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Incidence, prevalence and mortality of bullous pemphigoid in England 1998–2017: a population-based cohort study*

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Summary

Background A rising incidence and high mortality were found for bullous pemphigoid (BP) over a decade ago in the UK. Updated estimates of its epidemiology are required to understand the healthcare needs of an ageing population.

Objectives To determine the incidence, prevalence and mortality rates of BP in England from 1998 to 2017.

Methods We conducted a cohort study of longitudinal electronic health records using the Clinical Practice Research Datalink and linked Hospital Episode Statistics. Incidence was calculated per 100 000 person-years and annual point prevalence per 100 000 people. Multivariate analysis was used to determine incidence rate ratios by sociodemographic factors. Mortality was examined in an age-, sex- and practice-matched cohort, using linked Office of National Statistics death records. Hazard ratios (HRs) were stratified by matched set.

Results The incidence was 7·63 [95% confidence interval (CI) 7·35–7·93] per 100 000 person-years and rose with increasing age, particularly for elderly men. The annual increase in incidence was 0·9% (95% CI 0·2–1·7). The prevalence almost doubled over the observation period, reaching 47·99 (95% CI 43·09–53·46) per 100 000 people and 141·24 (95% CI 125·55–158·87) per 100 000 people over the age of 60 years. The risk of all-cause mortality was highest in the 2 years after diagnosis (HR 2·96; 95% CI 2·68–3·26) and remained raised thereafter (HR 1·54; 95% CI 1·36–1·74).

Conclusions We report a modest increase in the incidence rate of BP, but show that the burden of disease in the elderly population is considerable. Mortality is high, particularly in the first 2 years after diagnosis.

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Conflicts of interest
All authors declare no conflicts of interest.

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What is already known about this topic?

- Bullous pemphigoid (BP) is a blistering skin disorder which typically affects the elderly.
- BP poses a high burden on affected patients and has significant healthcare costs.
- The burden of disease in the UK was estimated over a decade ago and found to have a rising incidence and high mortality.

What does this study add?

- The incidence of BP in England was 7·63 (95% CI 7·35–7·93) per 100 000 person-years between 1998 and 2017.
- The burden of BP in the elderly population is substantial and it should not be considered a rare disease in these age groups.

- The risk of death was almost three times higher in the first 2 years after a diagnosis of BP compared with people without the disease and remained raised thereafter.

Bullous pemphigoid (BP) is a rare autoimmune disease, characterized by blistering of the skin. It is predominantly a disease of the elderly, and is associated with high morbidity, mortality and significant healthcare costs.[1,2] A previous study of BP in the UK estimated that the incidence was increasing by 17% per annum between 1996 and 2006.[3] However, this work was conducted over a decade ago and included only patients identified in primary care. More severe cases whose diagnosis was not returned to their general practitioner (GP), potentially because they died in hospital shortly after being diagnosed, would not have been captured. An updated estimate is required to quantify the burden of disease in England, which may be an important consideration when assessing the healthcare needs of an ageing population.

Routinely collected electronic healthcare records are valuable for examining a rare disease like BP, because of the availability of data on a large number of patients that are broadly representative of the UK population. Patients with BP can be identified using a validated method and code list with a positive predictive value of 93·2% [95% confidence interval (CI) 91·3–94·8).[4] The incidence and prevalence rates can be determined with high precision, while longitudinal follow-up allows long-term outcomes, such as death, to be examined. The aim of the present work was to determine the incidence, prevalence and mortality of BP in England between 1998 and 2017.

Patients and methods

Study design

Incidence and prevalence were examined using a retrospective cohort. An age-, sex- and practice-matched longitudinal cohort was used to compare the mortality of BP with the general population. We followed RECORD guidelines for the reporting of studies conducted using observational routinely collected health data.[5]

Data sources

Clinical Practice Research Datalink

The CPRD GOLD is a longitudinal database of UK general practices using the Vision software system. It contains anonymized healthcare records for approximately 17 million patients, with a current coverage of approximately 2·7 million (4%) of the UK population. Routinely collected clinical data generated from consultations, hospital discharges or specialist clinic letters are recorded using Read codes.[6] Diagnoses of BP are predominantly made in secondary care, but are subsequently returned to GPs and entered into primary care records.

The data in the GPRD have repeatedly been shown to be of good research quality.[7] At practice level, participating practices are assigned an 'up-to-standard' date on completion of regular audits confirming data quality. At the patient level, records are assessed and patients are deemed 'acceptable' if data checks indicate that their record meets prespecified quality standards.

Linked data

Approximately 75% of English practices, covering more than 10 million patients, have consented to provide patient-level information from linked resources.[8] The individual-level linked sources used in this study were Hospital Episode Statistics (HES) admitted patient care data and Office for National Statistics (ONS) death registration data. HES admitted patient care contains diagnoses for each hospitalization episode, coded using the International Classification of Diseases version 10 (ICD-10).[9,10] Death registration data contain the official date of death.

