

Using Linked Databases to Explore Healthcare Resource Use and Real-World Outcomes in a Rare Disease: Pompe Disease in England

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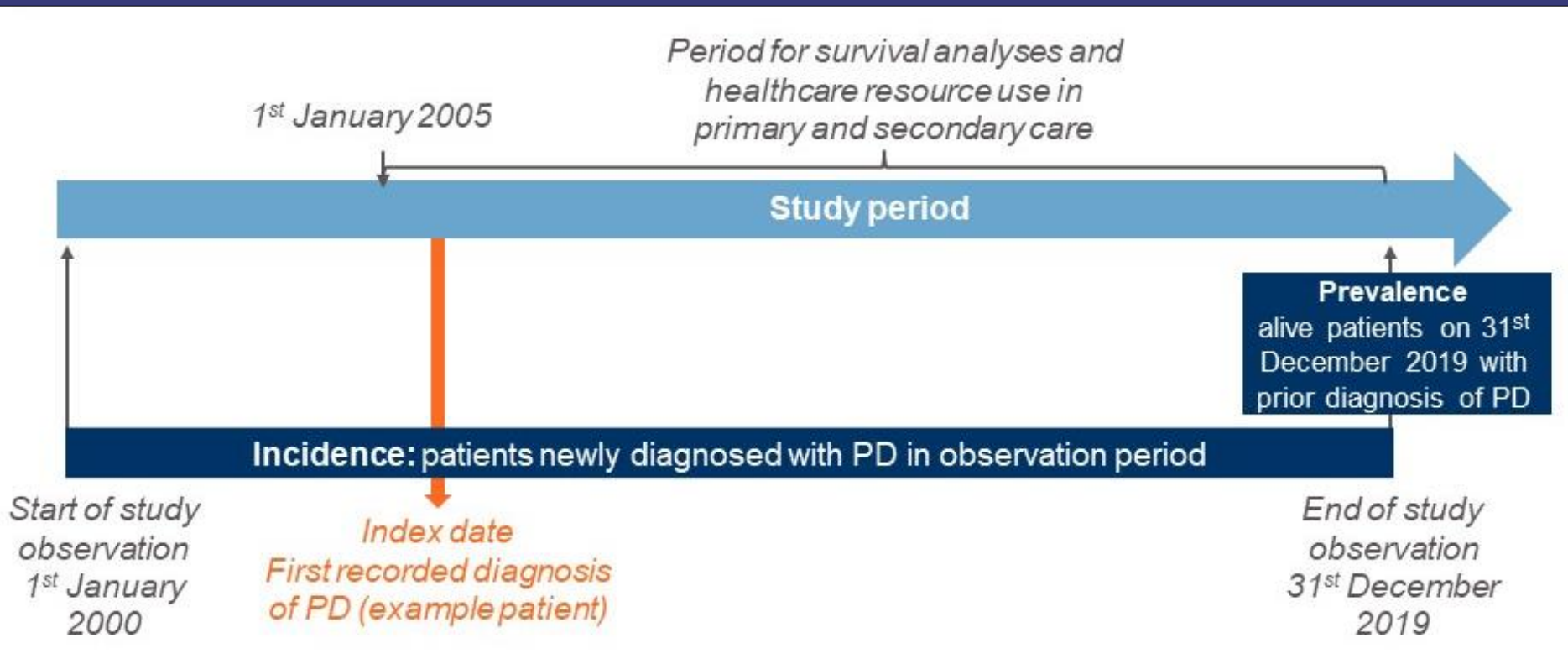
BACKGROUND

- Pompe disease (PD) is a rare autosomal recessive disorder in which acid α-glucosidase deficiency leads to intralysosomal accumulations of glycogen causing progressive muscle weakness and increasing risk of disability.^{1,2}
 - Both infantile- and late-onset forms are recognised (IOPD and LOPD respectively), with IOPD being associated with more severe symptoms.^{2,3}
 - Alglucosidase alfa (Myozyme), an enzyme-replacement therapy (ERT), is used to treat PD in adults and children and has been shown to improve ventilator-free survival in patients with IOPD.³
 - Prevalence of PD varies from country to country; estimated at one in 138,000 people to one in 14,000 people, but most quoted at one in 40,000 people.³
 - There is limited real-world evidence on the epidemiology of PD and associated burden on the National Healthcare System (NHS) in England.⁴
- Objectives**
- To estimate the incidence and prevalence of PD
 - To describe demographic and clinical characteristics and healthcare resource utilisation (HCRU) and associated cost in patients diagnosed with PD
 - To estimate the survival in patients diagnosed with PD

