions (5.3%) of associated HypoPT-related and non-HypoPT-related visits were observed (range of means for HypoPT-related vs non-HypoPT-related: 16.7–22.0% vs 14.6–18.5% for cardiac dysrhythmias, 14.6–18.8% vs 10.9–15.1% for heart failure, 5.3–8.2% vs 4.8–6.5% for peripheral vascular diseases) (Table 1).

Cardiac comorbidities recorded during ED visits, which included hypertension, cardiac dysrhythmias, coronary artery disease, and heart failure, were more common among HypoPT-related visits than non-HypoPT-related visits (range of means for HypoPT-related vs non-HypoPT-related: 21.0–38.0% vs 17.6–23.4% for hypertension, 11.9–19.0% vs 5.6–7.4% for cardiac dysrhythmias, 10.7–15.9% vs 5.5–6.5% for coronary artery disease, 9.5–15.5% vs 3.3–4.7% for heart failure) (Table 2).

Across all years, the proportions (range of means) of ED visits concluding with routine discharge were lower for HypoPT-related visits (27.9–38.4%) than for non-HypoPT-related visits (74.4–82.2%). In general, the proportions of ED visits concluding with inpatient admissions (57.7–68.0%) or short-term hospital transfers (1.4–2.6%) were higher among HypoPT-related visits than non-HypoPT-related visits (13.1–15.3% for inpatient admissions and 1.4–1.6% for short-term hospital transfers for non-HypoPT-related visits). Exceptions included 2016, where the proportions of ED visits concluding with a transfer to short-term hospitals were higher for non-HypoPT-related visits, and 2017, where no difference in the proportions was observed (Table 2).

Visit Statistics, Costs, and Charges

From 2010 to 2018, the rates of HypoPT-related inpatient hospitalizations and ED visits increased by 13.5% and 33.6%, respectively (Fig. 1A and 1B), while non-HypoPT-related inpatient hospitalizations and ED visits changed by less than 0.01% each (Fig. 2A and 2B). HypoPT-related inpatient hospitalizations had a longer mean LOS than non-HypoPT-related hospitalizations (range: 6.6–7.2 days vs 4.7–5.2 days, respectively, for matched cohorts) (Fig. 3). The marginal effect of HypoPT on the LOS for inpatient