Study population

Adult men and women registered with 410 HES-linked general practices in England during the period of 1 January 1998 to 31 December 2017 were included. Patients were eligible from the date their practice was deemed to be contributing up-to-standard data and their record was verified as 'acceptable' research quality.

Outcomes

For incidence and prevalence, the outcome was a diagnosis of BP in the CPRD or HES. The date of death was the outcome for the all-cause mortality analyses.

Case definition of bullous pemphigoid

A diagnosis of BP is usually made on referral to a dermatology department, where patients undergo clinical examination and laboratory investigations, usually a skin biopsy for histology and direct immunofluorescence. The diagnosis is consequently communicated to primary care, where it is entered in the CPRD using Read codes, or to the person's inpatient records, where it is entered in the HES admitted patient care records using ICD-10 codes.

People with BP were adult patients with a diagnostic code for BP in the CPRD or HES. An algorithm was applied to the CPRD to identify patients with Read codes for BP (M145, 'bullous pemphigoid'; M145·00, 'pemphigoid'; or M145z00, 'pemphigoid not otherwise specified').[4] A similar algorithm, using ICD-10 diagnostic codes, was applied to HES admitted patient care data (L12·0, 'bullous pemphigoid'; or L12·9, 'pemphigoid, unspecified'). The index date of diagnosis for people with BP was the first date of occurrence of the Read or ICD-10 code generated from the algorithm.

Incident diagnoses were those with an index date at least 1 year after their current registration date with their GP. The 1-year lag period was imposed to minimize the risk of prevalent cases being identified as incident ones.[11] Prevalent diagnoses were those with a record of BP at any point before the end of the observation period.

Matched disease-free individuals

Up to four disease-free unexposed individuals were selected randomly for each case and matched by age (within 1 year of date of birth), sex and general practice. They were assigned an index date, which was the date of diagnosis of BP of the case they were matched to. The matched disease-free individuals had to be alive and contributing data at the time of the index date.

Observation period

The observation period commenced on the latest of (i) 1 January 1998, (ii) the date the patient registered with their current practice, (iii) the practice's up-to-standard date, or (iv) the patient's 18th birthday.

The observation period terminated on the earliest of (i) 31 December 2017, (ii) the date of death, (iii) the date the patient left the practice, (iv) the practice's last data collection date, or (v) the most recent linkage date between CPRD and HES.

Statistical analysis

Incidence

The incidence rates per 100 000 person-years overall and by age (10-year bands), calendar period (3-year bands), sex, ethnicity, region and index of multiple deprivation were calculated. Poisson regression was used to determine incidence rate ratios (RRs) for each sociodemographic factor. For the unordered categorical factors, region and ethnicity, the group with the most person-years of follow-up was chosen as the reference category. Multivariate regression was used to adjust for age, sex and calendar period. A post hoc examination of the interaction between age and sex, adjusted for calendar period, was conducted.

The crude and age- and sex-adjusted annual changes in incidence were determined over the 20-year observation period. The crude incidence rate for each calendar year, with direct standardization to the European Standard Population of 2013, was determined.

Annual point prevalence

The number of individuals with BP contributing data on 31 July of each calendar year was divided by the total number of adults alive and contributing data at the same point in time.

Mortality

People with BP and their matched disease-free individuals were followed from their index date and all deaths in the cohort were identified. Crude mortality rates were calculated per 1000 person-years. Kaplan–Meier techniques were used to determine 1-year mortality and median survival time. All-cause mortality in people with vs. without BP was compared using Cox proportional hazards regression stratified by matched set to account for age, sex, general practice and calendar period. The proportional hazards assumption, tested using Schoenfeld's residual, was violated. The observation period was therefore divided into two follow-up periods: within 2 years and 2 years or more after the index date.

Study size

This was a population-based cohort study that used all available data. Assuming only one matched disease-free individual was found per patient with BP, this study would have > 90% power to detect a HR of 2·1 or greater at the 5% significance level.[3]

Sensitivity analyses

The incidence, prevalence and mortality of BP in the UK were established using all primary care data available in the CPRD, irrespective of linkages. The results were compared with the primary analyses, which included only patients registered with HES-linked practices. Incidence RRs for ethnicity were determined only after 2006 as ethnicity data were more poorly recorded for people who registered with the CPRD prior to this.[12]

Unless otherwise specified, the P-values presented were obtained from the likelihood ratio test and $P < 0{\cdot}05$ was considered statistically significant. Analyses were conducted with Stata 16 (2019; StataCorp LLC, College Station, TX, USA).

Ethical approval

The present study was approved by the Independent Scientific Advisory Committee for the CPRD (ISAC protocol no 18_224).

