Stable incidence and increasing prevalence of primary hyperparathyroidism in a population-based study in Scotland

Soto-Pedre, Enrique; Newey, Paul J.; Leese, Graham P.

Published in:
Journal of Clinical Endocrinology and Metabolism

DOI:
10.1210/clinem/dgad201

Publication date:
2023

The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, e1117–e1124
https://doi.org/10.1210/clinem/dgad201
Advance access publication 6 April 2023
Clinical Research Article

Stable Incidence and Increasing Prevalence of Primary Hyperparathyroidism in a Population-based Study in Scotland

Enrique Soto-Pedre,[1] Paul J. Newey,[2,3] and Graham P. Leese[1,2]

[1]Division of Population Health and Genomics, School of Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK
[2]Department of Endocrinology and Diabetes, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK
[3]Division of Molecular and Clinical Medicine, School of Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK

Correspondence: Enrique Soto-Pedre, MBBS, MSc, Division of Population Health and Genomics, School of Medicine, Ninewells Hospital and Medical School, Level 5, Mailbox 12, University of Dundee, Dundee DD1 9SY, Scotland, UK. Email: e.soto@dundee.ac.uk.

Abstract

Context: Previous studies, including our own, have demonstrated a highly variable incidence of primary hyperparathyroidism (PHPT) from year to year.

Objective: We planned to provide a current estimate of the incidence and prevalence of PHPT in a community-based study.

Methods: A population-based retrospective follow-up study was conducted in Tayside (Scotland) from 2007 to 2018. Record-linkage technology (demography, biochemistry, prescribing, hospital admissions, radiology, and mortality data) was used to identify all patients. Cases of PHPT were defined as those with at least 2 raised serum corrected calcium concentration CCA (> 2.55 mmol/L) and/or hospital admissions with PHPT diagnoses and/or surgery records with parathyroidectomy during the follow-up period. The number of prevalent and incident cases of PHPT per calendar year by age and sex were estimated.

Results: A total of 2118 people (72.3% female, mean age 65 years) were identified with an incident case of PHPT. The overall prevalence of PHPT over the 12 years of the study was 0.84% (95% CI, 0.68%-1.02%), steadily increasing from 0.71% in 2007 to 1.02% in 2018. From 2008, the incidence of PHPT was relatively stable from 4 to 6 cases per 10 000 person-years, declining from 11.5 per 10 000 person-years in 2007. The incidence varied from 0.59 per 10 000 person-years (95% CI, 0.40%-0.77%) for those aged 20 to 29 years, to 12.4 per 10 000 person-years (95% CI, 11.2%-13.3%) in those aged 70 to 79 years. Incidence of PHPT was 2.5 times higher in women than in men.

Conclusion: This study is the first showing a relatively steady annual incidence of PHPT at 4 to 6 per 10 000 person-years. This population-based study reports a PHPT prevalence of 0.84%.

Key Words: primary hyperparathyroidism, parathyroid gland, epidemiology, prevalence, incidence

Abbreviations: CCA, corrected calcium concentration; eGFR, estimated glomerular filtration rate; FFH, familial hypocalciuric hypercalcemia; GRO, General Registrar Office; ICD, International Classification of Diseases; NHS, National Health Service; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTX, parathyroidectomy.

Primary hyperparathyroidism (PHPT) is the third most prevalent endocrine disorder after diabetes mellitus and hypothyroidism. Over the years the prevalence has increased following the introduction of multichannel biochemistry analyzers, and increasing awareness of clinical conditions such as osteoporosis (1). Many prevalence studies have depended on patient referral to secondary or tertiary care centers; however, patients are frequently managed in primary care without referral, especially frail and older individuals, or asymptomatic patients with mild elevations of serum calcium (Ca). The reported prevalence of PHPT varies between 0.2% and 1.3% of the population across the world from the United States, Europe, Bahrain, and Korea (2-6). The prevalence of PHPT has been increasing with time (1-3) resulting in increased workload, whether that involves intensive investigations, parathyroidectomy (PTX), or even if that just involves annual monitoring of serum Ca.

It is unclear whether the true incidence of PHPT has increased or whether the rising prevalence just reflects improved ascertainment. PHPT incidence rates have been reported to vary over the years, ranging from 1.6 per 10 000 to 12 per 10 000 person-years (1-3, 7-9). This variation is observed both between and within centers, and 1 center has reported an incidence as high as 18 per 10 000 person-years (6). Studies with sufficient duration of follow-up demonstrate a cycling incidence (1-3), although this may reflect variable ascertainment. Although prevalence has increased (2, 3), there is no clearly reported sustained increase in incidence.

