Supporting information: Partner bereavement and risk of chronic urticaria, alopecia areata and vitiligo: cohort studies in the United Kingdom and Denmark

Contents

Appendix S1. Description of Funding sources and conflict of interest statement

Funding sources: This study was funded by the European Academy of Dermatology and Venerology (PPRC-2016-019), Psoriasisfonden (The Danish Psoriasis Foundation), Fabrikant Einar Willumsens Mindelegat (Manufacturer Einar Willumsen's Memorial Trust), Else og Mogens Wedell-Wedellsborgs Fond (Else and Mogens Wedell-Wedellsborgs Foundation), Torben og Alice Frimodts Fond (Torben and Alice Frimodts Foundation), A.P. Møller og Hustru Chastine Mc-Kinney Møllers Fond til almene Formaal (The A.P. Møller Foundation for the Advancement of Medical Science), Etly & Jørgen Stjerngrens Fond (Etly and Jørgen Stjerngrens Foundation).

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Appendix S2. Additional description of methods.

Settings

We conducted two cohort studies using study data from the UK (January 1997 to July 2017) and Denmark (January 1997 to December 2016). Both countries have publicly funded health care systems with universal health coverage [1, 2].

In the UK, we used the primary care data from the Clinical Practice Research Datalink (CPRD) Gold [3], with linked data from the Office for National Statistics (ONS) (deaths), Hospital Episode Statistics (HES) (hospital admissions), and the Index of Multiple Deprivation (IMD, socioeconomic deprivation).

In Denmark, we used data from nationwide registries on demographics, civil and vital status (Civil Registration System) [4], hospital contacts including inpatient stays, outpatient hospital clinic visits, and emergency department visits (Danish National Patient Registry) [5], and education duration (Danish Education Registries) [6]. Data were linked using the unique personal identifier assigned to all Danish residents at birth or upon immigration. We endeavoured to make the UK and Danish cohort studies as similar as possible to ensure comparability (see details of data sources in Appendix S4).

Couple identification

In the UK, we used the CPRD to identify partners using a previously developed algorithm [7-11]. We defined study initiation as the latest of the date an individual's GP practice met CPRD quality control standards or the study start date. In each household, we identified an opposite-sex couple with an age gap of ≤10 years and no person in the

same household aged within 15 years of either member of the couple on the study initiation date. We excluded couples in which both partners were <40 years or ≥95 years; in which either partner had a record of a morbidity code indicating residence in a communal establishment; or couples in households with >10 registered members.

In Denmark, we identified partners using an algorithm developed by Statistics Denmark that uses unique personal identifiers and determines partnership status (spouse/partner) by considering information on civil status, demographics, address, and close kinship (*e.g.*, parents, siblings, and children) [12].

Matched study population

Among eligible couples, we identified bereaved people (exposed) when their partner died. The date of bereavement was defined as the index date. In the UK, we obtained dates of death from ONS when available (59.8%) and from CPRD for individuals not linked to ONS (40.2%). In Denmark, we used death dates from the Civil Registration System.

We then matched each bereaved person to up to 10 non-bereaved partners (sampling with replacement) on age (within 1 year), sex, and county of residence (Denmark) or general practice (UK) on the index date. Individuals were only included in the comparison cohort if they had not experienced partner bereavement on or before the index date of their matched bereaved person. We excluded all individuals who died on the index date as they did not contribute person-time. We also excluded all individuals with a diagnosis of a relevant outcome (urticaria, alopecia areata, or vitiligo) before the index date. We required all study participants to have ≥1 year of healthcare registration

history prior to the index date in the UK, to allow adequate time for recording covariates and history of outcomes of interest. Details of the exclusion criteria are presented in Appendix S5.

Outcomes

In the UK, we identified chronic urticaria, alopecia areata, and vitiligo using relevant morbidity codes recorded in in primary (Read codes) or secondary care (*International Classification of Diseases*, *Eighth* and *Tenth Revisions* [ICD-8 and ICD-10] codes), and diagnostic algorithms (Appendix S5). Code lists are available for download: https://datacompass.lshtm.ac.uk/1544/ (UK) and Appendix S6 (Denmark). We followed all participants from their index date until diagnosis of a specific outcome (urticaria, alopecia areata, or vitiligo), date of last data collection from primary care practice (UK), transfer out of the practice by either member of the couple (UK), emigration of either member of the couple (Denmark), death, or the study end date, whichever occurred first. If an individual in the comparison cohort experienced bereavement, he/she was censored one day before bereavement and subsequently included in the bereaved cohort (Figure S1).

Covariates

As possible confounders, we included comorbidities (original Charlson Comorbidity Index (CCI) score) [13], lifestyle covariates (smoking and alcohol consumption), body mass index (BMI), and socioeconomic status (quintile of IMD [UK] and education duration [Denmark]) (Appendix S5).

We hypothesised that the level of stress associated with bereavement depends on whether a partner's death was unexpected. We therefore stratified the estimates by the degree to which the partner's death might be considered unexpected based on comorbidity level for the partner who died. We computed an age-adjusted CCI score based on comorbidities recorded up to one month before death of deceased partners. The age-adjusted CCI assigns 0 to 6 points to a range of chronic diseases according to their ability to predict death, with additional points given according to age [13]. Based on the total score, we classified the risk of partner death as low (0–3 points), intermediate (4–6 points), or high (≥7 points). As an alternative measure, we identified presence of terminal disease among partners as recorded before the date of death.

Statistical analysis

We used stratified Cox regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for chronic urticaria, alopecia areata, and vitiligo comparing those who were bereaved to those who were not bereaved. In the main analysis, we examined associations for the entire follow-up period. As we hypothesized that the effect of bereavement would be most pronounced during the short-term [10], we further examined the associations by time since the index date (for alopecia areata and vitiligo: 0–30 days, 0–90 days, 0–365 days, and 0–1095 days; for chronic urticaria: as our definition required two codes recorded six weeks apart, we categorised the follow-up time as 0–182 days, 0–365 days, and 0–1095 days). We initially constructed an unadjusted model stratified by matched set to account for the matching variables. In a second model, we additionally adjusted for CCI. In the fully-adjusted model, we further

adjusted for education duration (Denmark), IMD status (UK), BMI (UK) and lifestyle variables (UK).

In each setting, we stratified the main analysis by age, sex, and risk of partner death (deceased partner's age-adjusted CCI score and presence of terminal disease). We used likelihood ratio tests to explore possible effect modification by these characteristics.

We undertook complete-case analyses in the fully-adjusted models, which would be unbiased under the assumption that missingness was not associated with the outcome, conditional on the other variables. As lifestyle data are unlikely to be missing at random and we lacked data on probable predictors of missingness, imputation techniques were not appropriate for correcting potential biases [14]. We further investigated patterns of missingness using conditional logistic regression. In addition to fitting the unadjusted and adjusted models using the full sample, we also fitted the models on the sub-cohort without missing covariate data (complete-case subcohort) to allow comparison with the fully-adjusted model.

We assessed the assumption of proportional hazards for the overall study period and each specific time period by visual inspection of log-log plots. We further evaluated whether the HRs changed over time by stratifying the follow-up period since bereavement (0–182 days, 183–365 days, 366–1095 days, 1095+ days for chronic urticaria; 0–30 days, 31–90 days, 91–365 days, 366–1095 days, 1095+ days for alopecia areata and vitiligo).

We conducted several sensitivity analyses to test the robustness of the results (Table S1). All study analyses were pre-planned unless otherwise stated. We conducted all

analyses separately for the UK (using Stata/MP 15.1) and Denmark (using SAS 9.4). We combined the main results (from the adjusted models) in Stata using DerSimonian and Lairds' random-effects model [15].

Reference:

1. Majeed A. Universal health coverage in the United Kingdom. J Ambul Care Manage 2003;26(4):373-7.
2. Schmidt M, Schmidt SAJ, Adelborg K*, et al.* The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563-591.
3. Herrett E, Gallagher AM, Bhaskaran K*, et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44(3):827-36.
4. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29(8):541-9.
5. Schmidt M, Schmidt SA, Sandegaard JL*, et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-90.
6. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39(7 Suppl):91-4.
7. Shah SM, Carey IM, Harris T*, et al.* The effect of unexpected bereavement on mortality in older couples. Am J Public Health 2013;103(6):1140-5.
8. Shah SM, Carey IM, Harris T*, et al.* Do good health and material circumstances protect older people from the increased risk of death after bereavement? Am J Epidemiol 2012;176(8):689-98.
9. Schmidt SA, Vestergaard M, Pedersen HS*, et al.* Partner Bereavement and Risk of Herpes Zoster: Results from Two Population-Based Case-Control Studies in Denmark and the United Kingdom. Clin Infect Dis 2017;64(5):572-579.
10. Carey IM, Shah SM, DeWilde S*, et al.* Increased risk of acute cardiovascular events after partner bereavement: a matched cohort study. JAMA Intern Med 2014;174(4):598-605.
11. Wong AYS, Froslev T, Forbes HJ*, et al.* Partner bereavement and risk of psoriasis and atopic eczema: cohort studies in the United Kingdom and Denmark. Br J Dermatol 2019; 10.1111/bjd.18740.
12. Danmarks Statistik. *FAMILIE_TYPE*. https://www.dst.dk/da/Statistik/dokumentation/Times/forebyggelsesregistret/familie-type.
13. Charlson M, Szatrowski TP, Peterson J*, et al.* Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245-51.
14. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Stat Med 2010;29(28):2920-31.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45(Pt A):139-45.

Appendix S3. Additional description of results of additional and sensitivity analyses

Results

Patient characteristics

Figure S2 shows the study flowchart. Median age was approximately 74 years in the UK and 71 years in Denmark. Two-thirds of participants were women in both settings (Table S2). In both countries, bereaved individuals had a higher comorbidity burden, were more deprived (UK), more likely to be current smokers (UK), ex-drinkers (UK), obese (UK), and to have a shorter education duration (Denmark) than the non-bereaved comparison cohort at index date (Table S2).

Chronic urticaria

The pooled HR (adjusted for study participants' CCI scores) for the association between partner bereavement and chronic urticaria was 0.95 (95% CI, 0.85–1.07) (Figure S3). The number of events for chronic urticaria within 0–182 days since partner bereavement in both settings was small (Table S3). We observed no evidence of differences in risk of chronic urticaria within 0–365 days (HR 0.85, 95% CI, 0.55–1.31) or 0–1095 days (HR 0.87, 95% CI, 0.67–1.15) after bereavement (Figure S3).

Alopecia areata

The pooled HR (adjusted for study participants' CCI scores) for the association between partner bereavement and alopecia areata was 0.90 (95% CI, 0.73–1.12) (Figure S3). Very few events occurred within 0–30 days, 0–90 days and 0–365 days in either setting

(Table S3). We observed no evidence of higher HRs for alopecia areata within 0–1095 days (HR 1.01, 95% CI, 0.73–1.40) after bereavement.

Vitiligo

The pooled HR (adjusted for study participants' CCI scores) for the association between partner bereavement and vitiligo was 0.90 (95% CI, 0.74–1.10) (Figure S3). Very few events occurred within 0–30 days and 0–90 days since partner bereavement in either setting (Table S3). We observed no evidence of higher HRs for vitiligo associated with partner bereavement within 0–365 days in the UK (HR 1.30, 95% CI, 0.84–2.02) but were unable to estimate a reliable association using Danish data due to small number of events (Table 1). Similarly, we observed no evidence of a higher HR for vitiligo within 0–1095 days (HR 0.90, 95% CI, 0.47–1.75) after bereavement.

Subgroup analyses

Figure S4 and Tables S4-6 show the results of subgroup analyses by age, sex, and risk of partners' deaths for the entire follow-up period. For vitiligo, there was some evidence suggesting that the HR differed by sex (with a lower HR among men) in the UK. We did not observe substantial differences across other subgroups.

Additional analyses and sensitivity analysis

In the UK, missingness of lifestyle data was dependent on each outcome, conditional on bereavement status and other covariates (Table S7). However, HRs for the whole cohort and for the complete-case cohort were similar in unadjusted and adjusted models in both settings (Table S8). Some log-log plots did not show parallel lines

between bereaved and comparison persons, suggesting non-proportional hazards over time for chronic urticaria in Denmark and for vitiligo in the UK (Figure S6). We further investigated changes in HRs during several stratified follow-up periods (Table S7) and observed no significant difference in hazards for all outcomes in the UK. We found a lower HR for vitiligo (0.55, 95% CI, 0.07–4.14) within 0–30 days, and higher HRs within 31–90 days (2.05, 95% CI, 0.70–6.02), within 91–365 days (1.30, 95% CI 0.79–2.12), and within 366–1095 days (1.11, 95% CI, 0.76–1.62), and a lower HR after 1095 days since bereavement (0.56, 95% CI, 0.39–0.81) in the UK with wide CIs. We found a higher HR for alopecia areata within 366–1095 days (1.93, 95% CI 1.13–3.31), and a lower HR after 1095 days since bereavement (0.93, 95% CI 0.64–1.35) in Denmark. Results of all sensitivity analyses were similar to those of the main analysis (Tables S10–17).

Appendix S4. Additional discussion of results.

Based on routinely collected data in the UK and Denmark, our study showed no overall increased risk of chronic urticaria, alopecia areata, or vitiligo following partner bereavement.

Comparison with other studies

Limited prior epidemiological studies have investigated the association between stress and chronic urticaria. Consistent with our study, a 2018 case-control study did not find differences in the number of stressful life events during the past 12 months when comparing patients with chronic urticaria with controls [1]. The stress level was measured using the Social Readjustment Rating Scale [2], in which partner bereavement is considered as the most stressful item. However, only women were included, thus limiting the generalisability of study findings. In contrast, two cross-sectional studies reported that 16%-33% of patients with urticaria had experienced prior stressful life events [3, 4], most commonly the death of a close family member [4]. Notably, associations could not be established due to the absence of a control group [3, 4]. In a Taiwanese study, patients with chronic urticaria had more major life events during last 6 months, compared with controls, based on a semi-structured questionnaire [5].

Similar to chronic urticaria, current epidemiological evidence for an association between stress and alopecia areata is contradictory [6-12]. Only one case-control study [7] reported an increased risk associated with stressful life events in the past year,

measured using the Social Readjustment Rating Scale [2]. Another case-control study reported no difference in risk associated with recent stress, but a higher score in the presence of certain prior stressful life events including loss of a family member during childhood and emotional neglect by relatives [6]. Our findings are consistent with a third study that found no difference in stress scores between alopecia areata cases and controls [8]. The stress score was measured using the Life Event Scale, which contains 116 major life events including loss of spouse [13]. Further investigation showed that patients who attributed their illness to stressful life events reported more life events versus those who did not (mean difference 2.95) [8]. Similarly, four other studies reported no association between alopecia areata and psychological stress [9-12]. Unfortunately, low event rates of alopecia areata in our study limited our interpretation of the short-term effect of bereavement. Further investigation is needed to confirm our results.

Regarding vitiligo, one study reported no difference in the number of stressful events between cases and controls [14]. However, three other studies reported an increased risk of vitiligo associated with stress [7, 12, 15]. Of these, one study demonstrated a six-fold increased risk of vitiligo associated with stress [7]. In the UK setting, we observed a higher risk of diagnosing vitiligo in women but not in men. However, as men are less likely to present for a primary care consultation than women [16], we hypothesize that this sex difference is likely due to health-seeking behaviour rather than a protective role of bereavement in men. Another case-control study [15] observed more stressful life events, including death of spouse, among patients with vitiligo compared with controls, as measured by the Schedule of Recent Experience questionnaire [17]. However,

partner bereavement was not regarded as one of the 12 most frequently reported life events in the study [15]. A recent population-based matched cohort study also showed a significantly increased risk of vitiligo associated with stress-related disorders (HR 1.37) [12]. In our study, estimates were statistically imprecise in both settings, but a possibly increased risk of vitiligo associated with partner bereavement within 90 days in the UK was observed.

This is the first study to investigate the associations between partner bereavement and chronic urticaria, alopecia areata, and vitiligo. It included analysis of two large population-based cohorts in settings with universal healthcare. Unlike previous studies using diverse stressful life events as the exposure, we used partner bereavement as an extreme stressor, to minimise heterogeneity in exposure to different types of stress. Moreover, as recording of death is of high quality in both databases, partner bereavement represented a reliable measure with a specific onset compared with other stressful life events. Importantly, we used data from two countries to validate our findings.

Limitations

We were unable to measure the level and duration of stress arising from bereavement. However, the death of a partner is considered extremely stressful in most cases. Secondly, we may have misclassified partnership status, particularly in the UK setting where direct data on relationship status are unavailable. Moreover, we could not identify changes in partnership over time in the UK. We used relatively strict criteria to identify partners to reduce potential misclassification bias. Even if such misclassification was

present, bereavement of a significant household member was captured, which is also a stressful life event. Further, we used Danish data containing detailed information on partnership status to complement the UK findings. It is important to note that in Denmark skin disease outcomes were recorded in a hospital setting, resulting in a potential delay between actual disease onset and diagnosis and more likely representing severe cases. In contrast, mild/moderate cases diagnosed in primary care were captured in the UK setting. Moreover, as data were available since birth in the Danish setting, medical history of urticaria, alopecia areata, and vitiligo diagnosed in a hospital setting during childhood might be more completely recorded than in the UK setting. In the UK setting, there is missingness of BMI and lifestyle covariates, but results from sensitivity analyses showed little difference from the main analysis, suggesting that missing data is unlikely to affect our results. Finally, people with mild skin conditions may be less likely to seek medical advice in the period shortly after bereavement as these skin conditions are not life-threatening. This bias may have led specifically to underestimation during the short-term follow-up period and an overrepresentation of the most severe skin diseases.

Reference:

1. Ograczyk-Piotrowska A, Gerlicz-Kowalczuk Z, Pietrzak A*, et al.* Stress, itch and quality of life in chronic urticaria females. Postepy Dermatol Alergol 2018;35(2):156-160.
2. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. J Psychosom Res 1967;11(2):213-8.
3. Comert S, Celebioglu E, Karakaya G*, et al.* The general characteristics of acute urticaria attacks and the factors predictive of progression to chronic urticaria. Allergol Immunopathol (Madr) 2013;41(4):239-45.
4. Malhotra SK, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. Indian J Dermatol Venereol Leprol 2008;74(6):594-9.
5. Yang HY, Sun CC, Wu YC*, et al.* Stress, insomnia, and chronic idiopathic urticaria--a case-control study. J Formos Med Assoc 2005;104(4):254-63.