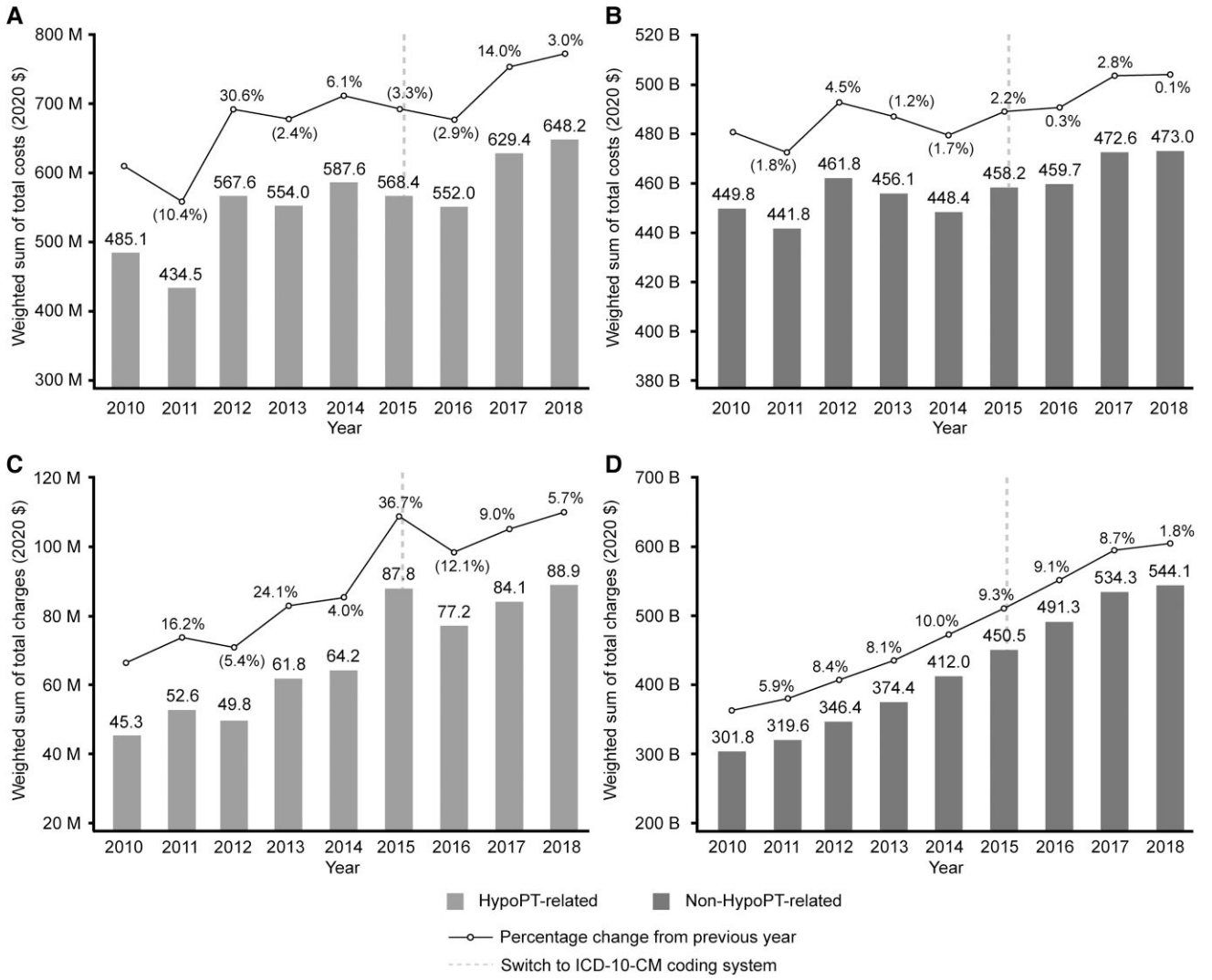

Figure 5. Weighted total sum in US dollars for (A) HypoPT-related and (B) non-HypoPT-related inpatient hospitalizations, and (C) HypoPT-related and (D) non-HypoPT-related ED visits. Percentages were calculated based on raw values. Brackets indicate decrease in percentage.

Abbreviations: B, billion; ED, emergency department; HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; M, million.

hospitalizations increased by 11.1% between 2010 and 2018 (Fig. 4).

The weighted sum of the total annual direct cost of HypoPT-related inpatient care increased from $485.1 million to $648.2 million, which corresponded to a total cost increase of 33.6% from 2010 to 2018. During the same period, the total cost for non-HypoPT-related inpatient hospitalizations increased by 5.2% (Fig. 5A and 5B). Mean total cost per inpatient hospitalization for HypoPT-related reasons was consistently higher across all years than that for non-HypoPT-related reasons in both unmatched and matched cohorts (Fig. 6A and 6B).

The marginal effect of HypoPT on total inpatient hospitalization costs per year increased by 45.8% from 2010 to 2018, ranging from $7139 to $10 407 (Fig. 7A), with a change of 15.2% observed for the total period between 2016 and 2018, after ICD-10-CM codes were implemented.

The weighted sum of the total charges for ED visits increased by 96.3% (calculated based on raw values) for HypoPT-related visits and 80.3% for non-HypoPT-related visits between 2010 and 2018 (Fig. 5C and 5D). The mean charges per ED visit were consistently higher for HypoPT-related visits than for non-HypoPT-related visits across all years, in both unmatched and matched cohorts (Fig. 6C and 6D). The differences in the rates of increase in costs and charges between HypoPT-related and non-HypoPT-related inpatient hospitalizations and ED visits during the study period were not statistically significant (results not shown).

In 2018, the marginal effect of HypoPT on ED visit charges was $1165. When the whole study period was considered, from 2010 to 2018, the overall marginal effect of HypoPT on ED visit charges increased by 26.9%.