Population-based studies are important for identifying the true prevalence of PHPT, as many affected individuals are

Received: 30 January 2023. **Editorial Decision:** 2 April 2023. **Corrected and Typeset:** 19 April 2023

asymptomatic and only approximately 50% of people with persistently raised serum Ca concentrations in primary care have a plasma parathyroid hormone (PTH) concentration analyzed (10). However, it has been shown that 90% to 96% of these patients do have PHPT (3, 10). Thus, in a community setting many people have unrecognized PHPT. Many of these are asymptomatic but may still have end-organ damage needing investigation and possible intervention. Thus it is recommended that surgery should at least be considered in all people with PHPT (11-13), as surgery may be cost-effective even in asymptomatic cases (14). Increasingly PHPT has been associated with nonclassic outcomes. In addition to renal stones, nephrocalcinosis, and fractures with osteoporosis, PHPT may also be linked to cardiovascular risk factors and outcomes (15-18), although confirmatory studies are required. However, PTX has been linked with improved insulin sensitivity (19-21), which could result in better cardiovascular outcomes. Randomized controlled trials are needed to test this hypothesis.

We aimed to obtain epidemiologic estimates of all identified cases of PHPT for the period 2007 to 2018 for the population of Tayside (Scotland) aged 20 years or older. Having an accurate estimate of the prevalence and incidence of PHPT is important to inform decisions about service planning and help influence research priorities, such as possible funding for randomized controlled trials on the effect of PTX for a wider group of patients with PHPT.

Materials and Methods

A population-based retrospective cohort study was performed among patients ever registered with a general practitioner in Tayside, a well-defined geographical region within Scotland (UK), with a mainly White population of 400 000 people. Anonymized data from medical records of patients were reviewed between 2007 and 2018 (the most recent data available). Every patient in Tayside has a unique National Health Service (NHS) patient identifier (Community Health Index —CHI) number that has been used for all health-related contacts, whether in primary, secondary, or private health care. This allowed the electronic linkage of all databases used.

The Biochemistry database was linked to other databases by the Health Informatics Centre Services/Farr Institute of Scotland at the University of Dundee (http://www.dundee.ac.uk/hic). These included demographic records (sex, birth, and migration), Scottish Morbidity Records (hospital admissions and surgical procedures), prescriptions dispensed, and the General Registrar Office (GRO) records on patient deaths.

The International Classification of Diseases (ICD) 10th revision codes (ICD10: C750, D351, D442, E210, E212, E213) were used to identify hospital inpatient events, and the Office of Population Censuses and Surveys Classification of Surgical Operations version 4 codes (OPCS-4: B14, B16, Z13.5) to identify operations, procedures and interventions during inpatient stays. Prescriptions were identified by means of the British National Formulary codes. To ensure data quality, Scottish Morbidity Records data are routinely subjected to a set of validation rules by the Information Services Division (ISD-NHS National Services Scotland) to evaluate and ensure these data sets are accurate, consistent, and comparable across time and between sources (22).

All analyses were performed on anonymized data sets. The study was approved by the East of Scotland Research Ethics Service-EoSRES (Health Informatics Centre [HIC] data sets V2, REC ref. 18/ES/0126, IRAS ID 143637), and informed consent had been obtained for all participants.

Primary Hyperparathyroidism Cohort Definition

An algorithm was developed for an initial-biochemistry–based diagnosis. Any individual with a raised outpatient serum corrected Ca concentration (ie, serum Ca concentration adjusted for serum albumin—CCA) greater than 2.55 mmol/L on 2 or more occasions during the follow-up period was identified as a probable PHPT diagnosis. For these patients, PTH concentration, serum and urine creatinine concentrations, and urine Ca concentrations were also examined. Patients with familial hypocalciuric hypercalcemia (FHH) from ICD codes (ICD10: E83.5) and/or tertiary hyperparathyroidism identified from having an estimated glomerular filtration rate (eGFR) less than or equal to 30 mL/min 36 months before or within 6 months after first raised serum CCA had been excluded at the early stage of data extraction process by the HIC (Dundee University, Scotland). Serum PTH measurements were performed with the Roche Modular E170 assay, and the Siemens Atellica CH Ca assay (ie, bromocresol purple colorimetric method) was used for quantitative determination of serum Ca. They were all performed at a central laboratory in the region. A locally derived formula for serum CCA was used: CCA mmol/L = total Ca mmol/L + (0.012 × [39.9 – albumin g/L]), where 39.9 was the Tayside mean serum albumin. The reference range for serum CCA was 2.10 to 2.55 mmol/L, for serum PTH was 1.0 to 6.9 pmol/L, and both remained unaltered during the study period.

Definite PHPT diagnoses were confirmed if a probable patient also ever had one or more of the following criteria: (a) serum PTH greater than 3 pmol/L, (b) increased 24-hour urinary Ca excretion greater than 7 mmol/day (280 mg/day), (c) histologically proven parathyroid tumor, (d) positive sestamibi Tc-99 scan results, and/or (e) hospital admissions with PHPT diagnoses or surgery records with parathyroidectomy (PTX). Thiazide and lithium prescriptions were retrieved. If a patient was on either drug after the first raised serum CCA they were still included. Thus, our patient cohort included all definite and probable diagnosed PHPT patients.