6. Taheri R, Behnam B, Tousi JA*, et al.* Triggering role of stressful life events in patients with alopecia areata. Acta Dermatovenerol Croat 2012;20(4):246-50.
7. Manolache L, Benea V. Stress in patients with alopecia areata and vitiligo. J Eur Acad Dermatol Venereol 2007;21(7):921-8.
8. Gulec AT, Tanriverdi N, Duru C*, et al.* The role of psychological factors in alopecia areata and the impact of the disease on the quality of life. Int J Dermatol 2004;43(5):352-6.
9. Brajac I, Tkalcic M, Dragojevic DM*, et al.* Roles of stress, stress perception and trait-anxiety in the onset and course of alopecia areata. J Dermatol 2003;30(12):871-8.
10. Picardi A, Pasquini P, Cattaruzza MS*, et al.* Psychosomatic factors in first-onset alopecia areata. Psychosomatics 2003;44(5):374-81.
11. van der Steen P, Boezeman J, Duller P*, et al.* Can alopecia areata be triggered by emotional stress? An uncontrolled evaluation of 178 patients with extensive hair loss. Acta Derm Venereol 1992;72(4):279-80.
12. Song H, Fang F, Tomasson G*, et al.* Association of Stress-Related Disorders With Subsequent Autoimmune Disease. JAMA 2018;319(23):2388-2400.
13. Sorias S. Research of the effects of stressful life events on patients and controls (in Turkish). Thesis. Izmir: Ege University, School of Medicine 1982.
14. Picardi A, Pasquini P, Cattaruzza MS*, et al.* Stressful life events, social support, attachment security and alexithymia in vitiligo. A case-control study. Psychother Psychosom 2003;72(3):150-8.
15. Papadopoulos L, Bor R, Legg C*, et al.* Impact of life events on the onset of vitiligo in adults: preliminary evidence for a psychological dimension in aetiology. Clin Exp Dermatol 1998;23(6):243-8.
16. Wang Y, Hunt K, Nazareth I*, et al.* Do men consult less than women? An analysis of routinely collected UK general practice data. BMJ Open 2013;3(8):e003320.
17. Amundson ME, Hart CA, Holmes TH. *The Schedule of Recent Experience (SRE)*: Washington: University of Washington Press; 1981.

Appendix S5. Information on data sources.

In the United Kingdom (UK) and Denmark, general practitioners coordinate all healthcare contacts, including referrals to specialists.

UK

We based the UK cohort study on data from the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), the Office for National Statistics (ONS), and the Index of Multiple Deprivation (IMD).

The CPRD covers approximately 7% of the UK population--a representative sample with regard to demographics (age, sex, and ethnicity) [1]. We used data from the CPRD Gold July 2017 build, which contains 14,942,430 patients whose care met acceptable quality standards across 718 general practices. The CPRD contains prospectively collected primary care records from general practices documented using Vision Software. Anonymised data include recorded symptoms and diagnoses (coded using Read codes), written prescriptions (coded using British National Formulary codes), health-related behaviors (smoking and alcohol consumption), anthropometric data (height and weight), and referrals to specialists. Approximately 60% of participating practices registered in England have consented to link their patient records to other data sources, including the HES, ONS and IMD.

The HES contains National Health Service inpatient hospital stay records in England, with linkage to the CPRD since 1997. Diagnoses are coded using the *International Classification of Diseases*, *Tenth Revision* (ICD-10), while procedures, including surgeries, are coded using the Office of Population and Censuses and Surveys (OPCS)

Classification of Interventions and Procedures codes, Version 4 [2]. Several diagnoses and procedures can be recorded for each care episode. Data on the order of diagnosis codes for a given episode are available, with the first-listed diagnosis typically constituting the main reason for admission. In the current study, the cohort used in the main analysis was not restricted to persons eligible for HES, because urticaria, alopecia areata and vitiligo are commonly diagnosed in the general practice setting. A sensitivity analysis restricted to cohort members with linked HES data was used to test the robustness of our results.

The ONS contains death registration data. Most information is supplied by the informant (usually a close relative of the deceased). Deaths are to be registered within five days, and on average 78% of deaths are registered within this time frame. The death registration data used in our study included all deaths registered from 2 January 1998 to 19 September 2017. Data on dates of death were available.

The English Indices of Deprivation [3] are based on several indicators covering aspects of material deprivation (housing, employment, income, access to services, education and skills, crime [personal and material victimisation at local level], and living environment). The Index of Multiple Deprivation (IMD) is calculated as a weighted sum of the domain indices. For practices in England that have consented to participate in the linkage program, the patient postcode of residence is mapped to the 2001 “lower layer super output area” (LSOA) boundaries using a postcode lookup file. Practice-level linkage uses the practice postcode, which is linked via LSOA, SOA (Northern Ireland), or datazone (Scotland) to the most recent versions of the different national Indices of

Deprivation. Both the patient-level and practice-level IMD contains quintiles of deprivation (1=least deprived, 5=most deprived).

Denmark

Denmark (population 5.7 million inhabitants) has a long tradition of registering health and social data about the population in nationwide registries. For this study, we used information recorded in the Civil Registration System [4], the Danish National Patient Registry [5], and the Danish Education Registry [6].

The Civil Registration System [4] contains computerised data on demographics, address, vital statistics, civil status, and identifiers of close relatives (spouse, children, and parents) for the entire Danish population since 1968. The Civil Registration System assigns a unique personal registration number to all Danish residents, which is used across the public sector to record information. This number enabled linkage of all data sources used in our study. We used the Civil Registration System to identify the study population, their partners, and vital status.

The Danish National Patient Registry [5] is a hospital registry established in 1977. It provides complete nationwide coverage of non-psychiatric inpatient stays since 1978 and psychiatric inpatient stays, outpatient specialty clinic (ambulatory) visits, and emergency room contacts since 1995. Each contact is registered with information on dates of admission and discharge or start and end of outpatient follow-up, the primary diagnosis (main reason for contact), optional secondary (contributory) diagnoses, surgical procedures, and certain non-surgical treatments and examinations. Diseases are recorded at discharge, outpatient contact, or surgery by the treating physician using

ICD-8 codes through 1993 and ICD-10 codes thereafter. We used the Danish National Patient Registry to identify comorbidities among members of the study cohorts and their deceased partners.

The Population Education Registry [6] includes information on the highest educational level attained by residents. It is based on administrative records from educational institutions and is supplemented with self-reported information for persons who completed their education before 1974 and for immigrants schooled outside Denmark. In 2007, 3% of ethnic Danes born in the 1945-1990 period had missing data. This number was higher for immigrants (up to 15%). It may be unreliable for younger people who are less likely to have attained their highest educational level.

References

1. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;**44**(3):827-36
2. NHS Digital. Hospital Episode Statistics (HES) 2019 [Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.] Accessed 12 July 2019.
3. Department for Communities and Local Government. The English Indices of Deprivation 2015 - Frequently Asked Questions (FAQs). 2015. [Available from: http://www.communities.gov.uk/publications/corporate/statistics/indices2010technicalreport.] Accessed 30 Aug 2019.
4. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29(8):541-9
5. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-90
6. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39(7 Suppl):91-4

Appendix S6. Algorithms for identifying study outcomes and covariates.

History of relevant study outcomes

Partners who had any diagnosis of relevant study outcomes recorded before cohort entry were classified as having a history of the outcomes and were therefore excluded from the analysis. In the UK, we used Read codes and *International Classification of Diseases, Tenth Revision* (ICD-10) codes to identify diagnoses in CPRD and HES when available. We used ICD-8 and ICD-10 codes in Denmark. In the analysis of chronic urticaria, we identified urticaria history, including codes for inducible forms urticaria and angioedema. For alopecia areata, all non-specific codes (including non-specific descriptions of areata or ophiasis) were used as exclusion criteria. For vitiligo, we included codes both for vitiligo and for hypopigmentation in the UK (not applicable in Denmark).

Study outcomes

In the UK, we identified chronic urticaria, alopecia areata, and vitiligo using relevant Read codes in CPRD primary care records. We also used ICD-10 codes identified from HES hospital records when available. In Denmark, we used ICD-8 and ICD-10 codes to identify inpatient, outpatient hospital clinic, and emergency room primary or secondary diagnoses from the Danish National Patient Registry.

In both settings, we defined chronic urticaria as at least two diagnoses recorded (on separate days) at least six weeks apart. The outcome date was identified as the second diagnosis. In Denmark, we excluded ICD-8 code “70890” and ICD-10 code “DL508D”. We defined alopecia areata and vitiligo outcomes as the first recorded diagnosis.

Lifestyle and education duration covariates

In the UK, categorization of lifestyle variables (smoking status, body mass index, and alcohol consumption) was based pragmatically on the status recorded closest to the index date. Records within 1 year before to 1 month after the index date were regarded as the best, records within 1 month after the index date to 1 year after as the second best, the record nearest to 1 year before the index date as third best, and the record nearest to 1 year after the index date as least best. We mainly used Additional Clinical Details files in the CPRD to identify lifestyle variables. For smoking, we further used Read codes and prescribing records of smoking cessation treatment (nicotine replacement therapy) in the CPRD and ICD-10 codes in the HES. For alcohol consumption, we also used Read codes and prescribing records of alcoholism treatment in the CPRD and ICD-10 codes in the HES. For body mass index, we obtained height and weight measurements recorded in the CPRD and calculated body mass index (weight/height$_2$).[1] We defined body mass index according to World Health Organization guidelines (BMI: <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m$_2$), alcohol consumption in the categories of current drinker, ex-drinker, and non-drinker, and smoking in the categories of current smoker, ex-smoker, and non-smoker.

In Denmark, we used information on educational duration recorded at Statistics Denmark using the variable “hfaudd”, which follows the International Standard Classification of Education (ISEC). We categorised education as short (ISEC level 2; hfaudd=10), medium (ISEC level 3; hfaudd=20–39), or long (ISEC levels 4 and 5; hfaudd=40–89). Short education corresponds to basic compulsory schooling of 7–10 years. Medium education corresponds to youth education, including general upper secondary school and vocational education and training (*e.g.*, skilled craftsman) leading

to a total of 11–12 years of schooling. Long education of ≥13 years includes higher education, such as that leading to jobs as a programmer, primary school teacher, nurse, or physician.

Comorbidity burden (variable for adjustment)

We defined comorbidity burden on the index date using the Charlson Comorbidity Index (CCI), which assigns 0 to 6 points to a range of chronic diseases.[2] CCI scores were categorized as low (0 points), intermediate (1–2 points), and high (≥3 points).

Socioeconomic deprivation (variable for adjustment)

In the UK, we used the quintiles of IMD as a measure of socioeconomic deprivation. When individual-level IMD status was missing, we used practice-level IMD.

References

1. Bhaskaran K, Forbes HJ, Douglas I, Leon DA, Smeeth L. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). BMJ open. 2013;3(9):e003389.
2. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245-1251.

Appendix S7. Code lists for defining partners' risk of death, outcomes, and other covariates in Denmark.

Age-adjusted Charlson Comorbidity Index and terminal disease

Score 1	ICD-8	ICD-10[a]	ATC
Myocardial infarction	”410”	”DI21” ”DI22” ”DI23”	
Congestive heart failure	”42709” ”42710” ”42711” ”42719” ”42899” ”78249”	”DI50” ”DI110” ”DI130” ”DI132”	
Peripheral vascular disease	”440” ”441” ”442” ”443” ”444” ”445”	”DI70” ”DI71” ”DI72” ”DI73” ”DI74” ”DI77”	
Cerebrovascular disease	”430” ”431” ”432” ”433” ”434” ”435” ”436” ”437” ”438”	”DI60” ”DI61” ”DI62” ”DI63” ”DI64” ”DI65” ”DI66” ”DI67” ”DI68” ”DI69” ”DG45” ”DG46”	
Dementia	“29009” “29010” “29011” “29018” “29019” “29309”	“DF00” “DF01” “DF02” “DF03” “DF051” “DG30”	
Chronic pulmonary disease	“490” “491” “492” “493” “515” “516” “517” “518”	“DJ40” “DJ41” “DJ42” “DJ43” “DJ44” “DJ45” “DJ46” “DJ47” “DJ60” “DJ61” “DJ62” “DJ63” “DJ64” “DJ65” “DJ66” “DJ67” “DJ684” “DJ701” “DJ703” “DJ841” “DJ920” “DJ961” “DJ982” “DJ983”	
Connective tissue disease	”712” ”716” ”734” ”446” ”13599”	”DM05” ”DM06” ”DM08” ”DM09” ”DM30” ”DM31” ”DM32” ”DM33” ”DM34” ”DM35” ”DM36” ”DD86”	
Ulcer disease	“53091” “53098” “531” “532” “533” “534”	“DK221” “DK25” “DK26” “DK27” “DK28”	
Mild liver disease	“571” “57301” “57304”	“DB18” “DK700” “DK701” “DK702” “DK703” “DK709” “DK71” “DK73” “DK74” “DK760”	
Diabetes types 1 and 2[b]	“249” “250”	“DE10” “DE11” “DE12” “DE13” “DE14” “DH360” “DO24” (except DO244)	“A10A” “A10B” (except A10BE01) “B04AX07” “C10AX04”

Score 2		
Hemiplegia	“344”	“DG81” “DG82”
Moderate to severe renal disease	“403” “404” “580” “581” “582” “583” “584” “59009” “59319” “75310” 75311” “75319” “75320” “792”	“DI12” “DI13” “DN00” “DN01” “DN02” “DN03” “DN04” “DN05” “DN07” “DN11” “DN14” “DN17” “DN18” “DN19” “DQ61”
Diabetes with end-organ damage	“24901” “24902” “24903” “24904” “24905” “24908” “25001” “25002” “25003” “25004” “25005” “25008”	“DE102” “DE103” “DE104” “DE105” “DE106” “DE107” “DE108” “DE112” “DE113” “DE114” “DE115” “DE116” “DE117” “DE118” “DE142” “DE143” “DE144” “DE145” “DE146” “DE147” “DE148”
Any tumor	”140” ”141” ”142” ”143” ”144” ”145” ”146” ”147” ”148” ”149” ”150” ”151” ”152” ”153” ”154” ”155” ”156” ”157” ”158” ”159” ”160” ”161” ”162” ”163” ”164” ”165” ”166” ”167” ”168” ”169” ”170” ”171” ”172” ”173” ”174” ”175” ”176” ”177” ”178” ”179” ”180” ”181” ”182” ”183” ”184” ”185” ”186” ”187” ”188” ”189” ”190” ”191” ”192” ”193” ”194”	”DC00” ”DC01” ”DC02” ”DC03” ”DC04” ”DC05” ”DC06” ”DC07” ”DC08” ”DC09” ”DC10” ”DC11” ”DC12” ”DC13” ”DC14” ”DC15” ”DC16” ”DC17” ”DC18” ”DC19” ”DC20” ”DC21” ”DC22” ”DC23” ”DC24” ”DC25” ”DC26” ”DC27” ”DC28” ”DC29” ”DC30” ”DC31” ”DC32” ”DC33” ”DC34” ”DC35” ”DC36” ”DC37” ”DC38” ”DC39” ”DC40” ”DC41” ”DC42” ”DC43” ”DC44” ”DC45” ”DC46” ”DC47” ”DC48” ”DC49” ”DC50” ”DC51” ”DC52” ”DC53” ”DC54” ”DC55” ”DC56” ”DC57” ”DC58” ”DC59” ”DC60” ”DC61” ”DC62” ”DC63” ”DC64” ”DC65” ”DC66” ”DC67” ”DC68” ”DC69” ”DC70” ”DC71” ”DC72” ”DC73 ”DC74” ”DC75”
Leukemia	”204” ”205” ”206” ”207”	”DC91” ”DC92” ”DC93” ”DC94” ”DC95”
Lymphoma	”200” ”201” ”202” ”203” ”27559”	”DC81” ”DC82” ”DC83”

		”DC84” ”DC85” ”DC88” ”DC90” ”DC96”	
Score 3			
Moderate to severe liver disease	“07000” “07002” “07004” “07006” “07008” “57300” “45600” “45601” “45609”	“DB150” “DB160” “DB162” “DB190” “DK704” “DK72” “DK766” “DI85”	
Score 6			
Metastatic solid tumor	”195” ”196” ”197” ”198” ”199”	”DC76” ”DC77” ”DC78” ”DC79” ”DC80”	
Acquired immune deficiency syndrome	“07983”	“DB21” “DB22” “DB23” “DB24”	
Points for age 1 point: 50-59 years 2 point: 60-69 years 3 points: 70-79 years 4 points: 80-89 years 5 points: 90-99 years			
Terminal disease (recorded for partners before their death)		“DZ515” “DZ756” From Danish National Patient Registry we also included supplementary codes “ZNAC14” “ZPZA05.	Prescription record for a terminal patient (that is, variable PATT with value “99”)

Note: All subcodes are included unless otherwise stated. We used both A diagnoses (reasons for hospital contact) and B diagnoses (any other secondary/ coexisting diseases of relevance) in all cases.
[a]All ICD-10 codes in the Danish National Patient Registry begin with “D”. For example, code DI21 represents code I21.
[b]Diabetes is identified as any previous diabetes diagnosis or two or more prescriptions for antidiabetic medications. Women identified solely on the basis of monotherapy with metformin (A10BA02) at ages 20–39 years were excluded, because polycystic ovarian syndrome may have been the indication for their prescription.

Covariate definitions (measured prior to the index date)

Variable	Notes
Highest attained education	Defined based on the variable “hfaudd” as short (hfaudd=10), medium (hfaudd=20–39), or long (hfaudd=40–89). See Supplementary material methods 2 for more detail.