METHODS

- This non-interventional, retrospective cohort study used the Clinical Practice Research Datalink (CPRD)⁵ linked at patient level to the Hospital Episode Statistics (HES).⁶
- Data Source**
- CPRD is a real-world research service that collects anonymised patient data from a network of general practitioner (GP) practices across the UK.
 - HES is a secondary care data warehouse containing details of all admissions, outpatient appointments and accident and emergency attendances at hospitals in England.
 - Mortality data was obtained through HES database linked to the Office for National Statistics database.⁷
- Study Observation Period**
- Starting on 1st January 2000 and ending on 31st December 2019:

Figure 1. Study schema



Inclusion Criteria

- Permanently registered acceptable patient in CPRD (sufficient quality to be involved in research studies)
- PD diagnosis anytime prior or during the study observation period in CPRD
- Patient with ≥365 days follow-up at any point in time after the first recorded diagnosis and prior to 31st of December 2019
- For objective 1:
 - For incidence estimates, only patients with the first recorded PD during the study observation period
 - For prevalence estimates, only patients alive on the 31st December 2019
- For HCRU and survival objectives :
 - Patients with a first recorded diagnosis after 1st January 2005 (because of introduction of Payment by Results by the NHS in 2005)

Exclusion Criteria

- Patient with a diagnosis of Fabry disease recorded in CPRD during or before the study observation period

Statistical Analyses

- Categorical variables were described with frequencies and percentages and quantitative variables with arithmetic means and standard deviation (SD).
- Healthcare resource use and cost-estimates were reported per patient-year. Costs were estimated using Personal Social Services Research Unit reference costs⁸ for primary care and NHS tariffs⁹ for secondary care.
- Incidence was estimated by dividing the number of newly recorded diagnoses of PD in a calendar year by the mid-year total study population.
- Prevalence was estimated on the 31st December 2019 as a point-prevalence counting all patients with PD diagnosis on or prior to 31st December 2019 and who were alive on that date; and dividing by the total study population on that date.