Statistical Analysis

The period of study for the analysis of prevalence and incidence was defined between January 1, 2007 and December 31, 2018. Any patient aged 20 years or older with at least 2 raised outpatient serum CCA measurements or hospital admissions with PHPT diagnoses or surgery records with PTX at any time within a year was considered a prevalent case. Period prevalence was then estimated as the number of prevalent cases divided by the estimated mid-year population originated from the GRO records for Scotland, and it was calculated for every calendar year and for the entire period of study. For each patient the date of entry into the study was the date at first event of diagnosis identified within this period, and it was assumed that a patient after diagnosis stayed prevalent for the rest of the study until death or moving out of the health area. Thus, the first date of raised serum CCA or hospital admission was used to establish the year of diagnosis. The incidence rate was calculated as the number of new (ie, incident) cases divided by the number of person-

years in the source population. Person-years were calculated for every calendar year separately and further combined for all calendar years to serve as the denominator of an overall incidence rate. Incidence rate was stratified by sex and 10-year age groups (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+); 95% CIs for these were calculated assuming a Poisson distribution. Standardized rates were calculated by applying the age/sex-stratified rates to the all-Scotland population 2014 census results. Data were entered into a STATA/MP version 15.1 software package (StataCorp) for statistical analysis and determination of statistical significance ($P < .05$). Logic checks were performed and frequency distributions for all variables were analyzed for out-of-range values. The mean and SD or the median and the interquartile range of the data were calculated to describe continuous variables. Analysis of variance and chi-square tests were used to compare means and frequencies among subgroups of patients respectively. Nonparametric methods were used where appropriate.

Results

A total of 2118 patients who met the criteria for PHPT were identified in Tayside between 2007 and 2018, and thus considered for the study (Fig. 1). Demographic characteristics of the final study cohort are shown in Table 1. The mean age at diagnosis was 64.6 years, 72.3% were women, 85% of patient cases were older than 50 years, and 94% were aged 40 years or older.

Prevalence and incidence rates of all identified cases of PHPT were estimated for the period 2007 to 2018 for the population of Tayside aged 20 years or older that increased from 308 727 to 330 015 people (Table 2). The overall prevalence of ever having had PHPT was 0.84%, and it was 2.5-fold greater in women (1.18%) than in men (0.48%). Prevalence increased over the calendar years from 0.71% in 2007 to 1.02% in 2018. The average year-on-year increase was 4.6% for women and 3.2% for men.

Crude incidence rates were about 2 times higher in women than in men, and were highest in 2007 (Table 3). When crude incidence rates were adjusted for age and sex using GRO for Scotland census results, the overall rate decreased from 11.1

Table 1. Description of patients at first event of diagnosis of primary hyperparathyroidism in Tayside (Scotland, UK) from 2007 to 2018

Characteristic	Total	Women	Men	P^a
Counts, n (%)	2118 (100)	1532 (72.3)	586 (27.7)	—
Age (y), mean (SD)	64.6 (14.4)	64.7 (14.2)	64.6 (14.8)	.882
Age group, n (%)				
20-29	38 (1.8)	24 (1.6)	14 (2.4)	.015
30-39	80 (3.8)	51 (3.3)	29 (4.9)	
40-49	191 (9.0)	141 (9.2)	50 (8.5)	
50-59	393 (18.5)	310 (20.2)	83 (14.2)	
60-69	577 (27.2)	401 (26.2)	176 (30.0)	
70-79	528 (24.9)	378 (24.7)	150 (25.6)	
80+	311 (14.6)	227 (14.8)	84 (14.3)	

[a]Difference between sex subgroups.