Discussion

HypoPT is associated with a substantial disease burden [12, 20] and high healthcare resource utilization [21]. However, to our knowledge, no study has quantified the long-term economic burden of HypoPT-related inpatient and ED care in the United States. This study demonstrates that, despite HypoPT being a rare disease, the rates of inpatient hospitalizations and ED visits related to this condition increased between 2010 to

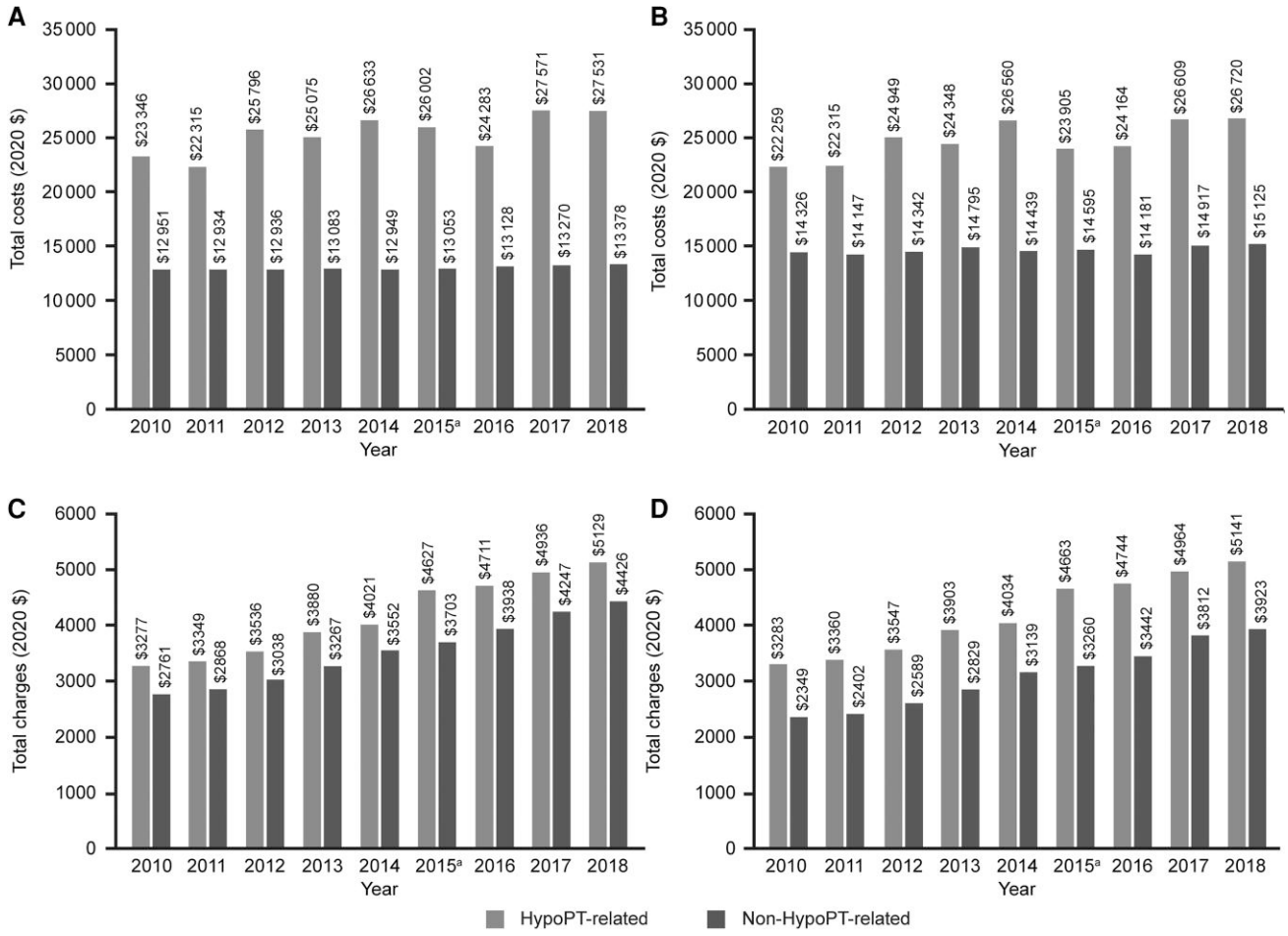

Figure 6. Mean inpatient hospitalization costs in US dollars in (A) matched and (B) unmatched cohorts and mean ED visit charges in (C) matched and (D) unmatched cohorts per event in HypoPT-related and non-HypoPT-related events. Matching was performed based on age, sex, race, elective vs nonelective admission (NIS only), vital status at discharge, primary expected payer, median household income, national quartile for patient ZIP code, hospital region, hospital size based on bed numbers (NIS only), control/ownership of hospital, and location and teaching status of the hospital. [a]Switch to ICD-10-CM coding system. Abbreviations: ED, emergency department; HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; NIS, National Inpatient Sample.

2018 and were associated with a greater increase in total and per visit costs than non-HypoPT-related inpatient and ED visits. In addition, HypoPT-related inpatient stays were longer, by approximately 2 days, than non-HypoPT-related inpatient hospitalizations. These data confirm that HypoPT is associated with substantial healthcare resource utilization, as has been previously demonstrated [8, 21].

The current study expands on accumulating evidence about the economic impact of HypoPT. Hadker et al conducted a web-based survey of patients with HypoPT [11]. They reported that during 1 year of observation, 79% of patients required at least 1 hospital admission or ED visit [11]. More recently, a US-based study by Murphy et al, in which an online survey was conducted, demonstrated that 