RESULTS

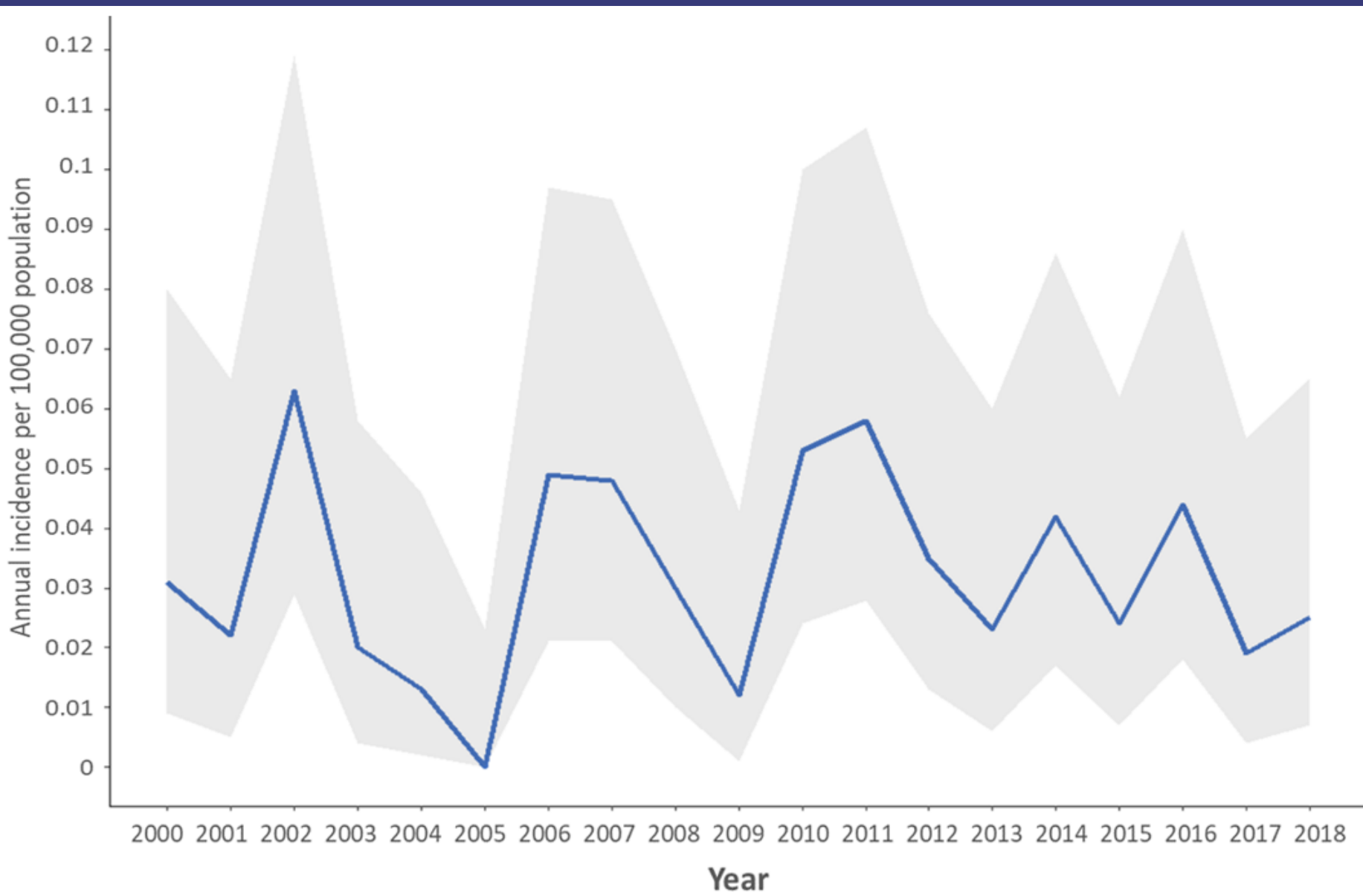
Study Population

- A total of 108 patients (mean age of 41 years) diagnosed with PD during the study period were identified in CPRD.
 - 12 (11.1%) patients with IOPD
 - 96 (88.9%) patients with LOPD
- Linked primary and secondary data was available for 53 patients.

Incidence and Prevalence of PD

- Average incidence for PD was 0.032 (95% CI: 0.026-0.039) per 100,000 persons (Figure 2).
- 94 patients were alive on 31st December 2019 providing a point prevalence of 0.706 (95% CI: 0.570-0.864) per 100,000 persons.

Figure 2. Incidence of Pompe disease by calendar year



Clinical Characteristics (Table 1)

- No cardiovascular involvement or hepatomegaly was reported prior to diagnosis.
- Musculoskeletal symptoms and respiratory infections were the most frequently reported symptoms.
- Approximately a third of LOPD patients had a record for Myozyme enzyme-replacement therapy (see Limitations) and one in seven had a record of wheelchair use.
- Mean weight for patients with IOPD was 20.7 kg (SD 11.3) and for LOPD was 77.3 kg (SD 20.1).

Table 1. Baseline characteristics

Patients' characteristics	Total cohort (n=108)
Age at first diagnosis of PD, years, Mean (SD)	41 (24)
Symptoms, n (%)	
Cardiovascular involvement	0
Hepatomegaly	0
Sleep Apnoea	9 (8.3%)
Asthma	17 (15.7%)
Musculoskeletal symptoms	23 (21.3%)
Walking or gait abnormalities	<5
Joint contractures	<5
Falls	<5
Respiratory infections	27 (25%)
Respiratory insufficiency	<5
Respiratory failure	10 (9.3%)
Ventilator dependence	8 (7.4%)

SD, standard deviation; events which occur in <5 people are not reported for privacy reasons.

Primary HCRU (Tables 2-3)

- Compared to LOPD, IOPD patients had a higher rate of GP appointments and consultations, and therefore higher associated costs.
- Ten most frequent referral departments post diagnosis of LOPD were (in order): orthopaedics, physiotherapy, ophthalmology, neurology, ear, nose & throat, gastroenterology, pain clinic, and musculoskeletal.

Table 2. Primary HCRU and associated costs (in GBP) for all patients, per patient-year during follow-up

Primary HCRU, Mean (SD)	LOPD (n= 96)	IOPD (n= 12)
GP visits	7.5 (8.5)	10.4 (13.4)
Consultations*	12 (12.3)	16.6 (19.9)
GP referral to secondary care	0.5 (0.8)	0.1 (0.2)
Prescription†	45.4 (55.8)	43.1 (33.9)
Cost, £, Mean (SD)		
GP visits	246 (281)	344 (443)
Consultations	270 (294)	364 (455)
Prescriptions	615 (1,018)	4,618 (3,356)

* Consultations were defined as a recorded contact with a healthcare professional including general practitioners or other allied professionals (e.g.: nurse, physiotherapist); † Primary healthcare prescribing was summarised as total number of prescriptions per patient year and included any issued prescription, repeat or acute.