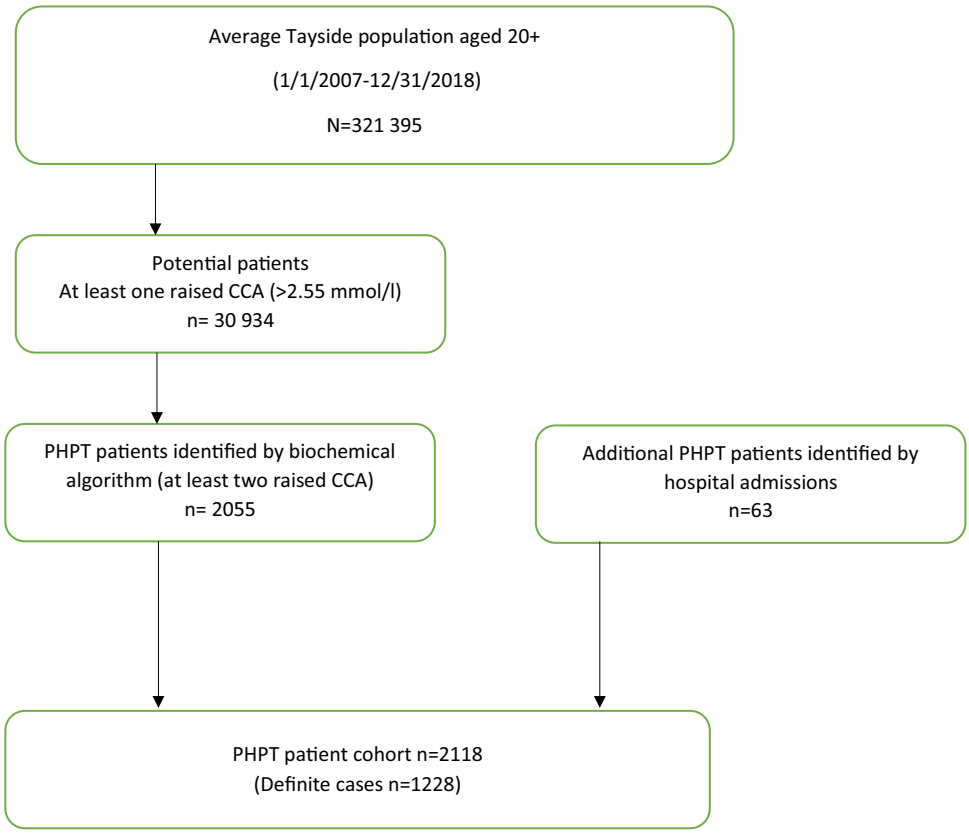

Figure 1. Flowchart describing the study cohort's generation process and the patients finally included in the epidemiologic study. CCA, serum corrected calcium; PHPT, primary hyperparathyroidism.

Table 2. Prevalence of primary hyperparathyroidism per calendar year by sex (2007-2018)

Year	Women		Men		Total	
	Cases/population	Prevalence per 1000	Cases/population	Prevalence per 1000	Cases/population	Prevalence per 1000
2007	1572/162 871	9.6	620/145 856	4.2	2192/308 727	7.1
2008	1642/163 996	10.0	635/147 562	4.3	2277/311 558	7.3
2009	1703/164 860	10.3	657/148 637	4.4	2360/313 497	7.5
2010	1749/165 775	10.6	672/150 111	4.5	2421/315 886	7.6
2011	1795/167 320	10.7	684/152 599	4.5	2479/319 919	7.7
2012	1886/168 311	11.2	708/154 041	4.6	2594/322 352	8.0
2013	1976/168 852	11.7	724/154 920	4.7	2700/323 772	8.3
2014	2070/169 896	12.2	757/156 121	4.8	2827/326 017	8.7
2015	2177/170 322	12.8	785/156 915	5.0	2962/327 237	9.1
2016	2297/170 750	13.5	814/157 536	5.2	3111/328 286	9.5
2017	2398/171 299	14.0	856/158 171	5.4	3254/329 470	9.8
2018	2482/171 334	14.5	883/158 681	5.6	3365/330 015	10.2
Overall	**—**	**11.8**	**—**	**4.75**	**—**	**8.4**
(95% CI)		**(9.9-13.8)**		**(3.6-6.2)**		**(6.8-10.2)**

per 10 000 person-years (95% CI, 9.9-12.3) in 2007 to 3.9 per 10 000 person-years (95% CI, 3.2-4.5) in 2018. The incidence rate of PHPT showed a small decrease for men and women from 2007 to 2011, and increased again from 2012 onward but overall remained relatively stable. The increased adjusted rate over the last year periods (2012-2017) remained between 6.3 and 8.4 per 10 000 person-years for women and 2.4 to 3.4 per 10 000 person-years for men, and 4.5 to 5.8 per 10 000 person-years overall.

When rates were examined by age groups for combined year periods (Table 4), the highest incidence rates of PHPT were found in those older than 60 years (aged 60-69 years: 9.7 per 10 000 person-years; aged 70-79 years: 12.2 per 10 000 person-years; aged 80+ years: 11.2 per 10 000 person-years) and for all year periods. Before age 60 years the incidence rates were much lower, but increased as well with age. Incidence rates showed a peak in women aged 70 to 79 years (Fig. 2). In men, no peak was found, and the rates ranged from 10 to 15 per 10 000 person-years in those people older than 60 years.

Discussion

In this population-based study we demonstrate an overall prevalence of PHPT of 0.84% over the years 2007 to 2018, with an increase in annual prevalence over that time from 0.71% to 1.02%. The prevalence of PHPT was almost 3 times greater in women than men. From 2011 onward the incidence of PHPT was fairly constant, from between 4 and 6 per 10 000 person-years, with no obvious trends or fluctuations.