Study participant's (conventional/non-age adjusted) Charlson Comorbidity Index score (grouped as low=0, intermediate=1–2, and high≥3).	Same coding as for risk of partners' deaths described above, but without age points and considering all records 5 years prior to the index date (including the month prior to the index date)

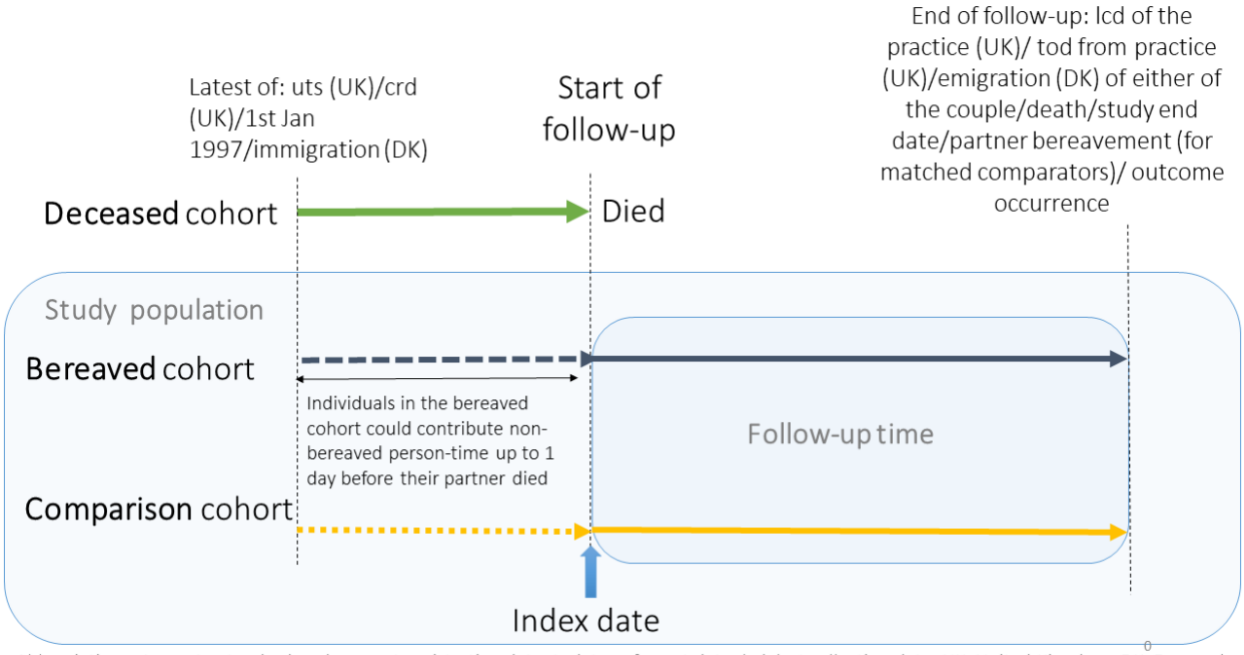
Note: All subcodes are included unless otherwise stated; all types of contacts (inpatient, outpatient and emergency) were considered. Admission date was used for all variables.

Outcome definitions

Outcome variable	**ICD-8**	**ICD-10**	**Notes**
Chronic urticaria	"708"	"DL282A" "DL50" "DL563"	Excluding ICD-8 code "70890" and ICD-10 code "DL508D".
Chronic urticaria and angioedema (for sensitivity analysis)	"708"	"DL282A" "DL50" "DL563" "DT783"	Excluding ICD-10 code "DL508D".
Alopecia areata	"70400"	"DL63"	"DL65" included in sensitivity analysis (see table 15).
Vitiligo	"70901"	"DL80" "DH027C"	

Note: We used both A diagnoses (reasons for hospital contact) and B diagnoses (any other secondary/ coexisting diseases of relevance) in all cases.

Figure S1. Illustration of follow-up periods for the study.



Abbreviation: uts, up-to-standard; crd, current registration date; tod, transfer out date; lcd, last collection date; UK, United Kingdom; DK, Denmark

Table S1. List of sensitivity analyses.

Sensitivity analysis	Justification	UK	Denmark
1. Repeated main analysis restricted to individuals with at least 3 years of registration history in data sources prior to their index date. (See Table S9)	General practitioners tend to record prevalent conditions when new patients register. By including individuals who recently registered with their general practitioner, we risk misclassifying prevalent outcomes as incident diagnoses in the study. This sensitivity analysis aimed to limit such misclassification.	Yes	Yes
2. Repeated main analysis restricted to individuals eligible for linkage to Hospital Episode Statistics/Office for National Statistics death registration data and those who had follow-up start date after date of Office for National Statistics linkage coverage (2 January 1998). (See Table S10)	Hospital admission records and more accurate death dates are available in linked Hospital Episode Statistics and Office for National Statistics data, providing more complete and accurate exposure and outcome data for this subset of patients.	Yes	No
3. Repeated main analysis without censoring persons from the comparison cohort at partner bereavement, at transfer of their partner out of the medical practice (UK) or at emigration of partner (Denmark) (*post-hoc*). (See Table S11)	To examine data as an intention-to-treat analysis, in order to limit potential bias due to informative censoring by death or loss to follow-up of partners.	Yes	Yes
4. Repeated main analysis after adding the end of partnership (separation/divorce) as a censoring criterion. (See Table S12)	To examine any impact of the change in partnership status resulting in persons no longer being at risk of exposure.	No	Yes
5. Repeated main analysis for chronic urticaria excluding codes that specify inducible forms (*e.g.*, allergic urticarial, heat- or cold-induced urticaria), except cholinergic urticaria, which could be specifically linked to stress. (See Table S13)	The codes describing inducible forms might indicate that chronic urticaria with other known triggers than stress. We excluded these codes to test the robustness of the outcome definition.	Yes	Yes
6. Repeated main analysis for urticaria including codes for angioedema. The first recorded	As patients with urticaria often present with angioedema, we included codes for angioedema to test	Yes	Yes

	urticaria/angioedema code was defined as the outcome. We categorised follow-up intervals since the index date as 0–30 days, 0–90 days, 0–182 days, 0–365 days, and 0–1095 days. (See Table S14)	the robustness of the outcome definition. We included the first recorded event of angioedema as an outcome representing acute urticaria.		
7.	Repeated main analysis for alopecia areata including additional codes that have non-specific descriptions for areata or ophiasis. (See Table S15)	As unspecific codes might also denote alopecia areata, this sensitivity analysis was to test the robustness of the outcome definition.	Yes	Yes
8.	Repeated main analysis for vitiligo including additional non-specific codes for hypopigmentation. (See Table S16)	As hypopigmentation could potentially represent vitiligo, this sensitivity analysis was performed to test the robustness of the outcome definition.	Yes	No

Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episodes Statistics; ONS, the Office for National Statistic

Figure S2. Flowcharts for inclusion in the UK and Denmark cohorts.

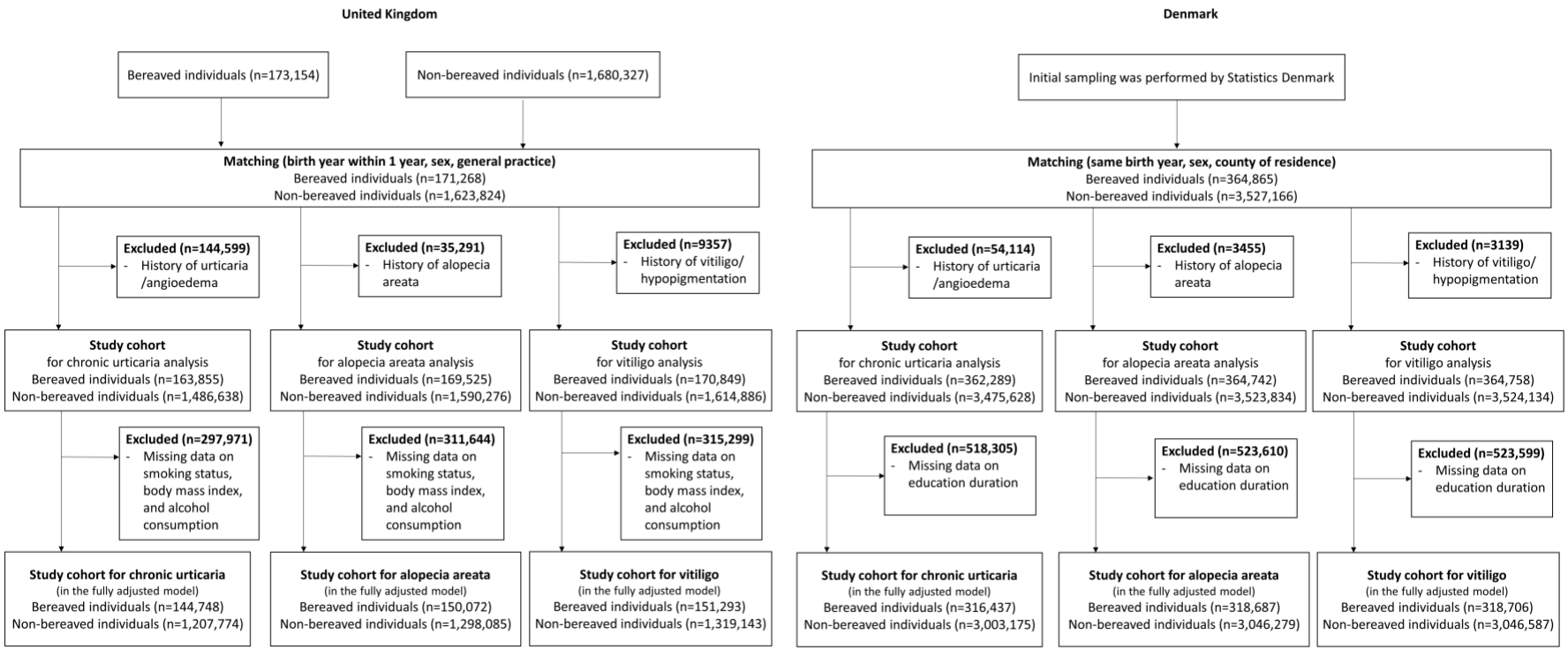


Table S2. Characteristics of the bereaved cohort and the matched comparison cohort, UK (1997-2017) and Denmark (1997-2016).

	The UK, No. (%)						Denmark, No. (%)					
	Chronic urticaria		Alopecia areata		Vitiligo		Chronic urticaria		Alopecia areata		Vitiligo	
	Bereaved cohort	Comparison cohort[a]	Bereaved cohort	Comparison cohort[b]	Bereaved cohort	Comparison cohort[c]	Bereaved cohort	Comparison cohort[a]	Bereaved cohort	Comparison cohort[b]	Bereaved cohort	Comparison cohort[c]
Total	163,855 (9.9)	1,486,638 (90.1)	169,525 (9.6)	1,590,276 (90.4)	170,849 (9.6)	1,614,886 (90.4)	362,289 (9.4)	3,475,628 (90.6)	364,742 (9.4)	3,523,834 (90.6)	364,758 (9.4)	3,524,134 (90.6)
Age at index date, years												
Range	31.9-101.4	31.4-100.4	31.9-101.4	31.4-100.4	31.9-101.4	31.4-100.4	16.5-100.3	16.1-100.7	16.5-100.3	16.1-100.7	16.5-100.3	16.1-100.7
Median (IQR)	74.6 (66.9-80.8)	73.9 (66.4-79.9)	74.6 (66.9-80.8)	73.9 (66.4-79.9)	74.6 (66.9-80.8)	73.8 (66.4-79.9)	71.4 (62.6-78.9)	70.9 (62.2-78.2)	71.4 (62.6-78.8)	70.9 (62.2-78.1)	71.4 (62.6-78.8)	70.9 (62.2-78.1)
Groups												
<50	2979 (1.8)	28,066 (1.9)	3,064 (1.8)	29,716 (1.9)	3079 (1.8)	30,087 (1.9)	24,588 (6.8)	243,605 (7.0)	24,768 (6.8)	247,124 (7.0)	24,770 (6.8)	247,186 (7.0)
50–59	15,235 (9.3)	146,486 (9.9)	15,724 (9.3)	156,454 (9.8)	15,861 (9.3)	158,948 (9.8)	46,585 (12.9)	462,142 (13.3)	46,934 (12.9)	468,980 (13.3)	46,944 (12.9)	469,146 (13.3)
60–69	37,696 (23.0)	361,154 (24.3)	39,057 (23.0)	387,274 (24.4)	39,353 (23.0)	393,454 (24.4)	92,898 (25.6)	922,440 (26.5)	93,582 (25.7)	935,918 (26.6)	93,588 (25.7)	936,032 (26.6)
70–79	61,630 (37.6)	585,679 (39.4)	63,783 (37.6)	627,049 (39.4)	64,334 (37.7)	637,390 (39.5)	120,795 (33.3)	1,183,992 (34.1)	121,561 (33.3)	1,199,809 (34.0)	121,565 (33.3)	1,199,833 (34.0)
≥80	46,315 (28.3)	365,253 (24.6)	47,897 (28.3)	389,783 (24.5)	48,222 (28.2)	395,007 (24.5)	77,423 (21.4)	663,449 (19.1)	77,897 (21.4)	672,003 (19.1)	77,891 (21.4)	671,937 (19.1)
Sex												
Women	106,648 (65.1)	961,405 (64.7)	110,746 (65.3)	1,036,152 (65.2)	111,989 (65.6)	1,059,373 (65.6)	241,680 (66.7)	2,314,753 (66.6)	243,429 (66.7)	2,349,052 (66.7)	243,443 (66.7)	2,349,372 (66.7)
Comorbidity burden[d]												
Mild	71,883 (43.9)	683,358 (46.0)	73,867 (43.6)	725,417 (45.6)	74,420 (43.6)	735,679 (45.6)	256,958 (70.9)	2,533,079 (72.9)	258,393 (70.8)	2,565,216 (72.8)	258,406 (70.8)	2,565,483 (72.8)
Moderate	59,994 (36.6)	533,377 (35.9)	62,288 (36.7)	572,723 (36.0)	62,756 (36.7)	582,122 (36.1)	87,482 (24.1)	787,135 (22.6)	88,280 (24.2)	800,054 (22.7)	88,283 (24.2)	800,076 (22.7)
Severe	31,978 (19.5)	269,903 (18.2)	33,370 (19.7)	292,136 (18.4)	33,673 (19.7)	297,085 (18.4)	17,849 (4.9)	155,414 (4.5)	18,069 (5.0)	158,564 (4.5)	18,069 (5.0)	158,575 (4.5)
Smoking status[e]												
Non-smoker	59,365 (36.2)	583,262 (39.2)	61,214 (36.1)	621,820 (39.1)	61,677 (36.1)	631,294 (39.1)	NA	NA	NA	NA	NA	NA
Ex-smoker	66,133 (40.4)	614,743 (41.4)	68,894 (40.6)	662,973 (41.7)	69,477 (40.7)	673,835 (41.7)	NA	NA	NA	NA	NA	NA
Current smoker	35,649 (21.8)	267,968 (18.0)	36,676 (21.6)	284,174 (17.9)	36,948 (21.6)	288,287 (17.9)	NA	NA	NA	NA	NA	NA
Missing	2708 (1.7)	20,665 (1.4)	2741 (1.6)	21,309 (1.3)	2747 (1.6)	21,470 (1.3)	NA	NA	NA	NA	NA	NA
Alcohol consumption[e]												
Non-drinker	19,208 (11.7)	157,917 (10.6)	19,804 (11.7)	168,180 (10.6)	19,972 (11.7)	171,274 (10.6)	NA	NA	NA	NA	NA	NA
Ex-drinker	21,180 (12.9)	171,353 (11.5)	22,025 (13.0)	184,371 (11.6)	22,218 (13.0)	187,890 (11.6)	NA	NA	NA	NA	NA	NA
Current drinker	110,560 (67.5)	1,053,548 (70.9)	114,560 (67.6)	1,129,116 (71.0)	115,451 (67.6)	1,145,926 (71.0)	NA	NA	NA	NA	NA	NA
Missing	12,907 (7.9)	103,820 (7.0)	13,136 (7.8)	108,609 (6.8)	13,208 (7.7)	109,796 (6.8)	NA	NA	NA	NA	NA	NA

Body Mass Index[e]												
<18.5 kg/m2	4085 (2.5)	26,340 (1.8)	4199 (2.5)	27,889 (1.8)	4248 (2.5)	28,570 (1.8)	NA	NA	NA	NA	NA	NA
18.5-24.9 kg/m2	55,751 (34.0)	506,330 (34.1)	57,613 (34.0)	541,165 (34.0)	58,121 (34.0)	550,099 (34.1)	NA	NA	NA	NA	NA	NA
25-29.9 kg/m2	56,807 (34.7)	548,764 (36.9)	58,877 (34.7)	587,725 (37.0)	59,274 (34.7)	596,208 (36.9)	NA	NA	NA	NA	NA	NA
≥30 kg/m2	34,303 (20.9)	306,963 (20.7)	35,704 (21.1)	331,200 (20.8)	36,015 (21.1)	336,604 (20.8)	NA	NA	NA	NA	NA	NA
Missing	12,909 (7.9)	98,241 (6.6)	13,132 (7.8)	102,297 (6.4)	13,191 (7.7)	103,405 (6.4)	NA	NA	NA	NA	NA	NA
Index of multiple deprivation[e]												
1 (least deprived)	38,093 (23.3)	369,238 (24.8)	39,607 (23.4)	398,004 (25.0)	39,945 (23.4)	404,771 (25.1)	NA	NA	NA	NA	NA	NA
2	34,100 (20.8)	321,566 (21.6)	35,327 (20.8)	344,763 (21.7)	35,589 (20.8)	349,826 (21.7)	NA	NA	NA	NA	NA	NA
3	35,477 (21.7)	322,413 (21.7)	36,574 (21.6)	343,604 (21.6)	36,840 (21.6)	348,372 (21.6)	NA	NA	NA	NA	NA	NA
4	31,965 (19.5)	274,562 (18.5)	32,937 (19.4)	291,003 (18.3)	33,176 (19.4)	295,376 (18.3)	NA	NA	NA	NA	NA	NA
5 (most deprived)	24,220 (14.8)	198,859 (13.4)	25,080 (14.8)	212,902 (13.4)	25,299 (14.8)	216,541 (13.4)	NA	NA	NA	NA	NA	NA
Education duration[f]												
Short	NA	NA	NA	NA	NA	NA	164,206 (45.3)	1,425,956 (41.0)	165,193 (45.3)	1,443,533 (41.0)	165,197 (45.3)	1,443,641 (41.0)
Medium	NA	NA	NA	NA	NA	NA	109,353 (30.2)	1,117,941 (32.2)	110,239 (30.2)	1,135,224 (32.2)	110,241 (30.2)	1,135,353 (32.2)
Long	NA	NA	NA	NA	NA	NA	43,456 (12.0)	561,037 (16.1)	43,835 (12.0)	570,878 (16.2)	43,848 (12.0)	570,948 (16.2)
Missing	NA	NA	NA	NA	NA	NA	45,274 (12.5)	370,694 (10.7)	45,475 (12.5)	374,199 (10.6)	45,472 (12.5)	374,192 (10.6)
Follow-up (years)												
Total	875,386	7,615,764	901,811	8,087,071	910,002	8,215,110	2,778,742	23,908,172	2,793,638	24,175,416	2,793,919	24,178,364
Median (IQR)	4.3 (1.8-8.1)	4.2 (1.8-7.6)	4.3 (1.8-8.0)	4.1 (1.8-7.5)	4.3 (1.8-8.1)	4.1 (1.8-7.5)	6.8 (3.1-11.7)	5.8 (2.5-10.4)	6.8 (3.1-11.7)	5.7 (2.5-10.4)	6.8 (3.1-11.7)	5.7 (2.5-10.4)

Abbreviations: IQR, interquartile range; NA, not applicable

[a]In the UK comparison cohort, 18.9% (15.3% of unique individuals) experienced bereavement after the end of their follow-up. In the Danish comparison cohort, 22.7% (17.1% of unique individuals) experienced bereavement after the end of their follow-up.