Results

Study population

There were 2658 incident individuals with BP identified during the observation period: 2468 from English HES-linked general practices in the CPRD (Figure 1) and an additional 190 individuals with a diagnosis of BP only in their HES records. Median age at presentation was 81 (interquartile range 72–87) years and 1497 (56·3%) of patients were women.

Incidence

The pooled incidence rate over the 20-year period was 7·63 (95% CI 7·35–7·93) per 100 000 person-years (Table 1). The crude incidence rate was 25% higher in women (RR 1·25, 95% CI 1·16–1·35), but after adjustment for age and calendar period, the incidence rates were 13% lower in women (RR 0·87, 95% CI 0·80–0·94) than men. Incidence rates rose dramatically with age, such that the highest rates were recorded in patients over 90 years. The increase in incidence in older age groups was more marked for men than women (*P*-value for interaction < 0·001, Figure 2). After adjustment for age, sex and calendar period, rates were highest in those of Asian ethnicity and lowest in those of unknown ethnicity compared to whites, but ethnicity data were missing in 26% of the whole study population. Incidence varied by geographic region, but not by level of deprivation.

Between 1998 and 2017, incidence increased by 1·2% (RR 1·012; 95% CI 1·005–1·020; P = 0·002) per calendar year. After adjustment for age and sex, the estimated annual increase in incidence was 0·9% (RR 1·009; 95% CI 1·002–1·017; P = 0·016). Overall increase in incidence over the 20-year study period (2017 vs. 1998) was 16·4% after adjustment for age and sex (RR 1·164; 95% CI 0·805–1·684; P = 0·420). Annual incidence rates, calculated by direct standardization to the European Standard Population, are illustrated in Figure S1 (see Supporting Information).

Prevalence

The prevalence of BP was 26·82 (95% CI 23·83–30·19) per 100 000 people in 1998 and increased to 47·99 (95% CI 43·09–53·46) per 100 000 in 2017 (Figure 3). The most recent estimate of the prevalence of BP in those aged over 60 years was 141·24 (95% CI 125·55–158·87) per 100 000 people in 2017. In the over-80s, the prevalence was 375·02 (95% CI 320·31–439·04) per 100 000.

Mortality

The cohort included 2639 people with BP and 10 463 matched disease-free individuals (details provided in Supporting Information; Text S1). Within the cohort 1237 deaths occurred in the individuals with BP and 3427 in those without, equating to a crude mortality rate (per 1000 person-years) of 138·82 (95% CI 131·30–146·78) for people with BP and 74·56 (95% CI 72·11–77·10) for people without (Table 2). The median survival time was 4·93 years for people with BP and 9·27 years for people without (Figure 4). The 1-year mortality for BP was 20·36% (95% CI 18·82–22·00) and 7·03% (95% CI 6·54–7·55) for disease-free individuals.

After stratifying by matched set to account for age, sex and general practice, the HR was 2·96 (95% CI 2·68–3·26) in the first 2 years and 1·54 (95% CI 1·36–1·74) thereafter (Table 2).

Sensitivity analyses

All results were confirmed in sensitivity analyses using patients from all of the CPRD compared with the main analysis, which examined HES-linked practices only (Texts S2–S4, Figures S2, S3, Tables S1, S2; see Supporting Information).

Discussion

Our main findings are as follows. The incidence of BP during the 20-year observation period was 7·63 (95% CI 7·35–7·93) per 100 000 person-years. The incidence was highest in the elderly, particularly in elderly men. Between 1998 and 2017, the incidence of BP increased by 0·9% (95% CI 0·2–1·7) per calendar year and the prevalence almost doubled from 26·82 (95% CI 23·83–30·19) per 100 000 people in 1998 to 47·99 (95% CI 43·09–53·46) per 100 000 people in 2017. Using the European definition of a rare disease (prevalence < 50 per 100 000 people),[13] we have for the first time shown that BP is not a rare disease in the elderly (≥ 60 years).

The risk of death within 2 years of diagnosis was almost three times higher in patients with BP than in matched disease-free individuals (HR 2·96, 95% CI 2·68–3·26). The mortality remained raised throughout the remainder of the observation period (HR 1·54, 95% CI 1·36–1·74).