Table 3. Number of patients with a primary care prescription during follow-up, organised by BNF Chapter

Primary care prescription, n (%)	LOPD (n= 96)	IOPD (n= 12)
Infections	77 (80.2%)	11 (91.7%)
Central nervous system	74 (77.1%)	9 (75%)
Nutrition & Blood	68 (70.8%)	12 (100%)
Gastrointestinal system	67 (69.8%)	11 (91.7%)
Skin	61 (63.5%)	8 (66.7%)
Musculoskeletal & Joint diseases	53 (55.2%)	5 (41.7%)
Cardiovascular system	52 (54.2%)	6 (50%)
Respiratory system	50 (52.1%)	9 (75%)
Ear, Nose & Oropharynx	44 (45.8%)	6 (50%)
Endocrine system	44 (45.8%)	0

BNF, British National Formulary; BNF is organised into Chapters and all NHS prescribed primary care treatment are listed in the BNF.

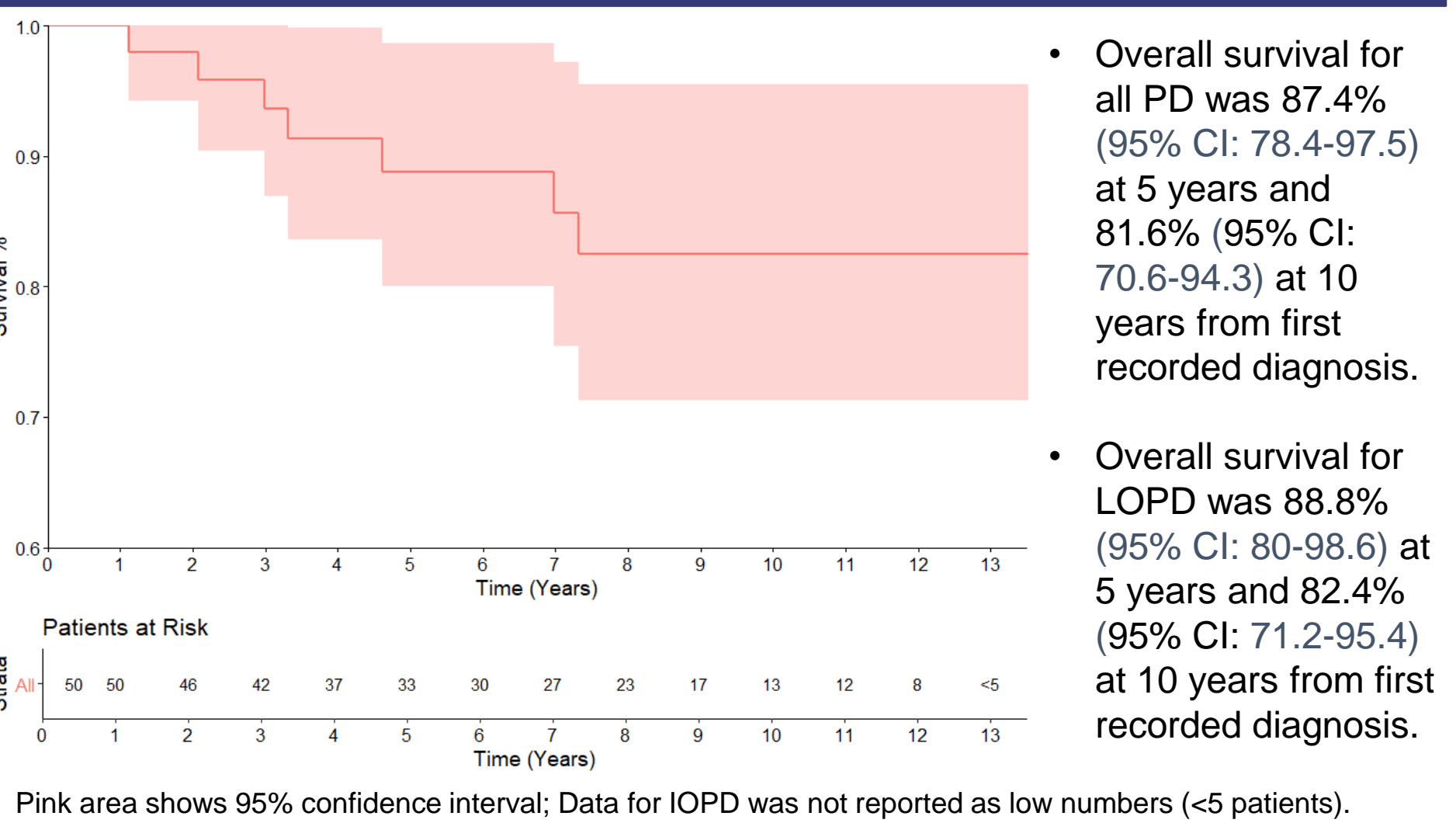
Table 4. Secondary HCRU and associated costs (in GBP) for all patients, per patient-year during follow-up