In our previous analysis the prevalence of PHPT increased from 0.18% in 1997 to 0.67% in 2006 (2) and the present study shows that this has steadily increased further to just over 1.0% in 2018. Increasing prevalence combined with a steady incidence is likely to be a result of the increasing life expectancy of these patients along with the general Scottish population during this period (23). This will particularly affect the prevalence in an older cohort of people, which is again consistent with PHPT being more common in older individuals. Compared to those in their 30s, the incidence of PHPT was nearly 9-fold greater compared to those aged in their 70s and more than twice the rate for those in their 50s (see Table 4). The largest number of people were diagnosed in their 60s (see Table 1). Our previous report described a hugely fluctuating incidence of PHPT between 1997 and 2006 (2), with variations from 4 to 11 cases per 10 000 person-years (Fig. 3). Other large studies showed a similar variation of 3 to 12 per 10 000 in Kaiser Permanente from 1995 to 2010 (3) and 8 to 12 per 10 000 in Rochester from 1965 to 2009 (1) from year to year. These variations have generally been thought to relate to variable ascertainment due to the increasing use of automated serum Ca measurements and screening for osteoporosis (1, 3). Other intriguing explanations have been considered such as variable use of estrogens and oral Ca supplements, increasing rates of obesity, more neck imaging or even an infective etiology, but all are thought unlikely to account for the large variations observed (1, 2). Interestingly, the present study shows a more stable incidence rate over the last 10 years (see Fig. 3). This may reflect that the effect of automated serum Ca testing and osteoporosis screening on diagnosing PHPT has stabilized, and that a steady state has now been reached. Until now there has been some speculation as to why the incidence of PHPT has fluctuated so much, paralleled with a lack of confidence in the true incidence. With time and establishment of widespread automated Ca analyses and implementation of osteoporosis services, it is possible that these factors no longer have the same effect on ascertainment of PHPT. With a more stable incidence of PHPT, this may reflect a rate that is nearer the "true" incidence and indicates that factors other than those mentioned earlier are not likely to have a major effect on PHPT incidence.

Our PHPT prevalence of 0.84% is higher than other studies. Our methodologies used electronic capture of raised serum Ca that was then refined with additional inclusion criteria. These methods are very similar to the Rochester study (1). We report similar incidence rates but unfortunately the authors of the Rochester study do not report on prevalence. Notably, the Scottish and Rochester definitions of PHPT were broader than those used by Kaiser Permanente (3), whose overall prevalence was approximately 0.16% in 2010

Table 3. Incidence rate (per 10 000 person-years) of primary hyperparathyroidism per year by sex (2007-2018)

Year	Women			Men			Total	
	Population	Crude	Adjusted[a]	Population	Crude	Adjusted[a]	Crude	Adjusted[a]
2007	162 871	15.29	14.52 (12.71-16.33)	145 856	7.27	7.50 (6.06-8.93)	11.49	11.14 (9.98-12.30)
2008	163 996	8.54	8.08 (6.74-9.43)	147 562	3.59	3.62 (2.64-4.60)	6.19	6.00 (5.15-6.85)
2009	164 860	6.55	6.18 (5.00-7.35)	148 637	3.23	3.23 (2.31-4.15)	4.97	4.78 (4.02-5.53)
2010	165 775	4.64	4.42 (3.42-5.41)	150 111	2.33	2.31 (1.54-3.07)	3.54	3.42 (2.79-4.06)
2011	167 320	4.66	4.34 (3.37-5.32)	152 599	1.83	1.86 (1.17-2.55)	3.31	3.15 (2.55-3.76)
2012	168 311	7.31	6.74 (5.54-7.94)	154 041	2.79	2.80 (1.96-3.64)	5.15	4.91 (4.16-5.66)
2013	168 852	6.57	6.31 (5.13-7.49)	154 920	2.45	2.47 (1.69-3.26)	4.60	4.46 (3.74-5.18)
2014	169 896	7.48	7.03 (5.80-8.27)	156 121	2.75	2.67 (1.87-3.47)	5.21	4.99 (4.24-5.74)
2015	170 322	8.22	7.55 (6.29-8.81)	156 915	3.38	3.31 (2.42-4.20)	5.89	5.58 (4.79-6.37)
2016	170 750	9.02	8.44 (7.09-9.78)	157 536	2.98	2.92 (2.08-3.75)	6.12	5.81 (5.01-6.62)
2017	171 299	7.36	6.71 (5.52-7.90)	158 171	3.48	3.35 (2.46-4.24)	5.49	5.16 (4.40-5.92)
2018	171 334	5.78	5.34 (4.28-6.40]	158 681	2.33	2.19 (1.48-2.90)	4.12	3.85 (3.20-4.50)

[a]Age-sex standardized (95% CI).