There are comparisons that can be made with other studies. An increasing incidence of BP has previously been reported in the UK using data from The Health Improvement Network (THIN) up to 2006.[3] The current data show a more modest increase in incidence over time, but a higher incidence rate across the whole observation period. The reasons for these differences are likely multifactorial, although largely driven by differences between the databases used. Significantly lower incidence rates have been reported for venous leg ulcers in THIN compared with the General Practice Research Database (the predecessor of CPRD) using data collected prior to 2000.[14] The low incidence rate of BP observed using THIN, particularly prior to 1998, may be artefactual and could explain why a more dramatic increase in incidence over time was found. Other factors that may explain the discrepancy include small differences in either the numerator or denominator between the present and the earlier study. For example, the present study used an algorithm to identify patients and included patients that had records of BP in HES, but not

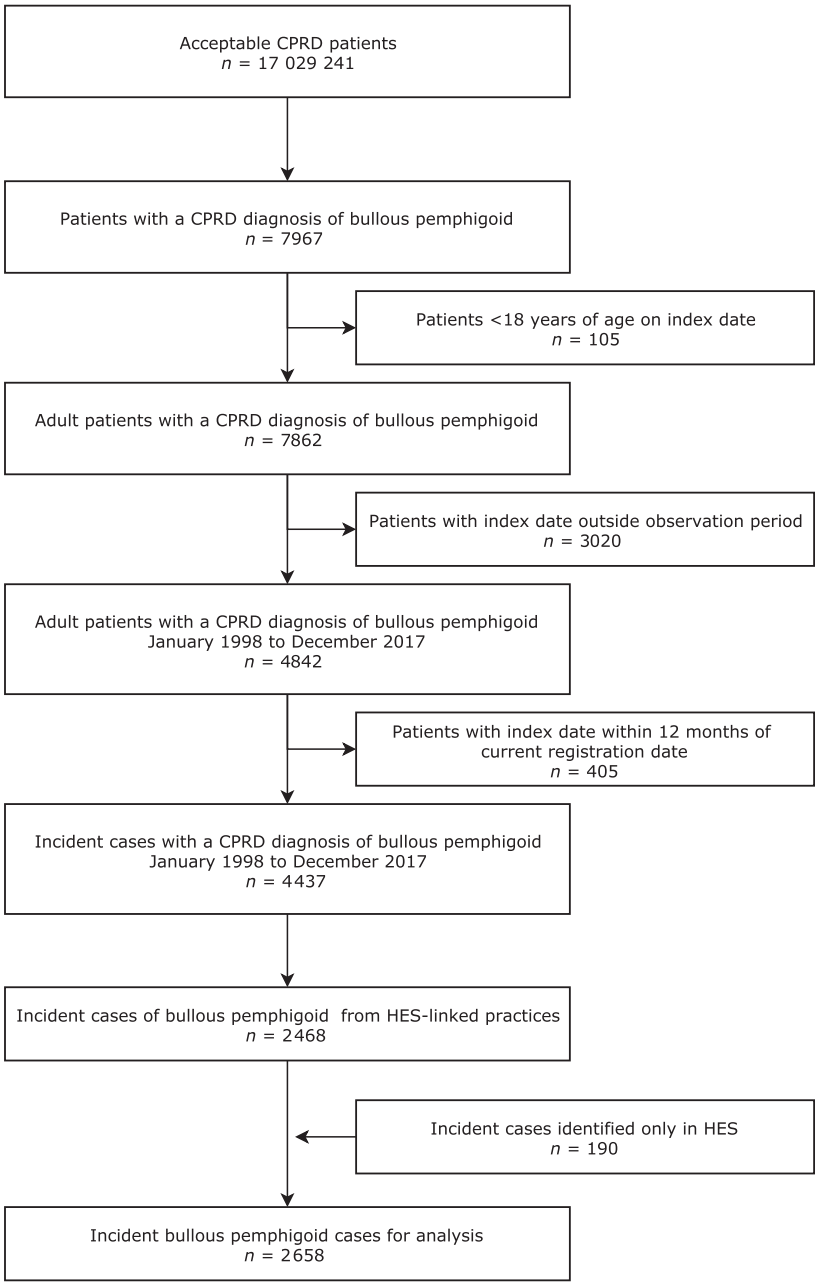

Figure 1 Algorithm used to identify incident adult individuals with bullous pemphigoid in the Clinical Practice Research Datalink (CPRD) between January 1998 and December 2017.

CPRD. Nevertheless, the absolute difference in incidence between the studies remains small and reduces over time.

Our incidence results are similar to those reported recently in Sweden.[15] Using the National Patient Register the authors reported an incidence of 7·1 (95% CI 6·5–7·7) per 100 000 person-years.[15] In contrast, studies conducted elsewhere in the world report lower results (Table S3; see Supporting Information).[3,15–28] This may be due to underlying differences in risk between populations or because of differences in methods. For example, other studies generally present rates for the population including children, who are rarely affected. In addition, other studies are generally smaller, hospital based and may not achieve complete capture of all cases within the defined denominator as patients managed in primary care or referred to other dermatology centres outside the geographical boundaries of the study are often missed.