[b]In the UK comparison cohort, 18.7% (15.1% of unique individuals) experienced bereavement after the end of their follow-up. In the Danish comparison cohort, 22.7% (17.0% of unique individuals) experienced bereavement after the end of their follow-up.

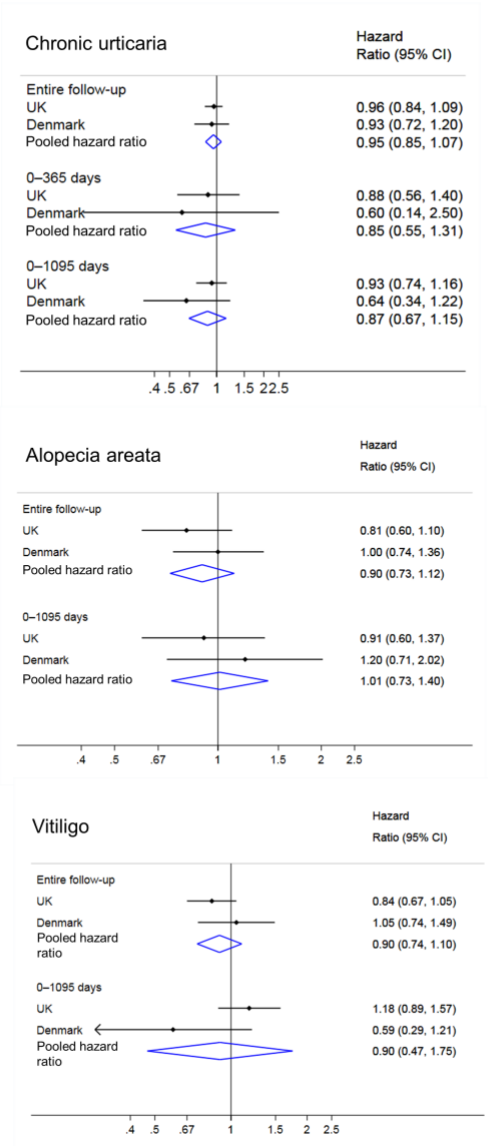
[c]In the UK comparison cohort, 18.7% (15.1% of unique individuals) experienced bereavement after the end of their follow-up. In the Danish comparison cohort, 22.7% (17.0% of unique individuals) experienced bereavement after the end of their follow-up.

[d]Comorbidity burden at index date was measured using the Charlson Comorbidity Index, categorised as low (0 point), moderate (1–2 points), and severe (≥3 points).

[e]Information on smoking status, alcohol consumption, body mass index, and index of multiple deprivation was not available in Denmark.

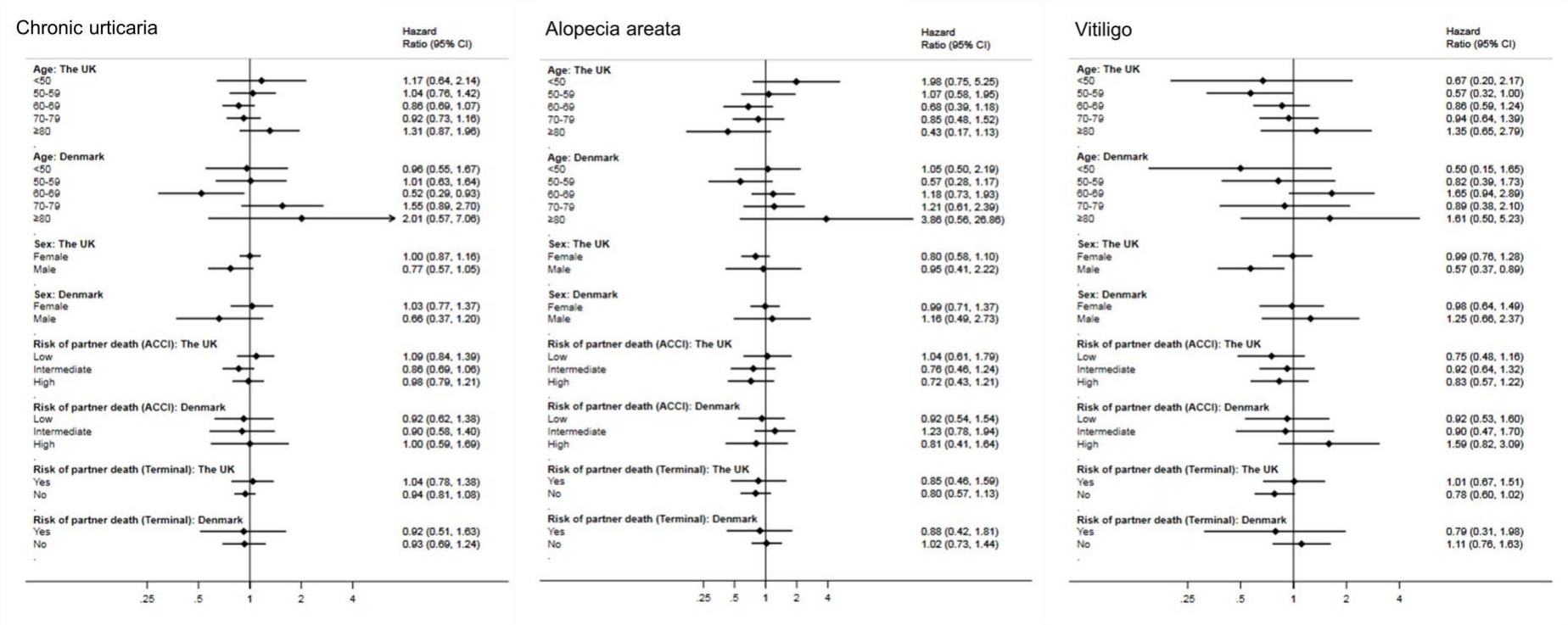
[f] Information on education duration was not available in the United Kingdom.

Figure S3. Pooled adjusted hazard ratios for the association between partner bereavement and chronic urticaria, alopecia areata, and vitiligo in the UK and Denmark.



Effects that could not be estimated due to small event number were not included in pooled meta-analysis. Hazard ratios adjusted for Charlson Comorbidity Index scores.

Figure S4. Adjusted hazard ratios of the association between partner bereavement and chronic urticaria, alopecia areata, and vitiligo by characteristics in the UK and Denmark.



Hazard ratios were adjusted for Charlson Comorbidity Index score. The risk of partner death was determined using the age-adjusted Charlson Comorbidity Index score (ACCI, categorized as low (0–3 points), intermediate (4–6 points), or high (≥7 points)) and presence of terminal disease (yes/no), respectively.

Table S3. Results of the main analysis of associations between partner bereavement and skin disorders in different follow-up time intervals, UK (1997–2017) and Denmark (1997–2016).

Time since index date	Bereaved cohort			Matched comparators			Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
	Number of events	Person-years at risk	Rate per 1,000	Number of events	Person-years at risk	Rate per 1,000			
The UK									
Chronic urticaria									
Entire follow-up	269	875,386	0.31	2483	7,615,764	0.33	0.96 (0.84-1.09)	0.96 (0.84-1.09)	0.97 (0.85-1.11)
0–182 days	[d]	78,004	[d]	[d]	713,353	[d]	0.31 (0.08-1.26)	0.31 (0.08-1.28)	0.41 (0.10-1.71)
0–365 days	20	150,221	0.13	214	1,376,313	0.16	0.88 (0.56-1.40)	0.88 (0.56-1.40)	0.96 (0.60-1.53)
0–1095 days	85	388,765	0.22	846	3,542,326	0.24	0.93 (0.74-1.16)	0.93 (0.74-1.16)	0.95 (0.75-1.20)
Alopecia areata									
Entire follow-up	49	901,811	0.05	525	8,087,071	0.06	0.82 (0.61-1.10)	0.81 (0.60-1.10)	0.85 (0.62-1.16)
0–30 days	[d]	13,817	[d]	[d]	129,863	[d]	NA	NA	NA
0–90 days	[d]	40,793	0.02	35	384,648	0.09	0.24 (0.03-1.73)	0.24 (0.03-1.74)	0.19 (0.02-1.48)
0–365 days	8	155,369	0.05	105	1,470,901	0.07	0.69 (0.33-1.41)	0.69 (0.34-1.42)	0.73 (0.35-1.54)
0–1095 days	26	401,742	0.06	247	3,779,874	0.07	0.91 (0.61-1.37)	0.91 (0.60-1.37)	0.91 (0.60-1.40)
Vitiligo									
Entire follow-up	87	910,002	0.10	972	8,215,110	0.12	0.84 (0.67-1.05)	0.84 (0.67-1.05)	0.85 (0.67-1.07)
0–30 days	[d]	13,925	[d]	[d]	131,873	[d]	0.55 (0.07-4.14)	0.63 (0.08-4.83)	0.80 (0.09-7.30)
0–90 days	5	41,110	0.12	39	390,610	0.10	1.33 (0.52-3.38)	1.32 (0.52-3.37)	1.49 (0.55-4.06)
0–365 days	23	156,584	0.15	177	1,493,648	0.12	1.30 (0.84-2.01)	1.30 (0.84-2.02)	1.32 (0.83-2.10)
0–1095 days	54	404,936	0.13	449	3,838,367	0.12	1.18 (0.89-1.58)	1.18 (0.89-1.57)	1.20 (0.89-1.62)
Denmark									
Chronic urticaria									
Entire follow-up	67	2,778,742	0.02	646	23,908,253	0.03	0.93 (0.72-1.20)	0.93 (0.72-1.20)	0.92 (0.70-1.20)
0–182 days	[d]	176,120	[d]	[d]	1,684,577	[d]	NA	NA	NA
0–365 days	[d]	345,359	[d]	[d]	3,288,129	[d]	0.61 (0.15-2.53)	0.60 (0.14-2.50)	0.66 (0.16-2.81)
0–1095 days	10	947,459	0.01	148	8,840,820	0.02	0.65 (0.34-1.24)	0.64 (0.34-1.22)	0.62 (0.31-1.22)
Alopecia areata									
Entire follow-up	48	2,793,638	0.02	417	24,175,497	0.02	1.01 (0.75-1.38)	1.00 (0.74-1.36)	0.98 (0.71-1.35)
0–30 days	[d]	29,816	[d]	[d]	288,053	[d]	NA	NA	NA
0–90 days	[d]	88,713	[d]	[d]	856,229	[d]	NA	NA	NA
0–365 days	[d]	347,651	[d]	[d]	3,333,059	[d]	NA	NA	NA
0–1095 days	16	953,497	0.02	129	8,957,716	0.01	1.23 (0.73-2.06)	1.20 (0.71-2.02)	1.14 (0.65-2.00)
Vitiligo									
Entire follow-up	36	2,793,919	0.01	314	24,178,445	0.01	1.08 (0.76-1.53)	1.05 (0.74-1.49)	1.17 (0.82-1.68)
0–30 days	[d]	29,817	[d]	[d]	288,077	[d]	NA	NA	NA
0–90 days	[d]	88,717	[d]	[d]	856,303	[d]	NA	NA	NA
0–365 days	[d]	347,669	[d]	[d]	3,333,348	[d]	0.18 (0.02-1.30)	0.16 (0.02-1.15)	0.22 (0.03-1.65)
0–1095 days	8	953,555	0.01	128	8,958,460	0.01	0.63 (0.31-1.28)	0.59 (0.29-1.21)	0.70 (0.34-1.45)

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable

[a]Computed using Cox regression stratified by matched set to account for matching variables of age, sex, county of residence (in Denmark) and general practice (in the UK).

[b]Adjusted for Charlson Comorbidity Index scores.

[c]Complete-case analysis was used to handle missing data for body mass index, smoking status and alcohol consumption (UK), and education duration (Denmark) in the fully adjusted model. Of note, the number of events, and person-years at risk in the bereaved and matched comparator cohorts presented in this table were calculated using the full cohort only. For chronic urticaria, the total number of bereaved and comparison persons was 144,748 and 1,207,774 respectively in the UK and 316,437 and 3,003,175 respectively in Denmark, after excluding those with missing values. For alopecia areata, the total number of bereaved and comparison persons was 150,072 and 1,298,085 respectively in the UK and 318,687 and 3,046,279 respectively in Denmark after excluding those with missing values. For vitiligo, the total number of bereaved and comparison persons was 151,293 and 1,319,143 respectively in the UK and 318,706 and 3,046,587 respectively in Denmark after excluding those with missing values.

[d]In accordance with the confidentiality rules of the CPRD/Danish registries, we have not presented results where numbers of events are less than five.

Table S4. Subgroup analysis for chronic urticaria during the entire follow-up period, UK (1997-2017) and Denmark (1997-2016).

Characteristics	Bereaved cohort				Matched comparators				Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]		Fully adjusted HR (95% CI)[c]
	Number of persons	Number of events	Person-years at risk	Rate per 1,000	Number of persons	Number of events	Person-years at risk	Rate per 1,000				
UK												
Age, years												
<50	2979	12	24,757	0.48	28,066	95	250,867	0.38	1.17 (0.63-2.14)	1.17 (0.64-2.14)	p=0.43	1.17 (0.61-2.23)
50–59	15,235	44	107,487	0.41	146,486	426	1,067,805	0.40	1.04 (0.76-1.43)	1.04 (0.76-1.42)		1.02 (0.73-1.42)
60–69	37,696	90	240,649	0.37	361,154	952	2,253,539	0.42	0.86 (0.69-1.07)	0.86 (0.69-1.07)		0.91 (0.73-1.14)
70–79	61,630	90	335,316	0.27	585,679	823	2,889,660	0.28	0.93 (0.74-1.16)	0.92 (0.73-1.16)		0.97 (0.77-1.23)
≥80	46,315	33	167,177	0.20	365,253	187	1,153,893	0.16	1.27 (0.84-1.90)	1.31 (0.87-1.96)		1.11 (0.70-1.76)
Sex												
Female	106,648	222	595,554	0.37	961,405	1905	4,944,695	0.39	1.01 (0.87-1.16)	1.00 (0.87-1.16)	p=0.13	1.02 (0.88-1.18)
Male	57,207	47	279,832	0.17	525,233	578	2,671,069	0.22	0.78 (0.57-1.06)	0.77 (0.57-1.05)		0.81 (0.59-1.11)
Risk of partner death (ACCI[d] score)												
Low (0–3 points)	25,292	71	174,085	0.41	241,561	655	1,669,674	0.39	1.09 (0.85-1.40)	1.09 (0.84-1.39)	p=0.37	1.14 (0.88-1.47)
Intermediate (4–6 points)	64,140	98	353,694	0.28	584,479	977	3,043,175	0.32	0.86 (0.69-1.06)	0.86 (0.69-1.06)		0.88 (0.70-1.10)
High (≥7 points)	74,423	100	347,607	0.29	660,598	851	2,902,914	0.29	0.98 (0.79-1.22)	0.98 (0.79-1.21)		0.97 (0.77-1.21)
Risk of partner death (terminal disease[e])												
Yes	41,866	56	189,182	0.30	384,398	476	1,686,290	0.28	1.04 (0.78-1.38)	1.04 (0.78-1.38)	p=0.53	1.02 (0.76-1.37)
No	121,989	213	686,204	0.31	1,102,240	2007	5,929,474	0.34	0.94 (0.81-1.08)	0.94 (0.81-1.08)		0.96 (0.83-1.12)
Denmark												
Age, years												
<50	24,588	[f]	265,049	[f]	243,605	[f]	2,630,605	[f]	0.97 (0.56-1.68)	0.96 (0.55-1.67)	p=0.14	0.93 (0.53-1.66)
50–59	46,585	[f]	477,581	[f]	462,142	[f]	4,607,889	[f]	1.02 (0.63-1.64)	1.01 (0.63-1.64)		1.04 (0.65-1.69)
60–69	92,898	[f]	814,643	[f]	922,440	[f]	7,356,318	[f]	0.51 (0.29-0.92)	0.52 (0.29-0.93)		0.56 (0.31-1.01)
70–79	120,795	[f]	861,584	[f]	1,183,992	[f]	6,875,173	[f]	1.52 (0.88-2.64)	1.55 (0.89-2.70)		1.46 (0.81-2.65)
≥80	77,423	[f]	359,885	[f]	663,449	[f]	2,438,268	[f]	1.79 (0.55-5.88)	2.01 (0.57-7.06)		2.11 (0.37-11.99)
Sex												
Female	241,680	55	1,957,840	0.03	2,314,753	460	15,920,481	0.03	1.03 (0.77-1.38)	1.03 (0.77-1.37)	p=0.09	1.02 (0.76-1.38)
Male	120,609	12	820,901	0.01	1,160,875	186	7,987,772	0.02	0.65 (0.36-1.17)	0.66 (0.37-1.20)		0.65 (0.35-1.20)
Risk of partner death (ACCI[d] score)												
Low (0–3 points)	95,075	27	902,331	0.03	938,938	290	8,417,254	0.03	0.92 (0.62-1.37)	0.92 (0.62-1.38)	p=0.94	0.91 (0.61-1.37)
Intermediate (4–6 points)	172,824	22	1,240,293	0.02	1,632,576	219	10,141,055	0.02	0.90 (0.58-1.40)	0.90 (0.58-1.40)		0.94 (0.60-1.49)
High (≥7 points)	94,390	18	636,117	0.03	904,114	137	5,349,944	0.03	1.00 (0.59-1.69)	1.00 (0.59-1.69)		0.93 (0.52-1.66)
Risk of partner death (terminal disease[e])												
Yes	82,802	13	531,259	0.02	811,148	127	4,794,775	0.03	0.94 (0.53-1.67)	0.92 (0.51-1.63)	p=0.82	0.90 (0.49-1.64)
No	279,487	54	2,247,483	0.02	2,664,480	519	19,113,478	0.03	0.93 (0.70-1.24)	0.93 (0.69-1.24)		0.92 (0.68-1.24)

Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].
[b]Adjusted for Charlson Comorbidity Index score.
[c]Complete-case analysis was used to handle missing data in the fully adjusted model. Notably, the number of events, person-years at risk, and rate per 1000 in the bereaved and matched comparator cohorts presented in this table were calculated in the full cohort for the unadjusted and adjusted models only. Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status in the UK. The total number of bereaved and comparison persons was 144,748 and 1,207,774 respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. Adjusted additionally for education duration in Denmark. The total number of bereaved and comparison persons was 316,437 and 3,003,175 respectively, after excluding patients with missing education duration.
[d]Age-adjusted Charlson Comorbidity Index scores were computed based on comorbidity recorded up to one month before the death of deceased partners. This index assigns 0 to 6 points to a range of chronic diseases according to their ability to predict death, with additional points given according to age.
[e]As an alternative measure for predicting partners' deaths, records for terminal disease among partners at their time of death were identified.
[f]In cases where there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S5. Subgroup analysis for alopecia areata during the entire follow-up period, UK (1997-2017) and Denmark (1997-2016).