42% of patients with HypoPT required a visit to the ED or urgent care facility for HypoPT-related concerns during 1 year of follow-up. Similarly, a retrospective chart review by Chen et al including 614 patients with HypoPT in the United States, Canada, the UK, France, Germany, Italy, and Spain found that over a 1-year period, 41% of patients had at least 1 ED visit and 19.5% had at least 1 inpatient hospitalization [21]. The study found that ED visits were generally due to HypoPT-related symptoms, while most inpatient hospitalizations were due to HypoPT-related comorbidities [21].

In a retrospective study conducted by Cipriani and colleagues in Italy between 2006 and 2013, the mean rate of hospitalization for patients with HypoPT was found to be 5.9 per 100 000 residents per year, with a decrease in hospitalizations observed across the years evaluated [16]. In the current study, rates of events reported on a patient level could not be evaluated due to the cross-sectional study design; however, increasing numbers of HypoPT-related inpatient admissions and ED visits were observed over the 9-year period.

The exact causes of ED visits and inpatient admissions could not be assessed in this study. However, a study by Gittoes et al using the HES database reported higher comorbidities, including renal complications and infections, among patients with post-surgical and nonsurgical chronic HypoPT than comparison groups (patients who underwent thyroid surgery and patients with hypothyroidism) [10]. In line with this UK-based study [10], a retrospective analysis of US claims data by Deering et al from 2014 to 2019 demonstrated that patients with chronic HypoPT had a higher number of inpatient hospitalizations, more ED visits, and a higher incidence of cardiac and renal complications than patients with transient post-surgical HypoPT [22, 23]. Understanding the reasons for the higher prevalence of HypoPT-related inpatient hospitalizations among patients with chronic HypoPT warrants further investigation.