The 1-year mortality of 20·36% in the present study is similar to previous estimates from the UK. Between 1996 and 2006, the 1-year mortality in the UK using THIN was 19% (95% CI 16·2–21·8).[3] Between 1991 and 2001 the 1-year mortality of the 83 incident cases identified from the Pathology and Immunology database of a single referral centre in

Table 1 Univariate and multivariate analysis of incidence of bullous pemphigoid in Hospital Episode Statistics-linked general practices and hospital inpatient records in England per 100 000 person-years

Variable	Person-years	Events	Incidence rate (CI)	Crude RR (CI)	P-value	Mutually adjusted incidence RRs (CI)	P-value
Pooled	34 825 210	2658	7·63 (7·35–7·93)	–		–	
Sex					< 0·001		< 0·001
Male	17 171 950	1161	6·76 (6·38–7·16)	1·00		1·00	
Female	17 653 250	1497	8·48 (8·06–8·92)	1·25 (1·16–1·35)		0·87 (0·80–0·94)	
Age group (years)					< 0·001[a]		< 0·001[a]
< 60	24 467 650	254	1·04 (0·92–1·17)	1·00		1·00	
60–69	4 765 380	264	5·54 (4·91–6·25)	5·34 (4·49–6·34)		5·34 (4·49–6·34)	
70–79	3 423 240	662	19·34 (17·92–20·87)	18·63 (16·12–21·53)		18·79 (16·26–21·72)	
80–89	1 812 280	1074	59·26 (55·82–62·92)	57·09 (49·79–65·45)		58·12 (50·67–66·67)	
≥ 90	356 660	404	113·27 (102·75–124·88)	109·12 (93·27–127·66)		112·88 (96·36–132·23)	
Calendar year(years)					0·007[a]		0·049[a]
1998–2000	3 702 250	247	6·67 (5·89–7·56)	1·00		1·00	
2001–2003	5 543 890	405	7·31 (6·63–8·05)	1·10 (0·94–1·28)		1·07 (0·91–1·26)	
2004–2006	6 288 600	470	7·47 (6·83–8·18)	1·12 (0·96–1·31)		1·09 (0·94–1·28)	
2007–2009	6 605 740	508	7·69 (7·05–8·39)	1·15 (0·99–1·34)		1·12 (0·96–1·30)	
2010–2012	6 369 500	534	8·38 (7·70–9·13)	1·26 (1·08–1·46)		1·20 (1·03–1·40)	
2013–2015	4 745 980	363	7·65 (6·90–8·48)	1·15 (0·98–1·35)		1·08 (0·92–1·27)	
2016–2017	1 569 240	131	8·35 (7·03–9·91)	1·25 (1·01–1·55)		1·21 (0·98–1·50)	
Ethnicity					< 0·001		< 0·001
White	23 950 960	2318	9·68 (9·29–10·08)	1·00		1·00	
Black[b]	484 490	14	2·89 (1·71–4·88)	0·30 (0·18–0·51)	< 0·001	0·80 (0·48–1·36)	0·415
Asian[b]	965 200	47	4·87 (3·66–6·48)	0·50 (0·38–0·67)	< 0·001	1·37 (1·03–1·84)	0·033
Other[b]	418 380	23	5·50 (3·65–8·27)	0·57 (0·38–0·86)	0·007	1·22 (0·81–1·84)	0·347
Unknown[b]	9 006 180	256	2·84 (2·52–3·21)	0·29 (0·26–0·33)	< 0·001	0·63 (0·55–0·72)	< 0·001
Region					< 0·001		0·020
North West	5 374 400	359	6·68 (6·02–7·41)	1·00		1·00	
North East	799 330	43	5·38 (3·99–7·25)	0·81 (0·59–1·11)		0·81 (0·59–1·11)	
Yorkshire & The Humber	1 402 950	100	7·13 (5·86–8·67)	1·07 (0·86–1·33)		1·02 (0·82–1·28)	
East Midlands	1 052 510	65	6·18 (4·84–7·88)	0·93 (0·71–1·20)		0·95 (0·73–1·24)	
West Midlands	4 254 880	307	7·22 (6·45–8·07)	1·08 (0·93–1·26)		0·99 (0·85–1·15)	
East of England	4 007 770	316	7·89 (7·06–8·80)	1·18 (1·02–1·37)		1·12 (0·96–1·30)	
South West	4 355 830	430	9·87 (8·98–10·85)	1·48 (1·29–1·70)		1·20 (1·04–1·38)	
South Central	4 543 990	377	8·30 (7·50–9·18)	1·24 (1·08–1·44)		1·14 (0·99–1·32)	
London	4 352 770	308	7·08 (6·33–7·91)	1·06 (0·91–1·23)		1·15 (0·99–1·34)	
South East Coast	4 680 780	353	7·54 (6·79–8·37)	1·13 (0·98–1·31)		0·99 (0·85–1·14)	
Deprivation					0·005*		0·208*
1	8 312 070	657	7·90 (7·32–8·53)	1·00		1·00	
2	7 702 910	601	7·80 (7·20–8·45)	0·99 (0·88–1·10)		0·94 (0·84–1·05)	
3	7 260 820	610	8·40 (7·76–9·10)	1·06 (0·95–1·19)		1·02 (0·91–1·14)	
4	6 272 660	438	6·98 (6·36–7·67)	0·88 (0·78–1·00)		0·91 (0·80–1·02)	
5	5 276 750	352	6·67 (6·01–7·41)	0·84 (0·74–0·96)		0·93 (0·81–1·06)	