Table 4. Incidence rate (per 10 000 person-years) of primary hyperparathyroidism per 3-year period by age group (2007-2018)

Age, y	2007-2009		2010-2012		2013-2015		2016-2018		Overall	
	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
20-29	0.79	0.79 (0.34-1.24)	0.24	0.24 (0.05-0.47)	0.53	0.54 (0.19-0.89)	0.77	0.79 (0.36-1.23)	0.58	0.59 (0.40-0.77)
30-39	1.92	1.92 (1.20-2.65)	1.02	1.03 (0.49-1.57)	1.29	1.30 (0.70-1.90)	1.42	1.42 (0.81-2.03)	1.41	1.42 (1.11-1.73)
40-49	3.70	3.72 (2.82-4.62)	2.26	2.28 (1.57-2.98)	2.60	2.61 (1.83-3.39)	2.78	2.80 (1.95-3.64)	2.85	2.86 (2.46-3.27)
50-59	7.27	7.36 (6.02-8.70)	3.84	3.89 (2.93-4.85)	5.94	6.00 (4.84-7.15)	6.17	6.24 (5.08-7.39)	5.81	5.87 (5.29-6.45)
60-69	14.10	14.12 (12.16-16.09)	6.74	6.76 (5.44-8.09)	9.96	10.02 (8.43-11.61)	8.17	8.21 (6.78-9.65)	9.67	9.71 (8.92-10.50)
70-79	19.02	18.60 (15.97-21.23)	9.39	9.24 (7.40-11.08)	11.43	11.23 (9.23-13.23)	10.28	10.18 (8.33-12.02)	12.44	12.24 (11.19-13.28)
80+	15.17	14.88 (11.73-18.03)	10.22	9.68 (7.29-12.08)	9.51	8.91 (6.71-11.12)	12.25	11.66 (9.19-14.14)	11.72	11.18 (9.91-12.45)

[a]Age-sex standardized (95% CI).

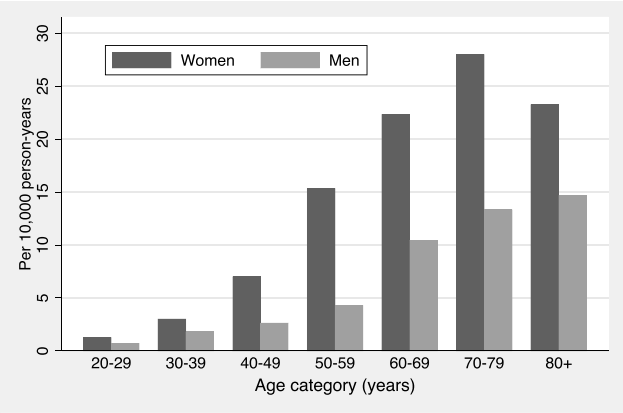

Figure 2. Incidence rates of primary hyperparathyroidism by age groups and sex.

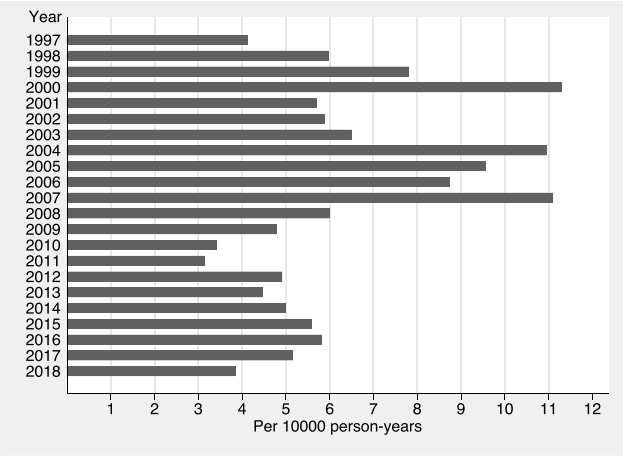

Figure 3. Incidence rates of primary hyperparathyroidism in Tayside (Scotland, UK) by calendar year (1997-2018). Thanks to Clinical Endocrinology for granting permission to use summary data for the period 1997 to 2006 (2).

(female and male), compared to our rate of 0.76% in 2010. Their definitions of all "classic" and "nonclassic" cases broadly align with our definition of "definite" cases, which represent 58% of our study cohort. Adjusting our definitions of PHPT to align more with the Kaiser Permanente definitions, rather than the Rochester definitions, would approximate to a prevalence of just around 0.44% (0.76% × 0.58). Our rates will include unrecognized PHPT such as people who biochemically fit the criteria but who have not had a formal diagnosis made. Prevalence rates from other smaller populations were reported to be 0.3% from a military hospital in Bahrain (6), 0.4% in an estimate from hospitalized patients in Korea (5), and 1.3% in a tertiary referral center (4).

Throughout all the age groups, 72% of people with PHPT were women, which was similar to other studies at 71% to 77% (1, 3). The proportion of women remained constant from 2007 to 2018, and dates back to 1997 (2), suggesting a quite stable population in Tayside. Although the incidence increases with age in all cohorts, the largest proportion of people were diagnosed in their 60s (27%). In our previous study (2), the largest group was in their 70s (29%). Another study showed an increasing age at diagnosis as time progresses (1), but their data goes back to 1985. In the present study 67% of diagnoses were over age 60 years, 85% were over age 50 years, and 94% over 40 years.