Secondary HCRU, Mean (SD)	LOPD (n= 96)	IOPD (n= 12)
Outpatient visit	2.7 (4.1)	1.6 (5.0)
Inpatient admissions	0.9 (2.6)	1.0 (2.5)
Non-elective admissions	0.2 (0.7)	0.7 (1.9)
Elective/day case admissions	0.8 (2.4)	0.3 (0.8)
Critical care admissions	0.01 (0.1)	0.05 (0.2)
Accident and emergency (A&E) attendances	0.2 (0.9)	0.4 (1.1)
Cost, £, Mean (SD)		
Outpatient visit	217 (309)	93 (451)
Inpatient admissions		
Non-elective admissions	386 (2,061)	3,616 (12,531)
Elective/day case admissions	338 (1,219)	553 (1,631)
Critical care admissions	65 (698)	2,585 (10,680)
A&E attendances	38 (138)	51 (147)

Secondary HCRU (Table 4)

- 40.6% of the LOPD patients had at least one admission during follow-up (a mean of 0.9 [SD 2.6] per patient-year).
- The majority of these admissions were day-cases or elective admissions (0.8 [SD 2.4] per patient-year).
- The highest A&E attendances was observed in IOPD patients while LOPD population had the highest rate of outpatient visits
- Primary and secondary HCRU associated costs were generally higher in IOPD patients.
- Ten percent of the LOPD patients had a critical care admission during the study period that costed a mean of £65 (SD 698) per patient year.
- The length of stay for elective, non-elective and critical care admissions were higher in IOPD than LOPD.

Figure 3. Kaplan-Meier survival plot for LOPD patients



LIMITATIONS

- Due to rarity of the diseases, low numbers of patients are available for research even from large datasets; small numbers raised the likelihood of biased estimates driven by outliers.
- Only patients with ≥365 days of follow-up post-index date during the study observation period were included in the analyses, therefore estimates of incidence and prevalence may have been underestimated.
- Validity and completeness of individual patient records cannot be assessed due to the nature of electronic health records data.
- The ERT is likely largely underreported as in another study in the UK 96% of the patients were on ERT.⁴ Moreover, according to the current practice, ERT is offered to all symptomatic patients.¹⁰
- Linkage between the two databases resulted in a loss of data. However, in our study, all patients included were registered with an English postcode, therefore secondary healthcare resource use could be evaluated assuming that patients not linkable to HES did not have any secondary care use during the observation period.
- The study was purely descriptive and did not be account for any confounding factors, therefore inferences are limited and comparisons of results between subgroup of patients may not be appropriate.

CONCLUSIONS

- The incidence and prevalence of PD as recorded in primary care electronic healthcare records were low and most patients were diagnosed in adulthood.
- 10-year survival was over 80%.
- Healthcare resource use appeared higher for IOPD than LOPD, although this was not statistically tested.
- Burden of non-elective and A&E admissions is an indicator of the high clinical burden of IOPD.
- PD is a rare condition; however, the clinical needs of the patients are significant, as evidenced by the volume of healthcare resource use and associated costs.

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ACKNOWLEDGMENTS

This study was sponsored by Sanofi and conducted by Harvey Walsh (part of OPEN Health company). The study was approved by Independent Scientific Advisory Committee (ISAC) for the data source (CPRD) with the reference number 20_161. Writing and editorial assistance were provided by Fatemeh Saberi Hosnijeh, of OPEN Health company, and funded by Sanofi.

DISCLOSURES

- SB, BH, and DH: Employees of OPEN Health, which has received consulting fees from Sanofi
- MK, LR, SC, and PS: Employees of Sanofi
- Fatemeh Saberi Hosnijeh and Myriam Alexander, of OPEN Health company, provided medical writing support.

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