[a]LR test for trend; [b]Wald's test; all other *P*-values are from LR test. Mutually adjusted model is adjusted for age, sex and calendar year. CI, confidence interval; HES, Hospital Episode Statistics; LR, likelihood-ratio test; RR, rate ratio

North-east Scotland was 25%.[23] A recent meta-analysis estimated the pooled 1-year mortality rate in European populations to be 26·7% (95% CI 22·2–31·2), although the heterogeneity between studies was large.[28] Survival in the first year after diagnosis appears marginally better in England than in the rest of Europe, but worse than the USA (15·1%, 95% CI 7·9–22·3). Such differences in mortality could be explained by differences between populations, methods of case and outcome ascertainment, temporal trends, or true differences in the mortality between nations.

The strengths of this study include a large sample size, a population that is representative of the UK general population, use of a validated approach to identify cases, accurate recording of death dates, and using linked primary and secondary care data to get a more comprehensive coverage of cases. Using routinely recorded data on a population level makes this study less susceptible to selection bias.

Case ascertainment is a limitation as it is reliant on the presence of clinical codes indicative of BP. Inaccurate recording may have affected the estimates. We know from previous

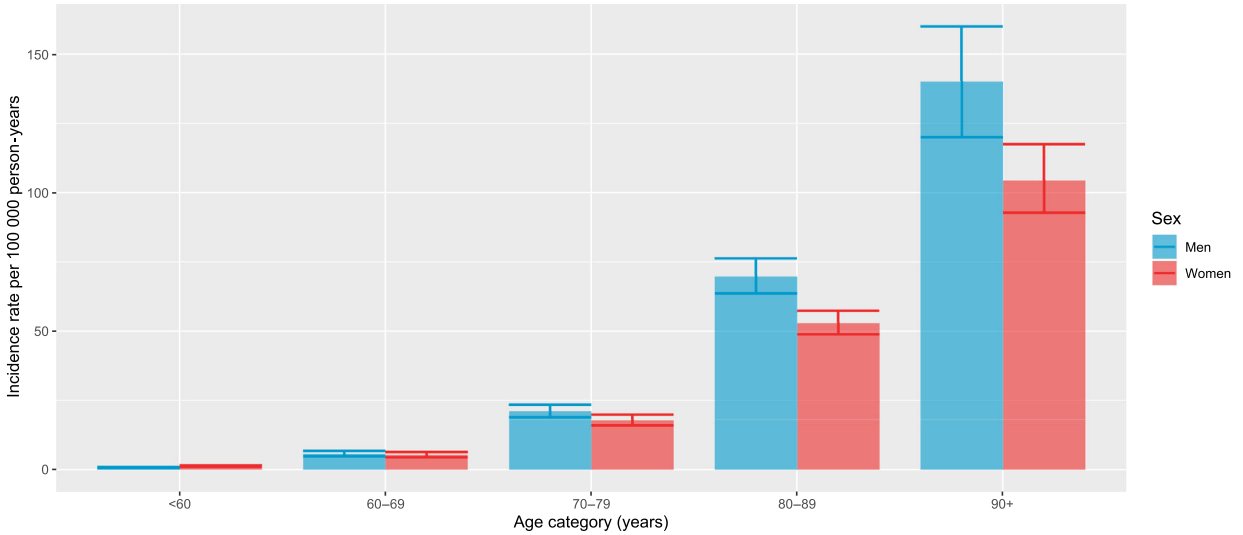

Figure 2 Crude incidence rate of bullous pemphigoid in English Hospital Episode Statistics-linked general practices and hospital inpatient records per 100 000 person-years per age category. Rates shown separately for men and women, with upper and lower limits of 95% confidence intervals.