Characteristics	Bereaved cohort				Matched comparators				Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]		Fully adjusted HR (95% CI)[c]
	Number of persons	Number of events	Person-years at risk	Rate per 1,000	Number of persons	Number of events	Person-years at risk	Rate per 1,000				
UK												
Age, years												
<50	3064	5	25,527	0.20	29,716	26	264,791	0.10	1.97 (0.74-5.23)	1.98 (0.75-5.25)	p=0.22	2.09 (0.77-5.67)
50–59	15,724	12	110,408	0.11	156,454	114	1,132,491	0.10	1.06 (0.58-1.95)	1.07 (0.58-1.95)		1.08 (0.58-2.01)
60–69	39,057	14	248,140	0.06	387,274	180	2,395,669	0.08	0.68 (0.39-1.18)	0.68 (0.39-1.18)		0.73 (0.42-1.29)
70–79	63,783	13	345,430	0.04	627,049	149	3,069,482	0.05	0.85 (0.48-1.52)	0.85 (0.48-1.52)		0.89 (0.48-1.65)
≥80	47,897	5	172,305	0.03	389,783	56	1,224,638	0.05	0.45 (0.17-1.16)	0.43 (0.17-1.13)		0.43 (0.17-1.14)
Sex												
Female	110,746	43	615,155	0.07	1,036,152	463	5,283,731	0.09	0.80 (0.58-1.10)	0.80 (0.58-1.10)	p=0.71	0.82 (0.59-1.15)
Male	58,779	6	286,656	0.02	554,124	62	2,803,340	0.02	0.94 (0.40-2.20)	0.95 (0.41-2.22)		1.07 (0.45-2.55)
Risk of partner death (ACCI[d] (score)												
Low (0–3 points)	26,024	15	178,650	0.08	256,054	138	1,760,207	0.08	1.04 (0.61-1.79)	1.04 (0.61-1.79)	p=0.59	1.08 (0.61-1.91)
Intermediate (4–6 points)	66,178	18	363,742	0.05	622,579	192	3,222,801	0.06	0.76 (0.46-1.24)	0.76 (0.46-1.24)		0.78 (0.47-1.30)
High (≥7 points)	77,323	16	359,419	0.04	711,643	195	3,104,063	0.06	0.73 (0.44-1.23)	0.72 (0.43-1.21)		0.78 (0.46-1.31)
Risk of partner death (terminal disease[e])												
Yes	43,572	11	196,172	0.06	415,694	121	1,810,408	0.07	0.85 (0.46-1.59)	0.85 (0.46-1.59)	p=0.87	0.87 (0.46-1.64)
No	125,953	38	705,638	0.05	1,174,582	404	6,276,663	0.06	0.81 (0.57-1.13)	0.80 (0.57-1.13)		0.84 (0.59-1.20)
Denmark												
Age, years												
<50	24,768	[f]	266,504	[f]	247,124	[f]	2,659,624	[f]	1.08 (0.52-2.23)	1.05 (0.50-2.19)	p=0.32	1.07 (0.50-2.29)
50–59	46,934	[f]	480,442	[f]	468,980	[f]	4,661,989	[f]	0.59 (0.29-1.21)	0.57 (0.28-1.17)		0.48 (0.22-1.05)
60–69	93,582	[f]	819,237	[f]	935,918	[f]	7,440,925	[f]	1.18 (0.72-1.92)	1.18 (0.73-1.93)		1.24 (0.74-2.06)
70–79	121,561	[f]	865,743	[f]	1,199,809	[f]	6,947,619	[f]	1.22 (0.62-2.41)	1.21 (0.61-2.39)		1.18 (0.57-2.45)
≥80	77,897	[f]	361,712	[f]	672,003	[f]	2,465,341	[f]	2.93 (0.53-16.10)	3.86 (0.56-26.86)		3.67 (0.13-100.76)
Sex												
Female	243,429	42	1,969,049	0.02	2,349,052	363	16,111,007	0.02	1.00 (0.72-1.38)	0.99 (0.71-1.37)	p=0.85	0.96 (0.68-1.36)
Male	121,313	6	824,589	0.01	1,174,782	54	8,064,491	0.01	1.16 (0.50-2.72)	1.16 (0.49-2.73)		1.16 (0.49-2.75)
Risk of partner death (ACCI[d] score)												
Low (0–3 points)	95,688	16	906,973	0.02	951,226	171	8,505,008	0.02	0.88 (0.53-1.47)	0.92 (0.54-1.54)	p=0.54	0.94 (0.55-1.62)
Intermediate (4–6 points)	173,923	23	1,246,555	0.02	1,654,302	160	10,252,423	0.02	1.24 (0.79-1.96)	1.23 (0.78-1.94)		1.13 (0.69-1.83)
High	95,131	9	640,110	0.01	918,306	86	5,418,065	0.02	0.86 (0.43-1.73)	0.81 (0.41-1.64)		0.86 (0.42-1.73)

(≥7 points)												
Risk of partner death (terminal disease[e])												
Yes	83,492	8	534,756	0.01	824,609	84	4,859,549	0.02	0.87 (0.42-1.80)	0.88 (0.42-1.81)	p=0.70	0.87 (0.42-1.82)
No	281,250	40	2,258,881	0.02	2,699,225	333	19,315,948	0.02	1.05 (0.75-1.47)	1.02 (0.73-1.44)		0.99 (0.69-1.42)

Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index score.

[c]Complete-case analysis was used to handle missing data in the fully adjusted model. Notably, the number of events, person-years at risk, and rate per 1000 in the bereaved and matched comparator cohorts presented in this table were calculated in the full cohort for the unadjusted and adjusted models only. Adjusted additionally for smoking status, body mass index, alcohol consumption and socioeconomic status in the UK. The total number of bereaved and comparison persons was 150,072 and 1,298,085, respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. Adjusted additionally for education duration in Denmark. The total number of bereaved and comparison persons was 318,687 and 3,046,279, respectively, after excluding patients with missing education duration.

[d]Age-adjusted Charlson Comorbidity Index scores were computed based on comorbidity recorded up to one month before the death of deceased partners. This index assigns 0 to 6 points to a range of chronic diseases according to their ability to predict death, with additional points given according to age.

[e]As an alternative measure for predicting partners' death, records for terminal disease among partners at their time of death were identified.

[f]In cases where there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S6. Subgroup analysis for vitiligo during the entire follow-up period, UK (1997-2017) and Denmark (1997-2016).

Characteristics	Bereaved cohort				Matched comparators				Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]		Fully adjusted HR (95% CI)[c]
	Number of persons	Number of events	Person-years at risk	Rate per 1,000	Number of persons	Number of events	Person-years at risk	Rate per 1,000				
UK												
Age, years												
<50	3079	[f]	25,739	[f]	30,087	[f]	268,485	[f]	0.67 (0.20-2.17)	0.67 (0.20-2.17)	p=0.40	0.72 (0.22-2.37)
50–59	15,861	[f]	111,645	[f]	158,948	[f]	1,151,651	[f]	0.57 (0.32-0.99)	0.57 (0.32-1.00)		0.61 (0.35-1.07)
60–69	39,353	[f]	250,206	[f]	393,454	[f]	2,434,484	[f]	0.86 (0.60-1.24)	0.86 (0.59-1.24)		0.87 (0.59-1.28)
70–79	64,334	[f]	348,896	[f]	637,390	[f]	3,120,542	[f]	0.94 (0.64-1.40)	0.94 (0.64-1.39)		0.96 (0.64-1.44)
≥80	48,222	[f]	173,516	[f]	395,007	[f]	1,239,948	[f]	1.36 (0.66-2.80)	1.35 (0.65-2.79)		1.17 (0.51-2.68)
Sex												
Female	111,989	66	622,971	0.11	1,059,373	612	5,404,679	0.11	0.99 (0.76-1.28)	0.99 (0.76-1.28)	p=0.03	1.01 (0.77-1.32)
Male	58,860	21	287,031	0.07	555,513	359	2,810,431	0.13	0.57 (0.37-0.90)	0.57 (0.37-0.89)		0.56 (0.35-0.90)
Risk of partner death (ACCI[d] score)												
Low (0–3 points)	26,193	22	180,103	0.12	259,431	298	1,784,612	0.17	0.75 (0.48-1.16)	0.75 (0.48-1.16)	p=0.76	0.77 (0.49-1.21)
Intermediate (4–6 points)	66,634	35	366,742	0.10	631,294	331	3,272,011	0.10	0.92 (0.64-1.32)	0.92 (0.64-1.32)		0.93 (0.64-1.35)
High (≥7 points)	78,022	30	363,157	0.08	724,161	342	3,158,487	0.11	0.83 (0.57-1.22)	0.83 (0.57-1.22)		0.84 (0.56-1.24)
Risk of partner death (terminal disease[e])												
Yes	43,949	27	198,054	0.14	422,759	251	1,840,666	0.14	1.01 (0.68-1.51)	1.01 (0.67-1.51)	p=0.30	1.06 (0.70-1.61)
No	126,900	60	711,948	0.08	1,192,127	720	6,374,444	0.11	0.78 (0.60-1.02)	0.78 (0.60-1.02)		0.78 (0.59-1.03)
Denmark												
Age, years												
<50	24,770	[f]	266,589	[f]	247,186	[f]	2,660,549	0.02	0.55 (0.17-1.78)	0.50 (0.15-1.65)	p=0.28	0.53 (0.16-1.78)
50–59	46,944	8	480,532	0.02	469,146	89	4,663,566	0.02	0.87 (0.42-1.80)	0.82 (0.39-1.73)		0.92 (0.43-1.96)
60–69	93,588	15	819,302	0.02	936,032	85	7,441,948	0.01	1.63 (0.93-2.86)	1.65 (0.94-2.89)		1.75 (0.99-3.10)
70–79	121,565	6	865,810	0.01	1,199,833	60	6,947,485	0.01	0.90 (0.38-2.10)	0.89 (0.38-2.10)		0.96 (0.40-2.28)
≥80	77,891	[f]	361,686	[f]	671,937	[f]	2,464,898	0.01	1.73 (0.55-5.47)	1.61 (0.50-5.23)		7.25 (0.61-86.29)
Sex												
Female	243,443	25	1,969,342	0.01	2,349,372	226	16,114,268	0.01	1.01 (0.66-1.53)	0.98 (0.64-1.49)	p=0.51	1.07 (0.69-1.65)
Male	121,315	11	824,577	0.01	1,174,762	88	8,064,177	0.01	1.28 (0.68-2.42)	1.25 (0.66-2.37)		1.40 (0.74-2.67)
Risk of partner death (ACCI[d] score)												
Low (0–3 points)	95,702	14	907,148	0.02	951,454	140	8,506,989	0.02	0.94 (0.54-1.64)	0.92 (0.53-1.60)	p=0.36	0.98 (0.56-1.73)
Intermediate (4–6 points)	173,920	11	1,246,605	0.01	1,654,263	113	10,252,408	0.01	0.91 (0.48-1.71)	0.90 (0.47-1.70)		0.95 (0.49-1.85)
High (≥7 points)	95,136	11	640,166	0.02	918,417	61	5,419,048	0.01	1.72 (0.89-3.31)	1.59 (0.82-3.09)		2.07 (1.04-4.11)
Risk of partner death (terminal disease[e])												
Yes	83,492	[f]	534,804	[f]	824,695	[f]	4,860,435	[f]	0.81 (0.32-2.02)	0.79 (0.31-1.98)	p=0.50	0.81 (0.32-2.03)
No	281,266	[f]	2,259,115	[f]	2,699,439	[f]	19,318,010	[f]	1.14 (0.78-1.67)	1.11 (0.76-1.63)		1.27 (0.86-1.88)

Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index

[c]Complete-case analysis was used to handle missing data in the fully adjusted model. Notably, the number of events, person-years at risk, and rate per 1000 in the bereaved and matched comparator cohorts presented in this table were calculated in the full cohort for the unadjusted and adjusted models only. Adjusted additionally for smoking status, body mass index, alcohol consumption and socioeconomic status in the UK. The total number of bereaved and comparison persons was 151,293 and 1,319,143, respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. Adjusted additionally for education duration in Denmark. The total number of bereaved and comparison persons was 318,706 and 3,046,587, respectively, after excluding patients with missing education duration.

[d]Age-adjusted Charlson Comorbidity Index scores were computed based on comorbidity recorded up to one month before the death of deceased partners. This index assigns 0 to 6 points to a range of chronic diseases according to their ability to predict death, with additional points given according to age.

[e]As an alternative measure for predicting partners' death, records for terminal disease among partners at their time of death were identified.

[f] In cases where there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S7. Patterns of missing data on smoking status, body mass index, and alcohol consumption in the UK.

Table 1.1. Missing data for smoking status.

	Chronic urticaria	**Alopecia areata**	**Vitiligo**
N (%)	23,373 (1.42)	24,050 (1.37)	24,217 (1.36)
Covariates	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**
Outcome	0.87 (0.19-3.98)	0.06 (0.01-0.31)	NA[a]
Exposure – partner bereavement	0.91 (0.72-1.14)	0.91 (0.72-1.15)	0.91 (0.72-1.15)
Body Mass Index			
Underweight	1	1	1
Normal weight	0.65 (0.39-1.07)	0.72 (0.43-1.19)	0.69 (0.42-1.13)
Overweight	0.80 (0.48-1.31)	0.90 (0.55-1.50)	0.86 (0.52-1.41)
Obese	0.76 (0.46-1.27)	0.89 (0.53-1.50)	0.83 (0.50-1.39)
Socioeconomic status			
1 (least deprived)	1	1	1
2	0.88 (0.61-1.29)	0.95 (0.65-1.39)	0.94 (0.65-1.35)
3	0.66 (0.44-1.00)	0.67 (0.44-1.01)	0.63 (0.42-0.95)
4	0.58 (0.38-0.90)	0.62 (0.40-0.95)	0.58 (0.38-0.88)
5 (most deprived)	0.55 (0.30-1.02)	0.54 (0.29-1.02)	0.52 (0.28-0.95)
Alcohol Status			
Non-drinker	1	1	1
Current drinker	1.04 (0.81-1.34)	1.00 (0.78-1.29)	1.02 (0.79-1.31)
Ex-drinker	0.59 (0.43-0.82)	0.54 (0.39-0.74)	0.55 (0.40-0.76)
Charlson Comorbidity Index score			
Mild (score 0)	1	1	1
Moderate (score 1–2)	0.77 (0.65-0.91)	0.75 (0.64-0.89)	0.76 (0.64-0.89)
Severe (score ≥3)	0.47 (0.37-0.59)	0.47 (0.37-0.60)	0.44 (0.35-0.56)

Abbreviations: CI, confidence interval; NA, not applicable

Conditional logistic regression was used with the following covariates to predict the missingness of smoking status (without missingness of smoking status being the reference): binary outcome variable (chronic urticaria/ alopecia areata/ vitiligo), binary exposure variable (partner bereavement), body mass index, socioeconomic status, alcohol consumption, and Charlson Comorbidity Index score.

[a]No individual had incident vitiligo and missingness of smoking status.

Table 1.2. Missing data for Body Mass Index.

	Chronic urticaria	**Alopecia areata**	**Vitiligo**
N (%)	111,150 (6.73)	115,429 (6.56)	116,596 (6.53)
Covariates	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**
Outcomes	0.35 (0.23-0.52)	0.44 (0.22-0.89)	0.27 (0.13-0.56)
Exposure – partner bereavement	1.20 (1.16-1.23)	1.20 (1.16-1.24)	1.20 (1.16-1.24)
Smoking status			
Non-smoker	1	1	1
Current smoker	1.08 (1.05-1.11)	1.07 (1.05-1.10)	1.08 (1.05-1.11)
Ex-smoker	0.62 (0.60-0.63)	0.61 (0.59-0.62)	0.61 (0.60-0.63)
Socioeconomic status			
1 (least deprived)	1	1	1
2	0.92 (0.89-0.96)	0.92 (0.89-0.96)	0.92 (0.88-0.95)
3	0.96 (0.91-1.00)	0.94 (0.90-0.98)	0.94 (0.90-0.98)
4	1.01 (0.96-1.06)	1.00 (0.95-1.05)	1.00 (0.95-1.05)
5 (most deprived)	0.99 (0.93-1.05)	0.98 (0.92-1.04)	0.98 (0.92-1.04)
Alcohol Status			
Non-drinker	1	1	1
Current drinker	0.56 (0.55-0.58)	0.56 (0.55-0.58)	0.57 (0.55-0.58)
Ex-drinker	0.34 (0.33-0.36)	0.33 (0.32-0.35)	0.34 (0.32-0.35)
Charlson Comorbidity Index score			
Mild (score 0)	1	1	1
Moderate (score 1–2)	0.69 (0.67-0.70)	0.68 (0.67-0.70)	0.69 (0.67-0.70)
Severe (score ≥3)	0.55 (0.53-0.57)	0.55 (0.53-0.57)	0.55 (0.53-0.56)

Abbreviations: CI, confidence interval

Conditional logistic regression was used with the following covariates to predict the missingness of body mass index (without missingness of body mass index being the reference): binary outcome variable (chronic urticaria/ alopecia areata/ vitiligo), binary exposure variable (partner bereavement), smoking status, socioeconomic status, alcohol consumption, and Charlson Comorbidity Index score.