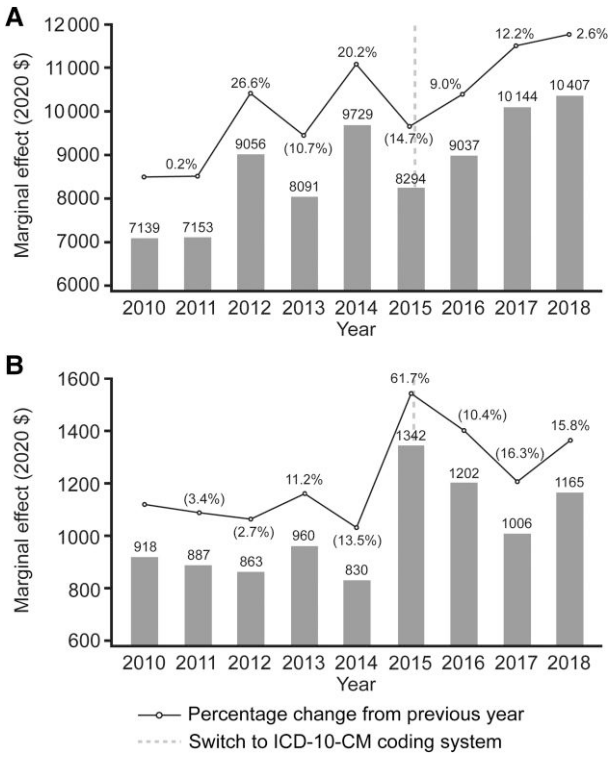

Figure 7. Marginal effect of HypoPT on (A) inpatient hospitalization costs and (B) ED visit charges by year compared with non-HypoPT-related events. Overall percentage change from 2010 to 2018: (A) 45.8%; (B) 26.9%. Brackets indicate decrease in percentage. Abbreviations: ED, emergency department; HypoPT, hypoparathyroidism; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

The mean LOS for HypoPT-related inpatient hospitalizations in our study was between 6.5 and 7.2 days and was consistently longer across all years than those reported for non-HypoPT-related stays. Our data are consistent with findings from a retrospective study in Spain by Darba et al where patients with HypoPT-related admissions spent a mean of 7.2 days in the hospital [24]. Similarly, the Italian study by Cipriani et al reported a mean LOS of 7.4 days for HypoPT-related hospitalizations between 2006 and 2013 [16].

Few studies have focused on costs and charges of HypoPT-related hospital visits. A study by Chen et al based on US healthcare claims for hospitalizations and ambulatory visits between 2010 and 2015 found that mean healthcare costs for HypoPT totaled $26 889 per year [25], a similar value to that observed in our own study. The HES database study conducted by Gittoes et al in the UK reported annual inpatient and outpatient costs of more than £30 000 for 2.7% of patients with HypoPT [10]. However, while the HES database study included costs for both inpatient and outpatient visits, the current study recorded only inpatient stays, which could account for the difference in total costs observed.

In a US-based longitudinal study by Leibson et al evaluating medical records from Olmsted County, Minnesota, in 2009 the annual cost of healthcare for patients with HypoPT in the United States was estimated to be about 3 times that for people without the condition [9]. In our study, the costs associated with HypoPT-related inpatient hospitalizations were roughly double those for nonrelated cases. Importantly, however, the 2 studies do not cover the same years, with Leibson et al reporting costs from 2006 through 2008 and also including outpatient costs [9]. In addition, the present study is based on national data, while the study by Leibson et al focused on medical records in one particular county [9].

We observed that the total annual direct cost of inpatient care for HypoPT-related hospital stays increased by 33.6% between 2010 and 2018, while that for non-HypoPT-related inpatient hospitalizations increased by 5.2%. In all years examined, hospital visits related to HypoPT had greater charges per visit compared with non-HypoPT-related visits, suggesting that patients with HypoPT may have a higher burden from the disease itself, which results in greater healthcare resource utilization as compared with the general population.

Strengths and Limitations

The primary strength of this study is the robust nature of the underlying data. By design, the NIS and the NEDS databases are nationally representative, allowing conclusions to be drawn about HypoPT-related care in the entire US population, which would not be possible with smaller databases. This study included analysis of a large number of both inpatient hospitalizations and ED visits longitudinally over 8 years. The latter allowed the impact of events such as the transition from ICD-9-CM to ICD-10-CM coding schemes on trends in HypoPT-related care to be observed. This study also discriminated between inpatient hospitalization and ED visits, thereby providing detailed and granular information about the pattern of healthcare utilization for patients with HypoPT in the United States.