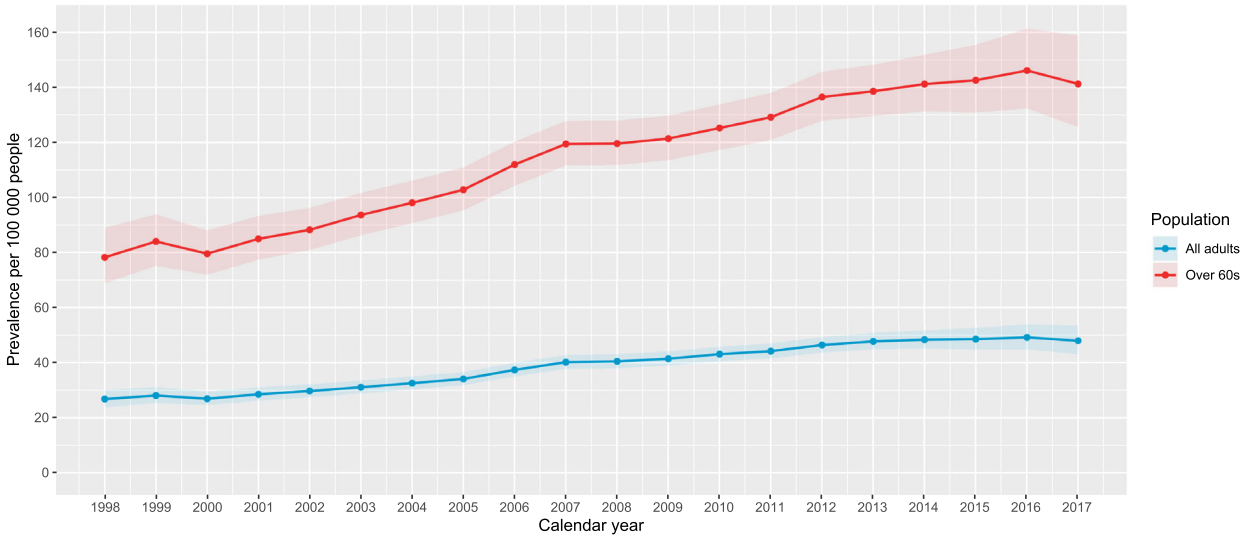

Figure 3 Point prevalence of bullous pemphigoid on 31 July of each calendar year in English Hospital Episode Statistics-linked general practices, per 100 000 people. Prevalence rates shown for all adults and for people aged over 60 years, with shading indicating the upper and lower limits of the 95% CI.

work that a small proportion of those identified with BP codes are likely to have other diagnoses, such as mucous membrane pemphigoid.[4] Inversely, some patients with BP may be missed as they are coded as having pemphigus vulgaris. However, the positive predictive value of the BP codes in this study is 93%, supporting our conclusions. Additionally, it is difficult to interpret findings related to ethnicity due to poor recording in those registered prior to 2006. Finally, our work has assumed that once a patient has developed BP they remain a prevalent case until the end of follow-up. In reality, patients may enter remission or become disease-free, and the true prevalence of BP may be more conservative than that presented.

The possible explanations for our findings follow here. The incidence of BP rises with increasing age, which may reflect an aetiology related to the biological process of ageing. This effect was more marked in men. An alternative explanation may be the age-related rise in prevalence of diseases associated with the development of BP, such as dementia and Parkinson's disease.[30,31] Alternatively, the relationship may reflect increasing use of drugs that induce BP in the elderly population. Variation in the incidence of BP was also observed between

Table 2 Hazard ratios (HRs) for death, stratified by matched set, comparing patients with bullous pemphigoid and matched disease-free people from Hospital Episode Statistics-linked general practices and hospital inpatient records in England. Mortality rates are presented per 1000 person-years

Variable	Person-years	Events	Mortality rate (95% CI)	Stratified HR[a] (95% CI)	P-value
Pooled[b]					
Controls	45 961·5	3427	74·56 (72·11–77·10)	–	
Cases	8910·7	1237	138·82 (131·30–146·78)		
< 2 years					
Controls	17 374·5	1270	73·10 (69·18–77·23)	1·00	< 0·001
Cases	3759·0	734	195·26 (181·64–209·91)	2·96 (2·68–3·26)	
≥ 2 years					
Controls	28 578·0	2157	75·45 (72·34–78·71)	1·00	< 0·001
Cases	5151·7	503	97·64 (89·47–106·55)	1·54 (1·36–1·74)	

[a]HR stratified by matched set to account for age, sex, general practice and calendar period; [b]stratified HR not calculated for the pooled follow-up period as the proportional hazards assumption was violated. CI, confidence interval