Table 1.3. Missing data for alcohol consumption

	Chronic urticaria	**Alopecia areata**	**Vitiligo**
N (%)	116,727 (7.07)	121,745 (6.92)	123,004 (6.89)
Covariates	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**	
Outcomes	0.90 (0.70-1.16)	1.27 (0.79-2.04)	0.92 (0.63-1.34)
Exposure – partner bereavement	1.09 (1.06-1.13)	1.09 (1.06-1.12)	1.09 (1.06-1.13)
Smoking status			
Non-smoker	1	1	1
Current smoker	0.92 (0.89-0.94)	0.92 (0.89-0.94)	0.91 (0.89-0.94)
Ex-smoker	0.70 (0.68-0.71)	0.70 (0.68-0.71)	0.70 (0.68-0.71)
Socioeconomic status			
1 (least deprived)	1	1	1
2	0.98 (0.94-1.01)	0.97 (0.93-1.00)	0.98 (0.94-1.01)
3	1.07 (1.03-1.12)	1.08 (1.03-1.12)	1.09 (1.04-1.13)
4	1.08 (1.03-1.13)	1.09 (1.04-1.14)	1.09 (1.04-1.14)
5 (most deprived)	1.01 (0.95-1.07)	1.00 (0.94-1.06)	1.00 (0.94-1.06)
Body Mass Index			
Underweight	1	1	1
Normal weight	0.58 (0.55-0.61)	0.58 (0.55-0.62)	0.58 (0.55-0.61)
Overweight	0.51 (0.48-0.54)	0.52 (0.49-0.55)	0.51 (0.48-0.54)
Obese	0.54 (0.51-0.58)	0.55 (0.52-0.58)	0.54 (0.51-0.58)
Charlson Comorbidity Index score			
Mild (score 0)	1	1	1
Moderate (score 1–2)	0.85 (0.83-0.87)	0.85 (0.83-0.87)	0.85 (0.83-0.87)
Severe (score ≥3)	0.76 (0.74-0.78)	0.76 (0.74-0.78)	0.76 (0.74-0.78)

Abbreviations: CI, confidence interval

Conditional logistic regression was used with the following covariates to predict the missingness of alcohol status (without missingness of alcohol status being the reference): binary outcome variable (chronic urticaria/ alopecia areata/ vitiligo), binary exposure variable (partner bereavement), smoking status, socioeconomic status, body mass index, and Charlson Comorbidity Index score.

Table S8. Hazard ratios among the whole cohort and the complete-case cohort.

	Full cohort		Complete case cohort		Full cohort		Complete case cohort	
UK								
Chronic urticaria	Bereaved Cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators
N	163,855	1,486,638	144,748	1,207,774	163,855	1,486,638	144,748	1,207,774
Time since index date	**Unadjusted HR (95% CI)[a]**				**Adjusted HR (95% CI)[b]**			
Entire follow-up period	0.96 (0.84-1.09)		0.96 (0.84-1.10)		0.96 (0.84-1.09)		0.96 (0.84-1.10)	
0–182 days	0.31 (0.08-1.26)		0.35 (0.08-1.43)		0.31 (0.08-1.28)		0.37 (0.09-1.52)	
0–365 days	0.88 (0.56-1.40)		0.93 (0.59-1.48)		0.88 (0.56-1.40)		0.94 (0.59-1.49)	
0–1095 days	0.93 (0.74-1.16)		0.94 (0.75-1.19)		0.93 (0.74-1.16)		0.94 (0.74-1.18)	
Alopecia areata	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators
N	169,525	1,590,276	150,072	1,298,085	169,525	1,590,276	150,072	1,298,085
Time since index date	**Unadjusted HR (95% CI)[a]**				**Adjusted HR (95% CI)[b]**			
Entire follow-up period	0.82 (0.61-1.10)		0.87 (0.64-1.19)		0.81 (0.60-1.10)		0.87 (0.64-1.19)	
0–30 days	NA		NA		NA		NA	
0–90 days	0.24 (0.03-1.73)		0.27 (0.04-1.99)		0.24 (0.03-1.74)		0.26 (0.04-1.93)	
0–365 days	0.69 (0.33-1.41)		0.76 (0.37-1.58)		0.69 (0.34-1.42)		0.77 (0.37-1.59)	
0–1095 days	0.91 (0.61-1.37)		0.94 (0.62-1.44)		0.91 (0.60-1.37)		0.94 (0.62-1.44)	
Vitiligo	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators
N	170,849	1,614,886	151,293	1,319,143	170,849	1,614,886	151,293	1,319,143
Time since index date	**Unadjusted HR (95% CI)[a]**				**Adjusted HR (95% CI)[b]**			
Entire follow-up period	0.84 (0.67-1.05)		0.83 (0.66-1.04)		0.84 (0.67-1.05)		0.83 (0.66-1.04)	
0–30 days	0.55 (0.07-4.14)		0.67 (0.09-5.11)		0.63 (0.08-4.83)		0.70 (0.09-5.47)	
0–90 days	1.33 (0.52-3.38)		1.55 (0.60-4.00)		1.32 (0.52-3.37)		1.51 (0.58-3.91)	
0–365 days	1.30 (0.84-2.01)		1.24 (0.78-1.95)		1.30 (0.84-2.02)		1.24 (0.78-1.96)	
0–1095 days	1.18 (0.89-1.58)		1.15 (0.85-1.55)		1.18 (0.89-1.57)		1.15 (0.85-1.55)	
Denmark								
Chronic urticaria	Bereaved Cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators
N	362,289	3,475,628	316,437	3,003,175	363,896	3,506,721	317,904	3,030,806
Time since index date	**Unadjusted HR (95% CI)[a]**				**Adjusted HR (95% CI)[b]**			
Entire follow-up period	1.01 (0.76-1.35)		0.92 (0.70-1.20)		1.01 (0.76-1.35)		0.92 (0.70-1.20)	
0–182 days	NA		NA		NA		NA	
0–365 days	0.88 (0.21-3.73)		0.60 (0.14-2.52)		0.91 (0.21-3.87)		0.60 (0.14-2.50)	
0–1095 days	0.81 (0.41-1.60)		0.62 (0.32-1.23)		0.80 (0.40-1.59)		0.61 (0.31-1.20)	
Alopecia areata	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators

N	364,742	3,523,834	318,687	3,046,279	364,742	3,523,834	318,687	3,046,279
Time since index date	**Unadjusted HR (95% CI)[a]**				**Adjusted HR (95% CI)[b]**			
Entire follow-up period	1.01 (0.75-1.38)		0.96 (0.70-1.32)		1.00 (0.74-1.36)		0.95 (0.69-1.31)	
0–30 days	NA		NA		NA		NA	
0–90 days	NA		NA		NA		NA	
0–365 days	NA		NA		NA		NA	
0–1095 days	1.23 (0.73-2.06)		1.14 (0.65-1.98)		1.20 (0.71-2.02)		1.11 (0.64-1.94)	
Vitiligo	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators	Bereaved cohort	Matched comparators
N	364,758	3,524,134	318,706	3,046,587	364,758	3,524,134	318,706	3,046,587
Time since index date	**Unadjusted HR (95% CI)[a]**				**Adjusted HR (95% CI)[b]**			
Entire follow-up period	1.08 (0.76-1.53)		1.18 (0.83-1.69)		1.05 (0.74-1.49)		1.16 (0.81-1.66)	
0–30 days	NA		NA		NA		NA	
0–90 days	NA		NA		NA		NA	
0–365 days	0.18 (0.02-1.30)		0.22 (0.03-1.62)		0.16 (0.02-1.15)		0.21 (0.03-1.57)	
0–1095 days	0.63 (0.31-1.28)		0.72 (0.35-1.48)		0.59 (0.29-1.21)		0.69 (0.33-1.42)	

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable

[a]Computed using Cox regression stratified by matched set to account for the matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index score.

Figure S5. Assessment of the assumption of proportional hazards.

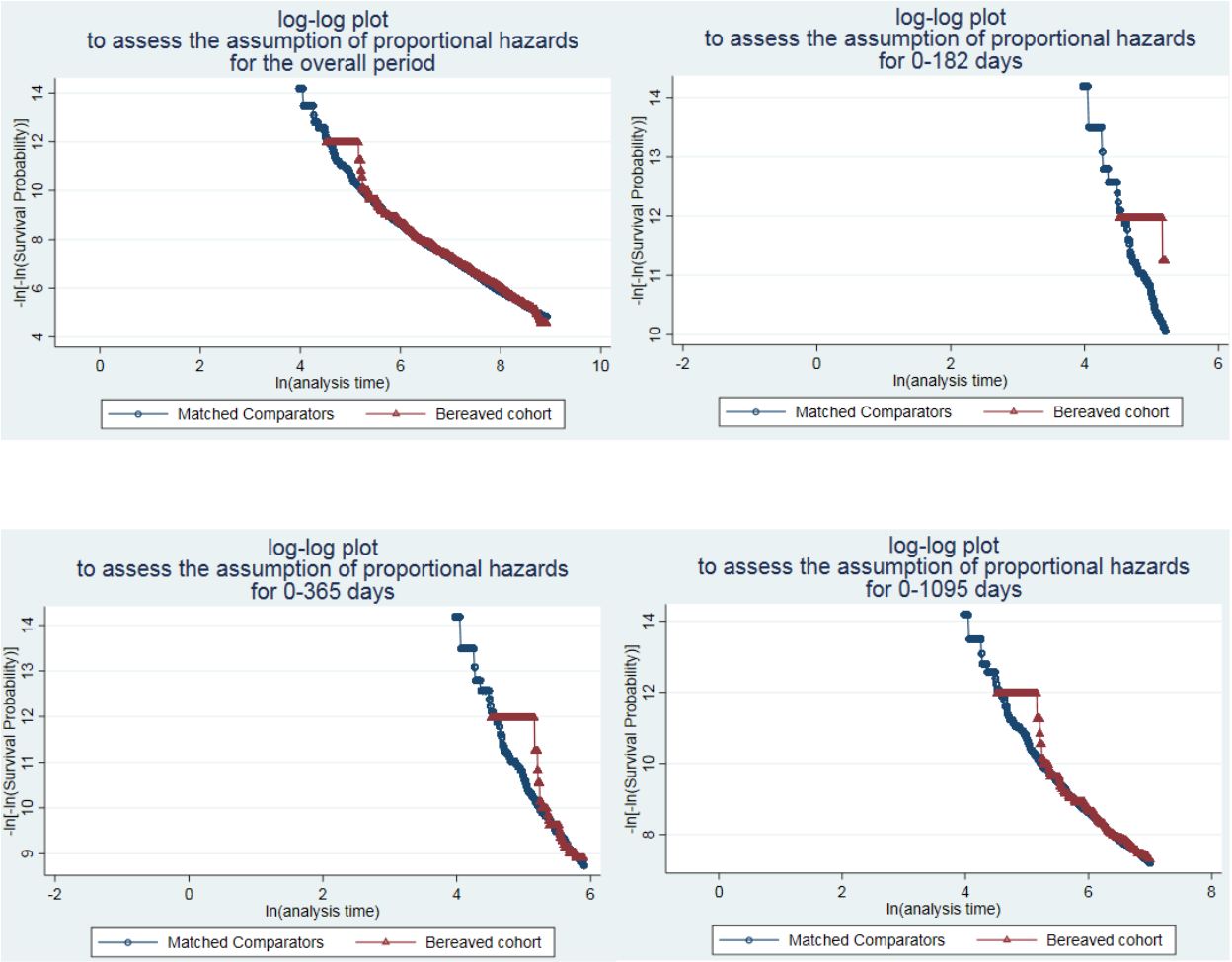


Figure 4.1. Log-log plot assessing the assumption of proportional hazards in the analysis of the association between partner bereavement and chronic urticaria in the UK.

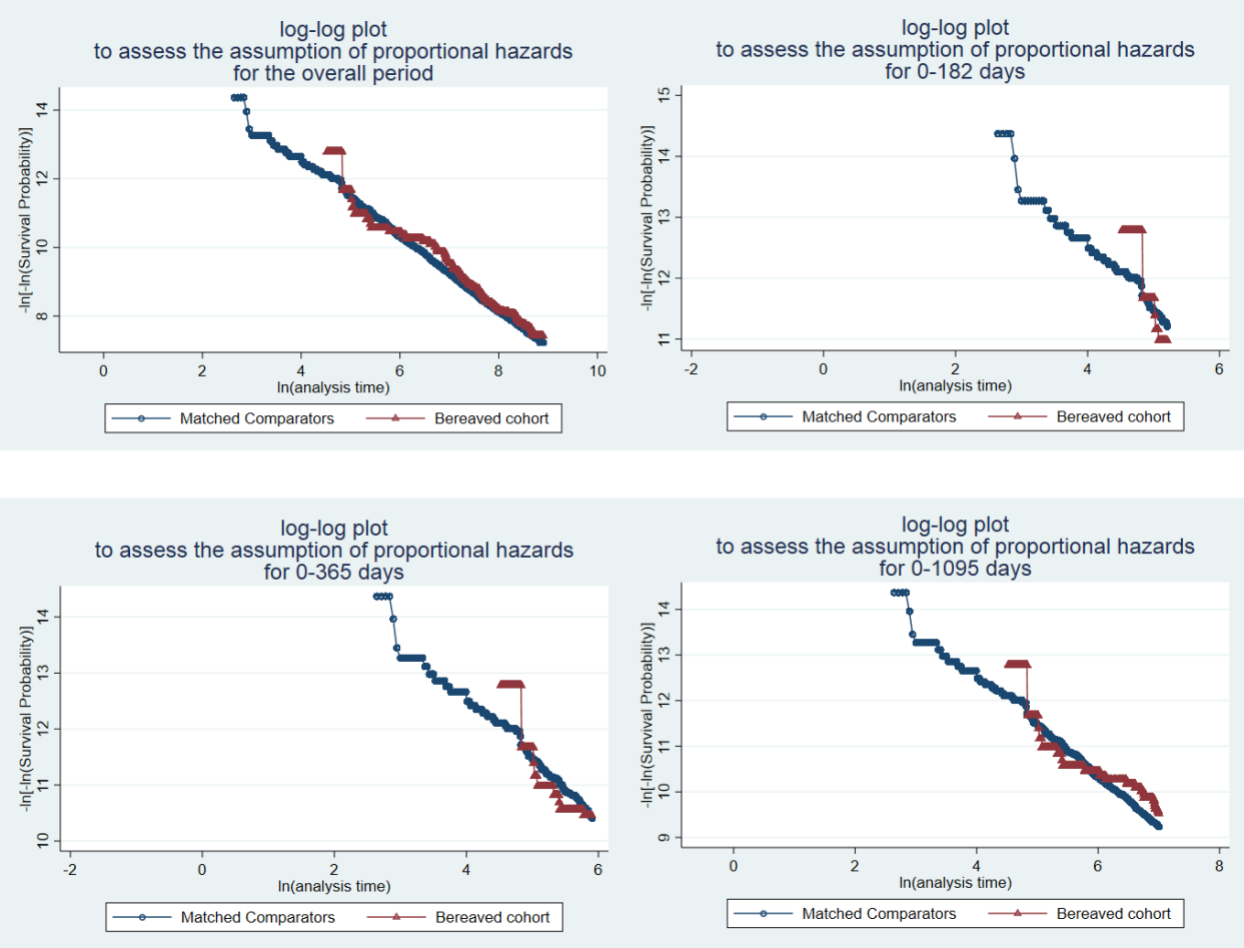
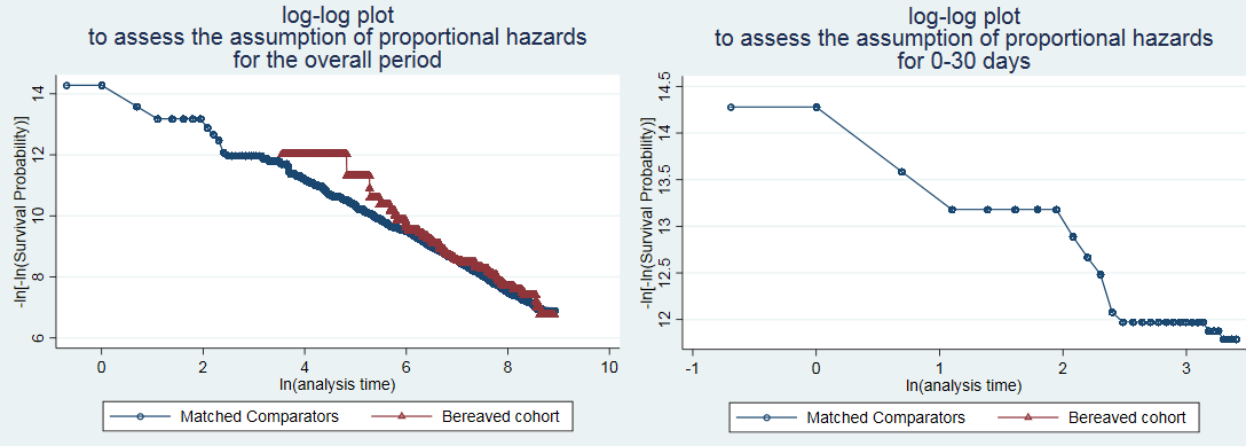
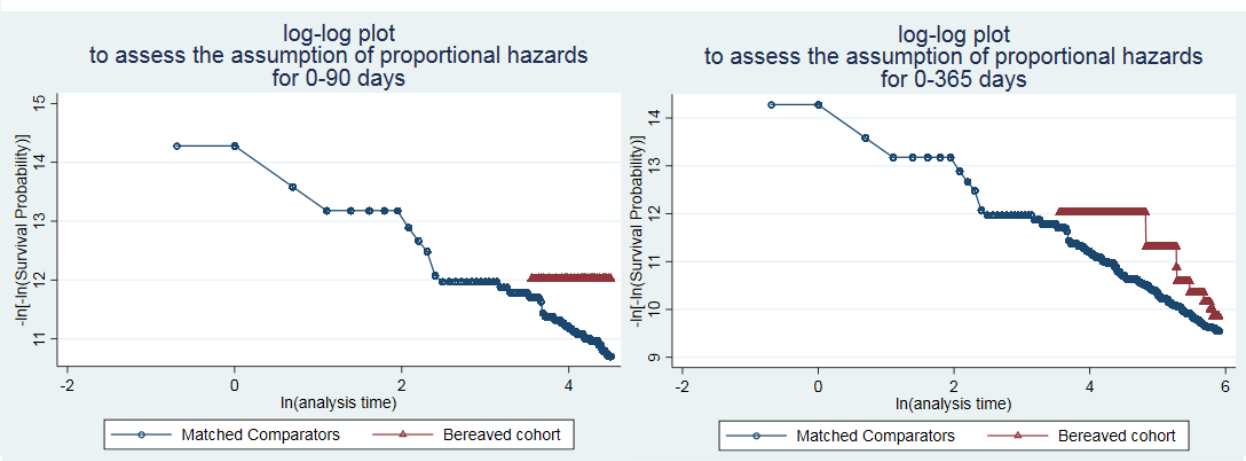


Figure 4.2. Log-log plot assessing the assumption of proportional hazards in the analysis of the association between partner bereavement and chronic urticaria in Denmark.