Obtaining epidemiologic estimates of PHPT is somewhat challenging because of controversy over the measurement of serum Ca concentration and whether serum measurements of total Ca should be adjusted for albumin concentration, and if so, which formula is the most appropriate (24). Locally determined formulas (ie, like ours) usually perform better than formulas taken from the literature. Additionally, because the algorithm employed for patient identification in the present study made use of longitudinal data (ie, ≥ 1 biochemical measurement for each patient over time), the effect of any potential misclassification of Ca state would be lower than using cross-sectional data (ie, just one measurement for each patient).

Limitations of the study include the biochemical algorithm used in the diagnosis of cases—not all cases were verified by a clinician. In a previous validation study of 798 cases comparing with case note review, the algorithm used was 98.5% accurate in correctly diagnosing PHPT (2). Furthermore, other recent Scottish data have indicated that 96% of cases with persistently raised serum Ca have PHPT (10). Also, other large studies have used a similar methodology (1, 3). Such a methodology has advantages in diagnosing what is mainly an asymptomatic disease, of which many cases are not referred to a secondary care center in the United Kingdom. It is possible that we may have included some cases of FHH, although FHH cases were excluded, and the prevalence of this condition is estimated to be less than 0.001% (25). In our experience most patients with tertiary hyperparathyroidism develop hypercalcemia before transplantation, when their eGFR would be low. Patients with any degree of hypercalcemia would have been excluded using our algorithm that identified those with an eGFR less than or equal to 30 mL/min 36 months before or within 6 months after first raised serum CCA. It is possible that a small number of patients may have developed de novo hypercalcemia after transplantation. Patients with significant hypercalcemia post transplantation will be started on cinacalcet. In Tayside there are only 10 people on cinacalcet after renal transplantation, and some of these would have had hypercalcemia pre transplant. Thus the number of people with de novo hypercalcemia after transplantation is likely to be 10, with a negligible effect on the study results given our size.

Patients who had curative PTX were not removed from the follow-up and stayed prevalent afterward. The main reason for not excluding these patients was to maintain consistency with the study previously conducted for the period 1996 to 2006 (2). Although we cannot provide specific data on PTX, this surgery is usually underused, especially in older patients (26). Most of our study cohort is older than 50 years (85.4%) and with a mean age of 64.6 years. Patients with disseminated cancer can have hypercalcemia, but in the vast majority of cases the cancer is diagnosed before hypercalcemia develops. However, despite this we acknowledge that patients in the probable PHPT group may have included a few with cancer-related hypercalcemia, and this would be most common in those who have later-stage malignancies (27). In addition, a small number of other conditions may also have been included such as sarcoidosis, hypervitaminosis D, and hyperthyroidism. We attempted to exclude patients on thiazide diuretics or lithium, unless their hypercalcemia predated a first

prescription of these drugs, but it is possible that some such patients may have been included. However it has been reported that 71% of people taking such drugs with hypercalcemia probably actually do have PHPT (28). We believe the effect of these potential limitations on our epidemiologic estimates would be very low considering the large sample size of our study cohort. An additional limitation to our study is the lack of ethnic diversity, with more than 95% being White. It is noted in other studies that Black women have the highest prevalence followed by White women, Asian, and then Hispanic women (3). Finally our study did not attempt to identify people with normocalcemic hyperparathyroidism, which has its own diagnostic challenges (29).

In conclusion, this population-based study of PHPT, for the first time, demonstrates a relatively stable annual incidence rate of 4 to 6 per 10 000 cases. By 2018 the prevalence had reached 1% of the Tayside population, increasing from 0.7% over the previous 12 years.

Acknowledgments

We acknowledge the support of the Health Data Research UK and the HIC at the University of Dundee (Scotland, UK) for managing and supplying the anonymized data.

Funding

This work was supported by the NHS Tayside Research Endowments.

Author Contributions

E.S.P. researched/analyzed data and wrote the manuscript. P.J.N. and G.P.L. planned the study, researched data, wrote the manuscript, and reviewed/edited the manuscript.

Disclosures

The authors have nothing to disclose.

Data Availability

These are consented data and because of the sensitive nature are stored in secure computing environments. Data can be shared based on specific requests but as such is not publicly available.