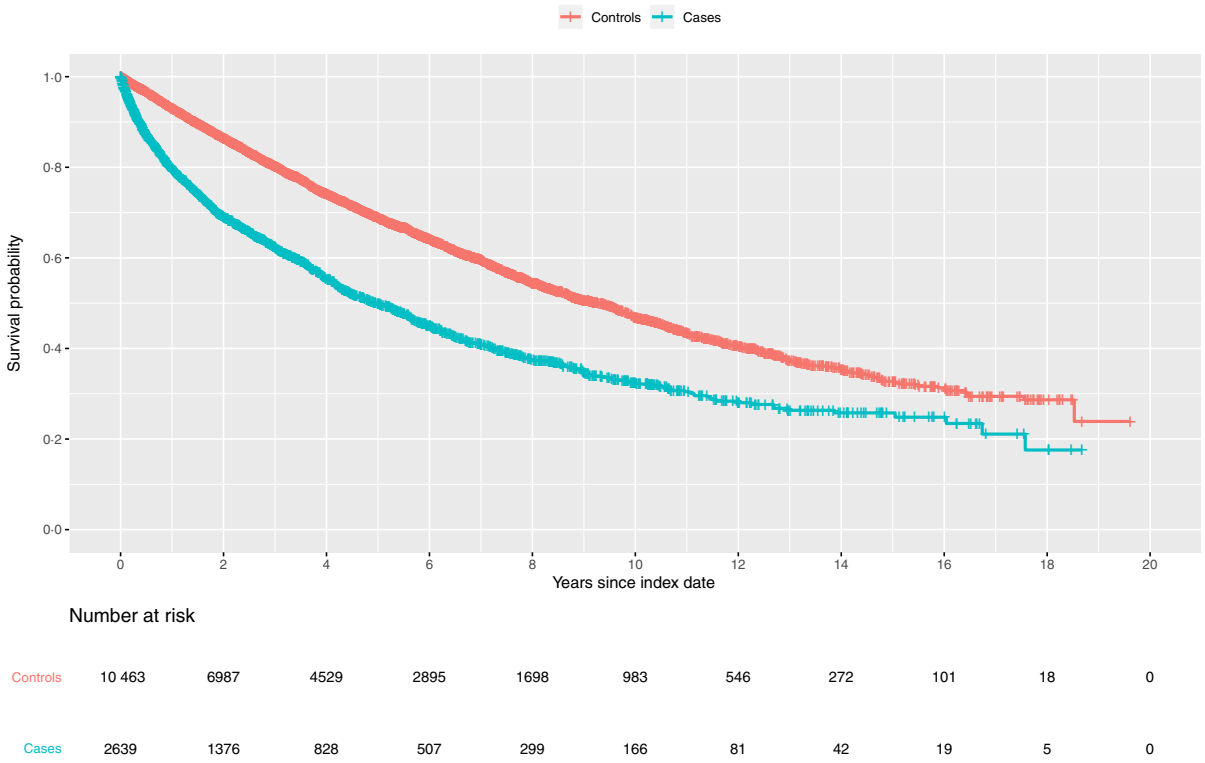

Figure 4 Kaplan–Meier curve for patients with and without bullous pemphigoid, showing mortality over time since index date and number of patients remaining in the study.

ethnic groups and geographic regions. The antidiabetic drug dipeptidyl peptidase-4 inhibitor (DPP-4i) is associated with an approximate doubling of the risk of BP[32–36] and the increased risk in Asians, compared with the white ethnic group, may partly relate to the increased levels of diabetes in this ethnic group. The rising trend for prescriptions of DPP-4i for diabetes throughout the study period may also contribute to the increased incidence observed.[37,38] Regional differences could point to environmental factors, perhaps to differences in incidence between urban and rural communities,[18] or could be due to differences in the prescribing patterns or awareness of BP in the medical communities. The rising prevalence of BP may be a result of the increasing incidence of the disease or may reflect that the English population is living longer.[39] Alternatively, it may be that the prevalence nearer the date of database inception may be underestimated. People with diagnoses prior to the inception of CPRD may not have had the disease entered retrospectively into their electronic records.

In terms of possible clinical implications of our findings, healthcare professionals should be made aware that BP is not a rare disease in the elderly. A greater awareness of the disease will hopefully reduce diagnostic delay. The mortality risk from BP has remained largely unchanged since it was last examined over a decade ago. Improved management, a better understanding of the aetiology, and examination of the causes of death in BP are still required.

In conclusion, BP is a rising concern for the ageing population of England. In the elderly population, it should no longer be considered a rare disease. Its incidence increases with age and it is associated with almost a three times greater chance of death in the first 2 years after diagnosis compared with disease-free individuals. The increased burden of disease, particularly in the elderly, requires earlier diagnosis, improved treatment and better understanding of the aetiology.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Univariate and multivariate analysis of incidence of bullous pemphigoid in UK primary care per 100 000 person years.

Table S2 HR for death, stratified by matched set, comparing patients with bullous pemphigoid and matched disease-free people from general practices in the UK.

Table S3 Published studies reporting the incidence or prevalence of bullous pemphigoid.

Figure S1. Age-adjusted incidence rate of bullous pemphigoid in English Hospital Episode Statistics-linked general practices and hospital inpatient records.

Figure S2. Point prevalence of bullous pemphigoid on 31 July of each calendar year in all of the CPRD, per 100 000 people.

Figure S3. Kaplan–Meier curve showing mortality over time since diagnosis of bullous pemphigoid or index date in disease-free individuals in all CPRD practices.

Text S1. Details of matching individuals with and without bullous pemphigoid for mortality analyses.

Text S2. Incidence sensitivity analysis.

Text S3. Prevalence sensitivity analysis.

Text S4. Mortality sensitivity analysis.

Powerpoint S1 Journal Club Slide Set.

Video S1 Author video.