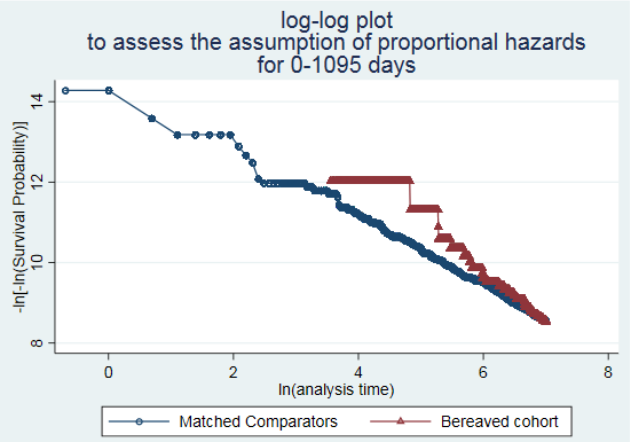


Figure 4.3. Log-log plot assessing the assumption of proportional hazards in the analysis of the association between partner bereavement and alopecia areata in the UK.

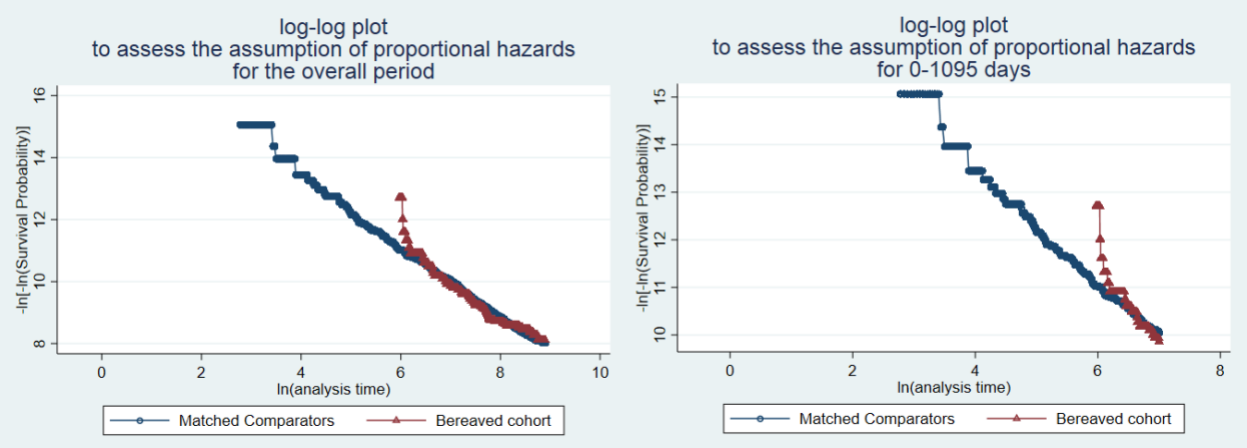


Figure 4.4. Log-log plot assessing the assumption of proportional hazards in the analysis of the association between partner bereavement and alopecia areata in Denmark.

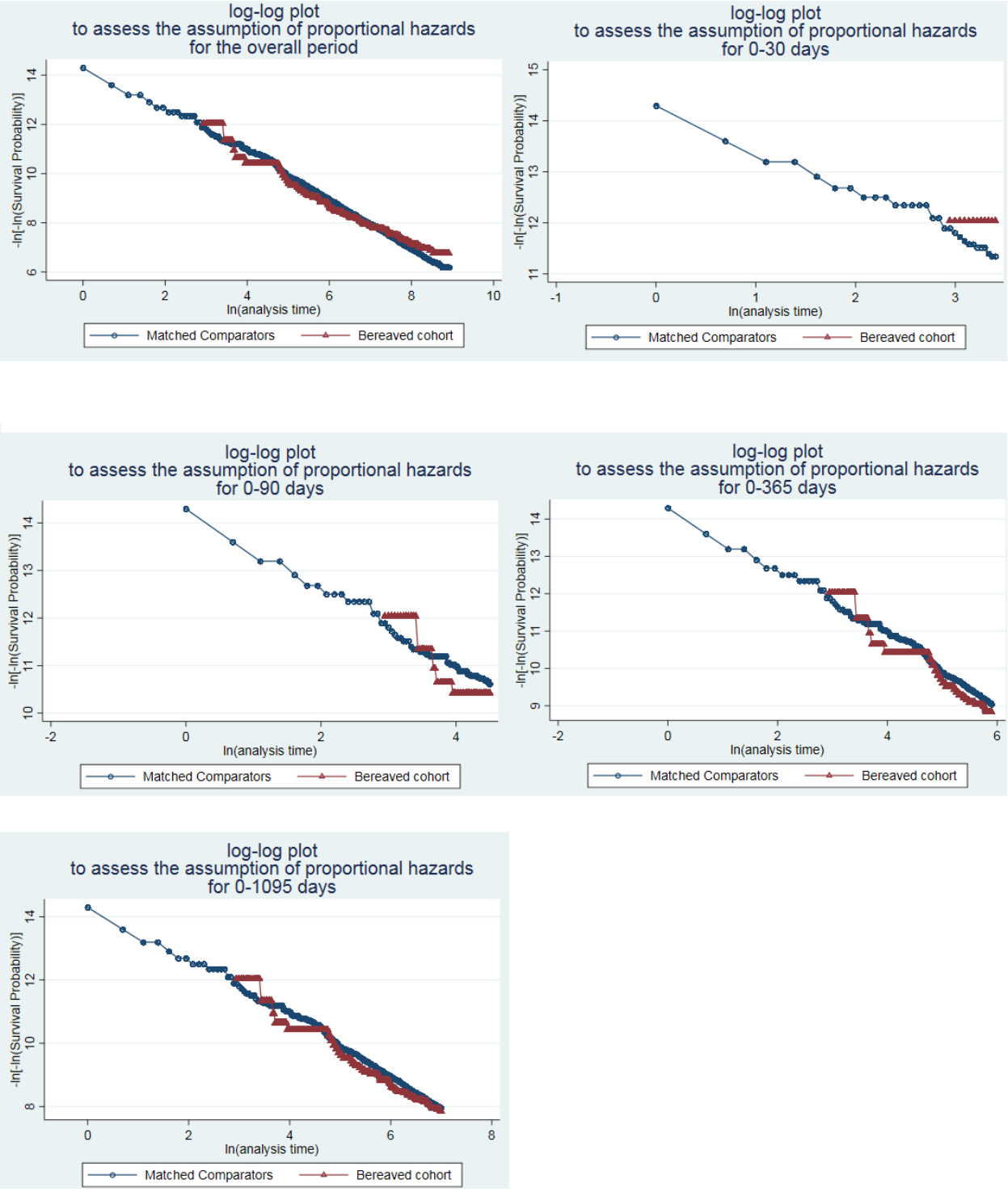


Figure 4.5. Log-log plot assessing the assumption of proportional hazards in the analysis of the association between partner bereavement and vitiligo in the UK.

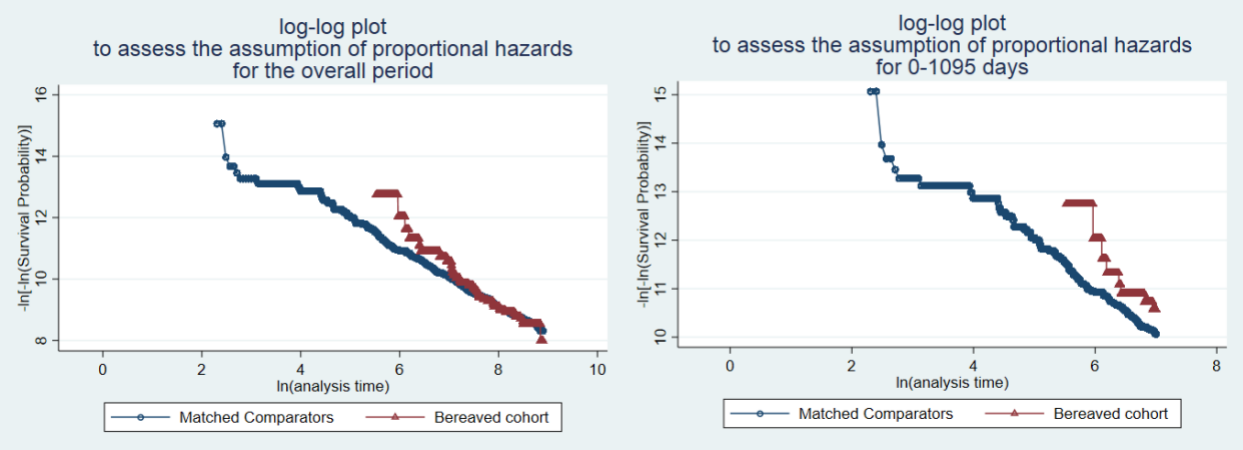


Figure 4.6. Log-log plot assessing the assumption of proportional hazards in the analysis of the association between partner bereavement and vitiligo in Denmark.

Table S9. Results of stratifying follow-up time since bereavement in the UK and Denmark.

	UK		Denmark	
	Unadjusted hazard ratio (95% CI)	**p-value**	**Unadjusted hazard ratio (95% CI)**	**p-value**
Chronic urticaria				
0-182 days	0.31 (0.08-1.26)		N/A	
183-365 days	1.12 (0.68-1.82)		0.77 (0.18-3.26)	
366-1095 days	0.94 (0.73-1.22)		0.67 (0.33-1.37)	
1095+ days	0.97 (0.83-1.14)	0.26	1.01 (0.76-1.34)	0.53
Alopecia areata				
0-30 days	NA		N/A	
31-90 days	0.33 (0.04-2.51)		N/A	
91-365 days	0.93 (0.43-2.03)		N/A	
366-1095 days	1.07 (0.65-1.76)		1.93 (1.13-3.31)	
1095+ days	0.73 (0.47-1.13)	0.22	0.93 (0.64-1.35)	0.03
Vitiligo				
0-30 days	0.55 (0.07-4.14)		N/A	
31-90 days	2.05 (0.70-6.02)		N/A	
91-365 days	1.30 (0.79-2.12)		0.23 (0.03-1.67)	
366-1095 days	1.11 (0.76-1.62)		0.97 (0.44-2.11)	
1095+ days	0.56 (0.39-0.81)	0.02	1.38 (0.92-2.07)	0.07

Abbreviations: NA, not applicable; CI, confidence interval

Table S10. Sensitivity analysis restricted to patients with more than 3 years of registration history.

UK									
Chronic urticaria									
Time since index date	**Bereaved cohort (N=142,981)**			**Matched comparators (N=1,246,768)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	213	731,333	0.29	1919	6,108,974	0.31	0.92 (0.80-1.07)	0.92 (0.79-1.06)	0.94 (0.80-1.09)
0–182 days	[d]	68,001	[d]	[d]	597,416	[d]	0.44 (0.11-1.81)	0.45 (0.11-1.88)	0.51 (0.12-2.19)
0–365 days	13	130,809	0.10	171	1,150,988	0.15	0.69 (0.39-1.21)	0.69 (0.39-1.21)	0.73 (0.41-1.29)
0–1095 days	72	336,633	0.21	675	2,944,013	0.23	0.95 (0.74-1.21)	0.94 (0.74-1.21)	0.96 (0.75-1.24)
Alopecia areata									
Time since index date	**Bereaved cohort (N=148,303)**			**Matched comparators (N=1,340,771)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	45	755,678	0.06	425	6,526,908	0.07	0.90 (0.66-1.24)	0.90 (0.66-1.23)	0.94 (0.68-1.30)
0–30 days	[d]	12,086	[d]	[d]	109,467	[d]	NA	NA	NA
0–90 days	[d]	35,672	[d]	[d]	324,081	[d]	0.33 (0.04-2.46)	0.33 (0.05-2.48)	0.24 (0.03-2.00)
0–365 days	8	135,635	0.06	88	1,236,678	0.07	0.81 (0.39-1.67)	0.81 (0.39-1.68)	0.84 (0.40-1.79)
0–1095 days	25	348,775	0.07	205	3,158,594	0.06	1.05 (0.69-1.60)	1.05 (0.69-1.59)	1.03 (0.66-1.59)
Vitiligo									
Time since index date	**Bereaved cohort (N=149,537)**			**Matched comparators (N=1,362,668)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	66	762,938	0.09	763	6,636,547	0.11	0.78 (0.60-1.00)	0.77 (0.60-1.00)	0.78 (0.59-1.01)
0–30 days	[d]	12,187	[d]	[d]	111,254	[d]	NA	NA	NA
0–90 days	[d]	35,968	[d]	[d]	329,379	[d]	0.33 (0.04-2.40)	0.31 (0.04-2.29)	0.30 (0.04-2.36)
0–365 days	17	136,767	0.12	147	1,256,832	0.12	1.11 (0.67-1.83)	1.11 (0.67-1.84)	1.10 (0.64-1.90)

0–1095 days	42	351,732	0.12	364	3,210,122	0.11	1.07 (0.77-1.48)	1.07 (0.77-1.48)	1.05 (0.74-1.48)
Denmark									
Chronic urticaria									
Time since index date	**Bereaved cohort (N=351,760)**			**Matched comparators (N=3,262,869)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	66	2,702,189	0.02	573	22,392,702	0.03	0.97 (0.75-1.26)	0.97 (0.74-1.26)	0.96 (0.73-1.26)
0–182 days	[d]	171,022	[d]	[d]	1,581,419	[d]	NA	NA	NA
0–365 days	[d]	335,408	[d]	[d]	3,086,616	[d]	0.73 (0.17-3.09)	0.72 (0.17-3.06)	0.80 (0.18-3.45)
0–1095 days	10	920,538	0.01	126	8,296,763	0.02	0.73 (0.38-1.39)	0.70 (0.37-1.35)	0.68 (0.34-1.35)
Alopecia areata									
Time since index date	**Bereaved cohort (N=354,133)**			**Matched comparators (N=3,307,474)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	46	2,716,654	0.02	366	22,639,423	0.02	1.03 (0.76-1.41)	1.03 (0.75-1.42)	1.03 (0.74-1.43)
0–30 days	[d]	28,949	[d]	[d]	270,369	[d]	NA	NA	NA
0–90 days	[d]	86,140	[d]	[d]	803,676	[d]	NA	NA	NA
0–365 days	[d]	337,628	[d]	[d]	3,128,185	[d]	NA	NA	NA
0–1095 days	15	926,392	0.02	111	8,404,920	0.01	1.26 (0.73-2.16)	1.25 (0.73-2.15)	1.16 (0.64-2.07)
Vitiligo									
Time since index date	**Bereaved cohort (N=354,145)**			**Matched comparators (N=3,307,708)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	33	2,716,921	0.01	288	22,641,769	0.01	1.02 (0.71-1.47)	0.99 (0.69-1.44)	1.11 (0.76-1.62)
0–30 days	[d]	28,950	[d]	[d]	270,388	[d]	NA	NA	NA
0–90 days	[d]	86,143	[d]	[d]	803,733	[d]	NA	NA	NA
0–365 days	[d]	337,643	[d]	[d]	3,128,413	[d]	0.19 (0.03-1.38)	0.16 (0.02-1.18)	0.23 (0.03-1.69)
0–1095 days	7	926,442	0.01	116	8,405,495	0.01	0.57 (0.27-1.23)	0.55 (0.25-1.18)	0.65 (0.30-1.41)

Abbreviations: HR, hazard ratio; NA, not applicable; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index

[c]Complete-case analysis was used to handle missing data in the fully adjusted model. Notably, the number of events, person-years at risk, and rate per 1000 in the bereaved and matched comparator cohorts presented in this table were calculated for the full cohort in the unadjusted and adjusted models only. Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status in the UK. For chronic urticaria, the total number of bereaved and comparison individuals was 127,484 and 1,027,109, respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. For alopecia areata, the total number of bereaved and comparison individuals was 132,488 and 1,109,370, respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. For vitiligo, the total number of bereaved and comparison individuals was 133,636 and 1,128,277, respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. Adjusted for education duration in Denmark. For chronic urticaria, the total number of bereaved and comparison subjects was 307,254 and 2,822,035 respectively after excluding patients with missing education duration. For alopecia areata, the total number of bereaved and comparison subjects was 309,433 and 2,862,084 respectively after excluding patients with missing education duration. For vitiligo, the total number of bereaved and comparison subjects was 309,448 and 2,862,330 respectively after excluding patients with missing education duration.

[d]In cases in which there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S11. Sensitivity analysis restricted to patients eligible for linkage to Hospital Episode Statistics/Office for National Statistics death registration data.

Chronic urticaria									
Time since index date	**Bereaved cohort (N=97,287)**			**Matched comparators (N=877,970)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	152	514,321	0.30	1502	4,466,821	0.34	0.89 (0.75-1.05)	0.89 (0.75-1.05)	0.92 (0.77-1.10)
0–182 days	[d]	46,247	[d]	[d]	421,147	[d]	0.25 (0.03-1.79)	0.25 (0.03-1.82)	0.28 (0.04-2.14)
0–365 days	13	89,034	0.15	133	812,581	0.16	0.91 (0.51-1.62)	0.91 (0.51-1.61)	0.95 (0.53-1.70)
0–1095 days	45	230,248	0.20	540	2,091,492	0.26	0.77 (0.57-1.05)	0.78 (0.57-1.06)	0.83 (0.61-1.13)
Alopecia areata									
Time since index date	**Bereaved cohort (N=100,750)**			**Matched comparators (N=940,751)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	32	530,315	0.06	300	4,752,727	0.06	0.93 (0.64-1.35)	0.92 (0.63-1.33)	0.95 (0.64-1.41)
0–30 days	[d]	8207	[d]	[d]	76,796	[d]	NA	NA	NA
0–90 days	[d]	24,217	[d]	[d]	227,467	[d]	0.44 (0.06-3.27)	0.41 (0.06-3.10)	0.34 (0.04-2.66)
0–365 days	7	92,172	0.08	63	869,907	0.07	1.02 (0.47-2.22)	1.04 (0.47-2.28)	1.17 (0.52-2.67)
0–1095 days	19	238,144	0.08	148	2,235,791	0.07	1.10 (0.68-1.78)	1.11 (0.68-1.80)	1.08 (0.65-1.81)
Vitiligo									
Time since index date	**Bereaved cohort (N=101,491)**			**Matched comparators (N=954,449)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	57	534,925	0.11	636	4,823,039	0.13	0.81 (0.61-1.07)	0.81 (0.61-1.07)	0.79 (0.59-1.05)
0–30 days	[d]	8267	[d]	[d]	77,916	[d]	0.81 (0.10-6.20)	0.83 (0.10-6.52)	1.26 (0.11-14.28)
0–90 days	5	24,395	0.20	27	230,789	0.12	1.87 (0.72-4.87)	1.80 (0.69-4.71)	1.76 (0.62-5.02)
0–365 days	14	92,853	0.15	123	882,511	0.14	1.13 (0.65-1.97)	1.13 (0.65-1.97)	1.02 (0.55-1.88)
0–1095 days	34	239,950	0.14	295	2,268,105	0.13	1.10 (0.77-1.58)	1.10 (0.76-1.58)	1.06 (0.72-1.55)

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].
[b]Adjusted for Charlson Comorbidity Index score.
[c]Complete-case analysis was used to handle missing data in the fully adjusted model. Notably, the number of events, person-years at risk, and rate per 1000 in bereaved and matched comparator cohorts presented in this table were calculated for the full cohort in the unadjusted and adjusted models only. Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status. For chronic urticaria, the total number of bereaved and comparison individuals was 85,696 and 710,525, respectively, after excluding patients with missing values for body mass index, alcohol consumption, and smoking status. For alopecia areata, the total number of bereaved and comparison individuals was 88,943 and 765,365, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status. For vitiligo, the total number of bereaved and comparison individuals was 89,624 and 777,122, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status.
[d]In cases in which there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S12. *Post-hoc* intention-to-treat analysis that did not censor follow-up on the date of experiencing partner bereavement, the transfer out of practice of their partner after the index date (UK), or emigration of partner (Denmark).