References

1. Griebeler ML, Kearns AE, Ryu E, Hathcock MA, Melton LJ III, Wermers RA. Secular trends in the incidence of primary hyperparathyroidism over five decades (1965-2010). *Bone*. 2015;73:1-7.
2. Yu N, Donnan PT, Murphy MJ, Leese GP. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clin Endocrinol (Oxf)*. 2009;71(4):485-493.
3. Yeh MW, Ituarte PHG, Zhou HC, *et al*. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab*. 2013;98(3):1122-1129.
4. Press DM, Siperstein AE, Berber E, *et al*. The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. *Surgery*. 2013;154(6):1232-1238.
5. Kim JK, Chai YJ, Chung JK, *et al*. The prevalence of primary hyperparathyroidism in Korea: a population-based analysis from patient medical records. *Ann Surg Treat Res*. 2018;94(5):235-239.
6. Abdulla J, Suwaifi YM. Prevalence and incidence of primary hyperparathyroidism in Bahrain: a retrospective study from one medical center. *Neuro Endocrinol Lett*. 2021;42(4):257-264.
7. Wermers RA, Khosla S, Atkinson EJ, *et al*. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006;21(1):171-177.
8. Abood A, Vestergaard P. Increasing incidence of primary hyperparathyroidism in Denmark. *Dan Med J*. 2013;60(2):A4567.
9. 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.
10. Sillars A, Livingstone R, Yates TM, *et al*. Calcium requests in a primary care; an observational audit of biochemical requests and frequency of abnormal results. *Clin Biochem*. 2023;113:40-44.
11. Khan AA, Hanley DA, Rizzoli R, *et al*. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int*. 2017;28(1):1-19.
12. NICE guidelines. Hyperparathyroidism (primary): diagnosis, assessment and initial management 2019. Accessed January 23, 2023. https://www.nice.org.uk/guidance/ng132
13. Bilezikian JP, Khan AA, Clarke BL, Mannstadt M, Potts JT, Brandi ML. The Fifth International Workshop on the Evaluation and Management of Primary Hyperparathyroidism. *J Bone Miner Res*. 2022;37(11):2290-2292.
14. Zanocco KA, Wu JX, Yeh MW. Parathyroidectomy for asymptomatic primary hyperparathyroidism: a revised cost-effectiveness analysis incorporating fracture risk reduction. *Surgery*. 2017;161(1):16-24.
15. Yu N, Donnan PT, Leese GP. A record linkage study of outcomes in patients with mild primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study (PEARS). *Clin Endocrinol (Oxf)*. 2011;75(2):169-176.
16. Han D, Trooskin S, Wang X. Prevalence of cardiovascular risk factors in male and female patients with primary hyperparathyroidism. *J Endocrinol Invest*. 2012;35(6):548-552.
17. Silverberg SJ, Clarke BT, Peacock M, *et al*. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3580-3594.
18. Wetzel J, Pilz S, Grübler MR, *et al*. Plasma parathyroid hormone and cardiovascular disease in treatment-naive patients with primary hyperparathyroidism: the EPATH trial. *J Clin Hypertens (Greenwich)*. 2017;19(11):1173-1180.
19. Rudman A, Pearson ER, Smith D, Srivastava R, Murphy MJ, Leese GP. Insulin resistance before and after parathyroidectomy in patients with primary hyperparathyroidism—a pilot study. *Endocr Res*. 2010;35(2):85-93.
20. Beysel S, Caliskan M, Kizilgul M, *et al*. Parathyroidectomy improves cardiovascular risk factors in normocalcemic and hypercalcemic primary hyperparathyroidism. *BMC Cardiovasc Disord*. 2019;19(1):106.
21. Yavari M, Feizi A, Haghighatdoost F, Ghaffari A, Rezvanian H. The influence of parathyroidectomy on cardiometabolic risk factors in patients with primary hyperparathyroidism: a systematic review and meta-analysis. *Endocrine*. 2021;72(1):72-85.
22. Public Health Scotland website. Data quality assurance; assessments of SMR. Accessed March 9, 2023. https://beta.isdscotland.org/products-and-services/data-quality-assurance/dqa-assessments/
23. NRS Scotland Life Expectancy. 1980–2018. Accessed January 23, 2023. https://webarchive.nrscotland.gov.uk/20210316073644mp_/https://www.nrscotland.gov.uk/files//statistics/life-expectancy-at-scotland-level/nat-life-16-18/nat-life-tabs-16-18-pub.pdf
24. Pekar JD, Grzych G, Durand G, *et al*. Calcium state estimation by total calcium: the evidence to end the never-ending story. *Clin Chem Lab Med*. 2020;58(2):222-231.
25. Dershem R, Gorvin CM, Metpally RPR, *et al*; Regeneron Genetics Center. Familial hypocalciuric hypercalcemia type 1 and

autosomal-dominant hypocalcemia type 1: prevalence in a large healthcare population. *Am J Hum Genet*. 2020;106(6):734-747.
26. Nilsson IL. Primary hyperparathyroidism: should surgery be performed on all patients? Current evidence and residual uncertainties. *J Intern Med*. 2019;285(2):149-164.
27. Goldner W. Cancer-related hypercalcemia. *J Oncol Pract*. 2016;12(5):426-432.
28. Griebeler ML, Kearns AE, Ryu E, *et al*. Thiazide-associated hypercalcemia: incidence and association with primary hyperparathyroidism over two decades. *J Clin Endocrinol Metab*. 2016;101(3):1166-1173.
29. Dawood NB, Yan KL, Shieh A, Livhits MJ, Yeh MW, Leung AM. Normocalcaemic primary hyperparathyroidism: an update on diagnostic and management challenges. *Clin Endocrinol (Oxf)*. 2020;93(5):519-527.