Several limitations should be acknowledged. While the data are generalizable to the United States, findings presented may not be reflective of healthcare systems in other countries. Furthermore, HypoPT-related hospital visits were identified in the NIS and the NEDS databases based on diagnosis codes, the validity of which depend on accurate recording, with asymptomatic disease likely not being represented. The NIS and the NEDS databases also lack relevant information about medication use, lifestyle characteristics, and disease severity; consequently, residual confounding may exist that cannot be accounted for. The definitions and measures used in the study may not align with those used in other studies conducted using different data sources, due to variations in the nature of the data found in each. Finally, the change from ICD-9-CM to ICD-10-CM codes in 2015 may have impacted the number of HypoPT-related inpatient hospitalizations recorded. It should also be noted that it is not possible to derive statements about per-person burden from the data because the NIS and the NEDS databases represent events rather than patients, and it is possible for a single patient to be recorded more than once, for example if hospitalized more than once or if hospitalized after an ED visit.

Conclusions

This study involving nationally representative data on US inpatient hospitalization and ED visits demonstrates that HypoPT is associated with a substantial economic burden, which appears to be increasing over time, raising concerns that HypoPT may not be controlled adequately in routine clinical practice. These findings therefore underscore the importance of increasing awareness and refinement of best practices in the management of HypoPT [26], as this may result in a

reduction of disease-associated complications and thus reduce the need for inpatient and ED care.

Acknowledgments

Medical writing support was provided by Valentina Bart, PhD, of PharmaGenesis Cardiff, Cardiff, UK, and funded by Takeda Pharmaceuticals U.S.A., Inc.

Disclosures

S.K. has served as an advisory board member for Lantheus Imaging and Ultromics and as a consultant for Shire, a Takeda company. E.O.G. has served as a consultant for Shire, a Takeda company, and is an employee of the US Department of Veterans Affairs. Opinions expressed in this article are those of the authors and do not necessarily represent the opinion of the Department of Veterans Affairs. O.A. and F.C. are employees of Takeda Pharmaceuticals U.S.A., Inc. and have stock ownership in Takeda Pharmaceuticals U.S.A., Inc. A.H., S.C., R.P., and E.E. are employed by RTI Health Solutions, and this study was performed under contract between RTI Health Solutions and Takeda Pharmaceuticals U.S.A., Inc. This study was funded by Takeda Pharmaceuticals U.S.A., Inc. Medical writing support was provided by Valentina Bart, PhD, of PharmaGenesis Cardiff, Cardiff, UK, and funded by Takeda Pharmaceuticals U.S.A., Inc.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