UK									
Chronic urticaria									
Time since index date	**Bereaved cohort (N=163,855)**			**Matched comparators (N=1,486,638)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	269	875,386	0.31	2915	8,858,283	0.33	0.95 (0.84-1.08)	0.95 (0.84-1.08)	0.97 (0.85-1.11)
0–182 days	[d]	78,004	[d]	[d]	720,219	[d]	0.32 (0.08-1.29)	0.32 (0.08-1.32)	0.42 (0.10-1.77)
0–365 days	20	150,221	0.13	218	1,402,128	0.16	0.88 (0.56-1.40)	0.89 (0.56-1.40)	0.96 (0.60-1.53)
0–1095 days	85	388,765	0.22	892	3,729,502	0.24	0.92 (0.73-1.15)	0.92 (0.73-1.15)	0.95 (0.76-1.20)
Alopecia areata									
Time since index date	**Bereaved cohort (N=169,525)**			**Matched comparators (N=1,590,276)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	49	901,811	0.05	568	9,399,311	0.06	0.86 (0.64-1.15)	0.86 (0.64-1.15)	0.89 (0.66-1.21)
0–30 days	[d]	13,817	[d]	[d]	130,074	[d]	NA	NA	NA
0–90 days	[d]	40,793	[d]	[d]	386,513	[d]	0.24 (0.03-1.76)	0.24 (0.03-1.77)	0.20 (0.03-1.55)
0–365 days	8	155,369	0.05	107	1,498,462	0.07	0.69 (0.33-1.41)	0.69 (0.34-1.43)	0.75 (0.36-1.57)
0–1095 days	26	401,742	0.06	262	3,979,166	0.07	0.91 (0.60-1.36)	0.91 (0.61-1.36)	0.92 (0.60-1.40)
Vitiligo									
Time since index date	**Bereaved cohort (N=170,849)**			**Matched comparators (N=1,614,886)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	87	910,002	0.10	1084	9,552,321	0.11	0.83 (0.67-1.04)	0.83 (0.67-1.04)	0.83 (0.66-1.05)

0–30 days	[d]	13,925	[d]	[d]	132,088	[d]	0.55 (0.07-4.14)	0.63 (0.08-4.83)	0.80 (0.09-7.30)
0–90 days	[d]	41,110	[d]	[d]	392,506	[d]	1.33 (0.52-3.39)	1.32 (0.52-3.38)	1.49 (0.55-4.06)
0–365 days	23	156,584	0.15	180	1,521,692	0.12	1.29 (0.84-2.00)	1.30 (0.84-2.00)	1.30 (0.82-2.07)
0–1095 days	54	404,936	0.13	471	4,041,190	0.12	1.18 (0.89-1.57)	1.18 (0.89-1.56)	1.18 (0.87-1.59)
Denmark									
Chronic urticaria									
Time since index date	**Bereaved cohort (N=362,289)**			**Matched comparators (N=3,475,628)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	67	2,778,742	0.02	728	28,198,922	0.03	0.96 (0.74-1.24)	0.96 (0.74-1.23)	0.95 (0.73-1.24)
0–182 days	[d]	176,120	[d]	[d]	1,699,065	[d]	NA	NA	NA
0–365 days	[d]	345,359	[d]	[d]	3,343,793	[d]	0.61 (0.15-2.56)	0.60 (0.14-2.51)	0.67 (0.16-2.84)
0–1095 days	10	947,459	0.01	149	9,270,910	0.02	0.68 (0.36-1.29)	0.66 (0.35-1.26)	0.63 (0.32-1.25)
Alopecia areata									
Time since index date	**Bereaved cohort (N=364,742)**			**Matched comparators (N=3,523,834)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	48	2,793,638	0.02	466	28,513,725	0.02	1.04 (0.77-1.41)	1.03 (0.76-1.39)	1.01 (0.74-1.38)
0–30 days	[d]	29,816	[d]	[d]	288,478	[d]	NA	NA	NA
0–90 days	[d]	88,713	[d]	[d]	859,927	[d]	NA	NA	NA
0–365 days	[d]	347,651	[d]	[d]	3,389,402	[d]	NA	NA	NA
0–1095 days	16	953,497	0.02	132	9,393,087	0.01	1.23 (0.73-2.07)	1.20 (0.71-2.03)	1.16 (0.66-2.02)
Vitiligo									
Time since index date	**Bereaved cohort (N=364,758)**			**Matched comparators (N=3,524,134)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	36	2,793,919	0.01	356	28,517,403	0.01	1.07 (0.76-1.52)	1.05 (0.74-1.49)	1.14 (0.80-1.63)
0–30 days	[d]	29,817	[d]	[d]	288,502	[d]	NA	NA	NA

0–90 days	[d]	88,717	[d]	[d]	860,001	[d]	NA	NA	NA
0–365 days	[d]	347,669	[d]	[d]	3,389,699	[d]	0.18 (0.03-1.31)	0.16 (0.02-1.16)	0.23 (0.03-1.66)
0–1095 days	8	953,555	0.01	129	9,393,874	0.01	0.64 (0.31-1.30)	0.60 (0.29-1.23)	0.71 (0.34-1.46)

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index

[c]Complete-case analysis was used to handle missing data in the fully adjusted model. Notably, the number of events, person-years at risk, and rate per 1000 in the bereaved and matched comparator cohorts presented in this table were calculated for the full cohort in the unadjusted and adjusted models only. Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status in the UK. For chronic urticaria, the total number of bereaved and comparison individuals was 144,748 and 1,207,774, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status. For alopecia areata, the total number of bereaved and comparison individuals was 150,072 and 1,298,085, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status. For vitiligo, the total number of bereaved and comparison individuals was 151,293 and 1,319,143, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status. Adjusted additionally for education duration in Denmark. For chronic urticaria, the total number of bereaved and comparison persons was 316,437 and 3,003,175, respectively, after excluding those with missing education duration. For alopecia areata, the total number of bereaved and comparison persons was 318,687 and 3,046,279, respectively, after excluding those with missing education duration. For vitiligo, the total number of bereaved and comparison persons was 318,706 and 3,046,587, respectively, after excluding those with missing education duration.

[d]In cases in which there were fewer than 5 patients the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S13. Sensitivity analysis of censoring at the end of partnership in Denmark.

Time since index date	Bereaved cohort			Matched comparators			Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
	Number of events	Person-years at risk	Rate per 1,000	Number of events	Person-years at risk	Rate per 1,000			
Chronic urticaria									
Entire follow-up period	67	2,778,742	0.02	624	23,591,188	0.03	0.94 (0.73-1.22)	0.94 (0.73-1.22)	0.93 (0.71-1.22)
0–182 days	[d]	176,120	[d]	[d]	1,684,140	[d]	NA	NA	NA
0–365 days	[d]	345,359	[d]	[d]	3,286,183	[d]	0.61 (0.15-2.53)	0.60 (0.14-2.49)	0.66 (0.16-2.81)
0–1095 days	10	947,459	0.01	146	8,819,854	0.02	0.66 (0.35-1.26)	0.65 (0.34-1.24)	0.63 (0.32-1.24)
Alopecia areata									
Entire follow-up period	48	2,793,638	0.02	414	23,854,670	0.02	0.99 (0.73-1.35)	0.98 (0.72-1.33)	0.96 (0.70-1.33)
0–30 days	[d]	29,816	[d]	[d]	288,042	[d]	NA	NA	NA
0–90 days	[d]	88,713	[d]	[d]	856,127	[d]	NA	NA	NA
0–365 days	[d]	347,651	[d]	[d]	3,331,079	[d]	NA	NA	NA
0–1095 days	16	953,497	0.02	129	8,936,421	0.01	1.22 (0.72-2.05)	1.19 (0.70-2.01)	1.14 (0.65-1.99)
Vitiligo									
Entire follow-up period	36	2,793,919	0.01	308	23,857,621	0.01	1.09 (0.77-1.54)	1.06 (0.74-1.50)	1.18 (0.83-1.70)
0–30 days	[d]	29,817	[d]	[d]	288,067	[d]	NA	NA	NA
0–90 days	[d]	88,717	[d]	[d]	856,200	[d]	NA	NA	NA
0–365 days	[d]	347,669	[d]	[d]	3,331,365	[d]	0.18 (0.02-1.30)	0.16 (0.02-1.15)	0.22 (0.03-1.65)
0–1095 days	8	953,555	0.01	128	8,937,150	0.01	0.62 (0.30-1.28)	0.59 (0.29-1.21)	0.70 (0.34-1.44)

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, and county of residence].
[b]Adjusted for Charlson Comorbidity Index score.
[c]Adjusted additionally for education duration. For chronic urticaria, the total number of bereaved and comparison persons was 316,437 and 3,003,175, respectively, after excluding those with missing education duration. For alopecia areata, the total number of bereaved and comparison persons was 318,687 and 3,046,279, respectively, after excluding those with missing education duration. For vitiligo, the total number of bereaved and comparison persons was 318,706 and 3,046,587, respectively, after excluding those with missing education duration.
[d]In cases in which there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S14. Sensitivity analysis excluding codes that specify inducible forms of urticaria.

UK									
Time since index date	**Bereaved cohort (N=163,855)**			**Matched comparators (N=1,486,638)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	247	875,466	0.28	2316	7,616,510	0.30	0.94 (0.82-1.08)	0.94 (0.82-1.08)	0.97 (0.84-1.11)
0–182 days	[d]	78,004	[d]	[d]	713,353	[d]	0.33 (0.08-1.36)	0.34 (0.08-1.38)	0.46 (0.11-1.93)
0–365 days	19	150,221	0.13	196	1,376,318	0.14	0.93 (0.58-1.49)	0.93 (0.58-1.48)	1.00 (0.62-1.62)
0–1095 days	80	388,771	0.21	778	3,542,405	0.22	0.95 (0.75-1.19)	0.94 (0.75-1.19)	0.99 (0.78-1.26)
Denmark									
Time since index date	**Bereaved cohort (N=362,289)**			**Matched comparators (N=3,475,628)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	55	2,778,818	0.02	478	23,909,290	0.02	1.01 (0.76-1.35)	1.01 (0.76-1.35)	1.00 (0.74-1.35)
0–182 days	[d]	176,120	[d]	[d]	1,684,577	[d]	NA	NA	NA
0–365 days	[d]	345,359	[d]	[d]	3,288,132	[d]	0.88 (0.21-3.73)	0.91 (0.21-3.87)	0.98 (0.22-4.38)
0–1095 days	9	947,461	0.01	109	8,840,863	0.01	0.81 (0.41-1.60)	0.80 (0.40-1.59)	0.75 (0.36-1.55)

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark), and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index score.

[c]Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status. The total number of bereaved and comparison individuals was 144,748 and 1,207,774, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status Adjusted additionally for education duration in Denmark. The total number of bereaved and comparison persons was 316,437 and 3,003,175 respectively after excluding those with missing education duration.

[d]In cases in which there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S15. Sensitivity analysis including codes for angioedema.

UK									
Time since index date	**Bereaved cohort (N=163,885)**			**Matched comparators (N=1,486,638)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	2278	865,383	2.63	20,746	7,532,665	2.75	0.98 (0.93-1.02)	0.98 (0.93-1.02)	0.98 (0.94-1.03)
0–30 days	28	13,353	2.10	347	121,390	2.86	0.75 (0.51-1.10)	0.74 (0.50-1.08)	0.69 (0.46-1.05)
0–90 days	101	39,416	2.56	1022	359,544	2.84	0.92 (0.75-1.13)	0.92 (0.75-1.12)	0.86 (0.69-1.08)
0–182 days	236	77,952	3.03	2047	712,859	2.87	1.07 (0.94-1.23)	1.07 (0.93-1.23)	1.07 (0.93-1.23)
0–365 days	442	150,013	2.95	3877	1,374,488	2.82	1.05 (0.96-1.16)	1.05 (0.95-1.16)	1.04 (0.93-1.15)
0–1095 days	1115	387,263	2.88	10,142	3,529,251	2.87	1.02 (0.96-1.08)	1.02 (0.95-1.08)	1.02 (0.96-1.09)
Denmark									
Time since index date	**Bereaved cohort (N=362,289)**			**Matched comparators (N=3,475,628)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up period	1,558	2,771,093	0.56	13,177	23,840,103	0.55	1.03 (0.97-1.08)	1.02 (0.96-1.07)	1.02 (0.96-1.08)
0–30 days	17	29,615	0.57	140	284,108	0.49	1.15 (0.69-1.91)	1.16 (0.70-1.93)	1.05 (0.60-1.84)
0–90 days	50	88,114	0.57	433	844,495	0.51	1.12 (0.84-1.50)	1.11 (0.83-1.49)	1.06 (0.78-1.45)
0–182 days	93	176,098	0.53	884	1,684,364	0.52	1.02 (0.83-1.27)	1.01 (0.82-1.26)	0.99 (0.79-1.24)
0–365 days	188	345,272	0.54	1,730	3,287,297	0.53	1.04 (0.89-1.21)	1.03 (0.89-1.20)	1.02 (0.87-1.20)
0–1095 days	524	946,751	0.55	4,697	8,834,402	0.53	1.05 (0.96-1.16)	1.04 (0.95-1.14)	1.03 (0.93-1.13)

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index score.

[c]Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status. The total number of bereaved and comparison individuals was 144,748 and 1,207,774, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status. Adjusted additionally for education duration in Denmark. The total number of bereaved and comparison persons was 316,437 and 3,003,175, respectively, after excluding those with missing education duration.

[d]In cases in which there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S16. Sensitivity analysis including additional non-specific codes for alopecia areata.

UK									
Time since index date	**Bereaved cohort (N=169,525)**			**Matched comparators (N=1,590,276)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up	429	901,811	0.48	4321	8,087,071	0.53	0.89 (0.81-0.99)	0.89 (0.80-0.98)	0.86 (0.77-0.96)
0–30 days	[d]	13,817	[d]	[d]	129,863	[d]	0.28 (0.07-1.14)	0.27 (0.07-1.11)	0.30 (0.07-1.22)
0–90 days	8	40,793	0.20	199	384,648	0.52	0.37 (0.18-0.76)	0.37 (0.18-0.75)	0.40 (0.19-0.81)
0–365 days	71	155,369	0.46	748	1,470,901	0.51	0.91 (0.71-1.16)	0.90 (0.71-1.16)	0.92 (0.72-1.18)
0–1095 days	178	401,742	0.44	2028	3,779,874	0.54	0.83 (0.71-0.96)	0.82 (0.70-0.96)	0.82 (0.70-0.96)
Denmark									
Time since index date	**Bereaved cohort (N=364,742)**			**Matched comparators (N=3,523,834)**			**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Fully adjusted HR (95% CI)[c]**
	Number of events	**Person-years at risk**	**Rate per 1,000**	**Number of events**	**Person-years at risk**	**Rate per 1,000**			
Entire follow-up	48	2,793,638	0.02	417	24,175,497	0.02	1.01 (0.75-1.38)	1.00 (0.74-1.36)	0.98 (0.71-1.35)
0–30 days	[d]	29,816	0.00	[d]	288,053	[d]	NA	NA	NA
0–90 days	[d]	88,713	[d]	[d]	856,229	[d]	NA	NA	NA
0–365 days	[d]	347,651	[d]	[d]	3,333,059	[d]	NA	NA	NA
0–1095 days	16	953,497	0.02	129	8,957,716	0.01	1.23 (0.73-2.06)	1.20 (0.71-2.02)	1.14 (0.65-2.00)

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Computed using Cox regression stratified by matched set to account for matching variables [age, sex, county of residence (in Denmark) and general practice (in the UK)].

[b]Adjusted for Charlson Comorbidity Index score.

[c]Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status. The total number of bereaved and comparison individuals was 150,072 and 1,298,085, respectively, after excluding those with missing values for body mass index, alcohol consumption, and smoking status. Adjusted additionally for education duration in Denmark. The total number of bereaved and comparison persons was 318,687 and 3,046,279, respectively, after excluding those with missing education duration.

[d]In cases in which there were fewer than 5 patients, the exact number was withheld in accordance with the confidentiality rules of the CPRD/Danish registries.

Table S17. Sensitivity analysis including additional non-specific codes for vitiligo.

Time since index date	Bereaved cohort (N=170,849)			Matched comparators (N=1,614,886)			Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]
	Number of events	Person-years at risk	Rate per 1,000	Number of events	Person-years at risk	Rate per 1,000			
Entire follow-up period	105	910,002	0.12	1086	8,215,110	0.13	0.91 (0.74-1.11)	0.91 (0.74-1.11)	0.93 (0.75-1.15)
0–30 days	[d]	13,925	[d]	[d]	131,873	[d]	0.55 (0.07-4.14)	0.63 (0.08-4.83)	0.80 (0.09-7.30)
0–90 days	5	41,110	0.12	41	390,610	0.10	1.26 (0.50-3.19)	1.28 (0.50-3.27)	1.43 (0.53-3.85)
0–365 days	26	156,584	0.17	200	1,493,648	0.13	1.30 (0.86-1.95)	1.31 (0.87-1.97)	1.36 (0.88-2.10)
0–1095 days	65	404,936	0.16	508	3,838,367	0.13	1.26 (0.97-1.64)	1.26 (0.97-1.64)	1.30 (0.99-1.71)

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Adjusted for Charlson Comorbidity Index scores.

[b]Adjusted additionally for smoking status, body mass index, alcohol consumption, and socioeconomic status. The total number of bereaved and comparison individuals was 151,293 and 1,319,143, respectively, after excluding those with missing values for body mass index, alcohol consumption and smoking status.