1. Clarke BL, Brown EM, Collins MT, *et al.* Epidemiology and diagnosis of hypoparathyroidism. *J Clin Endocrinol Metab*. 2016;101(6):2284-2299. doi: 10.1210/jc.2015-3908
2. Clarke B, Leibson C, Emerson J, Ransom J, Lagast H. Co-morbid medical conditions associated with prevalent hypoparathyroidism: a population-based study. Abstract presented at ASBMR Annual Meeting; San Diego, CA. 2011.
3. Bilezikian JP, Khan A, Potts JT Jr, *et al.* Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. *J Bone Miner Res*. 2011;26(10):2317-2337. doi: 10.1002/jbmr.483
4. Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med*. 2008;359(4):391-403. doi: 10.1056/NEJMcp0803050
5. Fonseca OA, Calverly JR. Neurological manifestations of hypoparathyroidism. *Arch Intern Med*. 1967;120(2):202-206. doi:10.1001/archinte.1967.00300020074009
6. Gosmanova EO, Chen K, Rejnmark L, *et al.* Risk of chronic kidney disease and estimated glomerular filtration rate decline in patients with chronic hypoparathyroidism: a retrospective cohort study. *Adv Ther*. 2021;38(4):1876-1888. doi: 10.1007/s12325-021-01658-1
7. Gosmanova EO, Chen K, Ketteler M, *et al.* Risk of cardiovascular conditions in patients with chronic hypoparathyroidism: a retrospective cohort study. *Adv Ther*. 2021;38(8):4246-4257. doi: 10.1007/s12325-021-01787-7
8. Khan AA, AbuAlrob H, Punthakee Z, *et al.* Canadian National Hypoparathyroidism Registry: an overview of hypoparathyroidism in Canada. *Endocrine*. 2021;72(2):553-561. doi: 10.1007/s12020-021-02629-w
9. Leibson C, Clarke B, Ransom J, Lagast H. Medical care costs for persons with and without prevalent hypoparathyroidism: a population-based study. Abstract presented at ASBMR Annual Meeting; San Diego, CA. 2011.
10. Gittoes NJ, Iqbal K, Marelli C, *et al.* Quantifying the real-world clinical and economic burden of chronic hypoparathyroidism on secondary care in England: a multi-arm, retrospective cohort study. Abstract presented at European Congress of Endocrinology; Online. 2021. doi: 10.1530/endoabs.73.AEP93
11. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract*. 2014;20(7):671-679. doi: 10.4158/EP13328.OR
12. Murphy D, Sanders B, Gulley L, *et al.* Disease burden of patients living with hypoparathyroidism: results from the voices of Hypopara survey. *J Endocrine Soc*. 2021;5(Suppl_1):2. doi: 10.1210/jendso/bvab048.529
13. Agency for Healthcare Research and Quality. Introduction to the HCUP National Inpatient Sample (NIS). Updated September 13, 2021. Accessed June 22, 2022. https://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2019.jsp
14. Agency for Healthcare Research and Quality. Introduction to the HCUP Nationwide Emergency Department Sample (NEDS) Updated September 21, 2021. Accessed June 22, 2022. https://www.hcup-us.ahrq.gov/db/nation/neds/NEDS_Introduction_2019.jsp
15. US Food and Drug Administration. Natpara prescribing information. Accessed January 20, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125511s020lbl.pdf
16. Cipriani C, Pepe J, Biamonte F, *et al.* The epidemiology of hypoparathyroidism in Italy: an 8-year register-based study. *Calcif Tissue Int*. 2017;100(3):278-285. doi: 10.1007/s00223-016-0222-7
17. Agency for Healthcare Research and Quality. HCUP-US cost-to-charge ratio for inpatient files. Accessed March 23, 2022. https://www.hcup-us.ahrq.gov/db/ccr/ip-ccr/ip-ccr.jsp
18. US Bureau of Labor Statistics. Measuring price change in the CPI: medical care. Accessed September 5, 2022. https://www.bls.gov/cpi/factsheets/medical-care.htm
19. Wedderburn R. Quasi-likelihood functions, generalized linear models, and the Gauss-Newton method. *Biometrika*. 1974;61(3):8. doi: 10.2307/2334725
20. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *J Bone Miner Res*. 2013;28(12):2570-2576. doi: 10.1002/jbmr.2004
21. Chen K, Krasner A, Li N, Xiang CQ, Totev T, Xie J. Clinical burden and healthcare resource utilization among patients with chronic hypoparathyroidism, overall and by adequately vs not adequately controlled disease: a multi-country chart review. *J Med Econ*. 2019;22(11):1141-1152. doi: 10.1080/13696998.2019.1624081
22. Deering KL, Loustau P, Culler MD, Allas S, Weiss B, Astolfi D. Healthcare resource utilization burden of patients with hypoparathyroidism in the United States. Poster presented at AMCP NEXUS; Denver, CO. 2021.
23. Deering KL, Loustau P, Culler MD, *et al.* Clinical burden of patients with hypoparathyroidism in the United States: a claims data analysis. Poster presented at ASBMR; Online. 2021.
24. Darbà J, Marsà A. Epidemiology and management of parathyroid gland disorders in Spain over 15 years: a retrospective multicentre analysis. *PLoS One*. 2020;15(3):e0230130.doi: 10.1371/journal.pone.0230130
25. Chen K, Qin S, Weycker D, *et al.* Abstract #1090: economic burden of chronic hypoparathyroidism in US clinical practice. *Endocr Pract*. 2017;23(Suppl 3):260.
26. Bollerslev J, Rejnmark L, Zahn A, *et al.* European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE educational program of parathyroid disorders. *Eur J Endocrinol*. 2022;186(2):R33-R63. doi: 10.1530/EJE-21-1044