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Partner bereavement and risk of psoriasis and atopic eczema: cohort studies in the U.K. and Denmark*

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Summary

Background Stress is commonly cited as a risk factor for psoriasis and atopic eczema, but such evidence is limited.
Objectives To investigate the association between partner bereavement (an extreme life stressor) and psoriasis or atopic eczema.
Methods We conducted cohort studies using data from the U.K. Clinical Practice Research Datalink (1997–2017) and Danish nationwide registries (1997–2016). The exposed cohort was partners who experienced partner bereavement. The comparison cohort was up to 10 nonbereaved partners, matched to each bereaved partner by age, sex, county of residence (Denmark) and general practice (U.K.). Outcomes were the first recorded diagnosis of psoriasis or atopic eczema. We estimated hazard ratios (HRs) and confidence intervals (CIs) using a stratified Cox proportional hazards model in both settings, which were then pooled in a meta-analysis.
Results The pooled adjusted HR for the association between bereavement and psoriasis was 1·01 (95% CI 0·98–1·04) across the entire follow-up. Similar results were found in other shorter follow-up periods. Pooled adjusted HRs for the association between bereavement and atopic eczema were 0·97 (95% CI 0·84–1·12) across the entire follow-up, 1·09 (95% CI 0·86–1·38) within 0–30 days, 1·18 (95% CI 1·04–1·35) within 0–90 days, 1·14 (95% CI 1·06–1·22) within 0–365 days and 1·07 (95% CI 1·02–1·12) within 0–1095 days.
Conclusions We found a modest increase in the risk of atopic eczema within 3 years following bereavement, which peaked in the first 3 months. Acute stress may play a role in triggering onset of new atopic eczema or relapse of atopic eczema previously in remission. We observed no evidence for increased long-term risk of psoriasis and atopic eczema following bereavement.

What's already known about this topic?

- Psychological stress is commonly cited as a risk factor for psoriasis and atopic eczema. However, clinical evidence supporting such associations is limited.
- Current epidemiological evidence for the relationship is limited by small sample sizes and difficulty measuring stress.

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Conflicts of interest
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What does this study add?

- In two population-based cohort studies, there was no evidence of an increased risk of psoriasis associated with partner bereavement.
- There was a short-term increased risk of atopic eczema in the 3 years following partner bereavement, which peaked during the first year. However, there was no evidence of an increased long-term risk of atopic eczema.
- Acute stress may trigger onset or relapse of atopic eczema, leading to an increased risk of atopic eczema in the short term following partner bereavement.

Psoriasis and atopic eczema are inflammatory skin disorders associated with substantial morbidity, representing major health burdens.[1] The prevalence of psoriasis ranges from 1·2% to 8·5% in Europe[2] and from 2% to 3% in the U.K.[3] and Denmark.[4] Atopic eczema affects at least 15% of children and 7% of adults globally.[5,6] In addition, psoriasis and atopic eczema have a range of health consequences, including depression,[7,8] cardiovascular diseases[9,10] and increased mortality,[11,12] leading to substantial health expenditure.[13–15] Thus, understanding the aetiology of psoriasis and atopic eczema is a major priority.

Psychological stress is commonly cited as an important factor associated with psoriasis and atopic eczema. It has been postulated that stress activates the hypothalamic–pituitary–adrenal axis, resulting in increased levels of T helper and natural killer cells. Importantly, T cells are involved in the pathogenesis of psoriasis and atopic eczema.[16–19] However, clinical evidence supporting associations between stress and these conditions is limited.[20]

A recent systematic review investigating the association between stress and psoriasis found that existing studies were limited by small sample size, difficulty in measuring stress, and misclassification of negative life events due to recall bias.[21] Addressing these limitations requires population-based epidemiological studies with precise timing of negative life events.

According to the Social Readjustment Rating Scale, partner bereavement is perceived as one of the most stressful acute life events.[22] It impacts most people negatively irrespectively of coping mechanisms.[23,24] Therefore, partner bereavement is often used to elucidate the role of extreme stressors in important health outcomes, including cardiovascular disease,[25,26] infection[27,28] and death.[29,30]

Given uncertainty about the role of stress as a trigger of disease onset, we investigated whether partner bereavement was associated with new onset of psoriasis and atopic eczema in two population-based matched-cohort studies. We examined whether the associations differed by (i) time since bereavement and (ii) whether the death of a partner was expected.

Patients and methods

Setting

In the U.K. we used primary care data from the Clinical Practice Research Datalink (CPRD)[31] and linked death data from the Office for National Statistics (ONS), hospital admissions data from Hospital Episode Statistics and deprivation data from the Index of Multiple Deprivation.

In Denmark we used nationwide registries linked using the unique personal identifier assigned to all Danish residents. We defined the study population and obtained demographic information, including civil and vital status, from the Danish Civil Registration System.[32] Other registries provided data on hospital contacts including inpatients, outpatient hospital clinics and emergency records (Danish National Patient Registry),[33] dispensed prescriptions (Danish National Prescription Registry)[34] and education (Population Education Registry).[35]

We aimed for the U.K. and Danish studies to be as similar as possible to ensure comparability (Appendix S1; see Supporting Information). We used data from 1 January 1997 to 31 July 2017 in the U.K. and from 1 January 1997 to 31 December 2016 in Denmark.

Couple identification

In the U.K., we identified partners eligible for inclusion using a previously developed algorithm.[26,27,29,30] Individuals were eligible for inclusion from the latest of either the date of the practice meeting CPRD quality control standards or the study start date. We identified eligible opposite-sex couples in the same household, with an age gap of ≤ 10 years and with no younger adults in the same household aged within 15 years of either of

the couple. We excluded couples where both partners were < 40 years old or ≥ 95 years old; either partner had a code indicating residence in a communal establishment; and couples who belonged to households with > 10 registered members.

In Denmark we identified partners using an algorithm developed by Statistics Denmark, which registers the unique personal identifiers of a person's spouse or partner by combining data on civil status, demographics, address and close kinship (e.g. parents, siblings and children). Because more detailed data were available in Denmark, we allowed an age difference of up to 15 years between partners.[27]

Matched study population

Among eligible couples, we identified the partner who died first and included the surviving partner in the bereaved cohort. We considered the date of the partner's death as the index date for the bereaved partner. In the U.K., we used dates of death from the ONS when available (59·8%) and from CPRD for those without ONS linkage (40·2%).

For each bereaved person, we then identified a matched comparison cohort by sampling (with replacement) up to 10 partners on age, sex (both settings), county of residence (Denmark) and general practice membership (U.K.) on the index date. We did not include individuals in the comparison cohort who had experienced the death of a partner prior to the index date. We excluded couples who both died on the index date as they did not contribute person time. We required all individuals to have ≥ 1 year of registration history prior to the index date in the U.K., to allow adequate time for recording of covariates and history of psoriasis and atopic eczema.

Outcomes

We considered the first-ever recorded diagnosis of psoriasis or atopic eczema after bereavement to represent recent onset of psoriasis or atopic eczema, based on relevant morbidity codes (Read codes and International Classification of Diseases, 8th and 10th Revision codes) and validated diagnostic algorithms (Appendix S2 for the U.K. and Appendix S3 for Denmark; see Supporting Information).[36–38] Code lists for the U.K. are available online (https://datacompass.lshtm.ac.uk/1262). We excluded individuals with any diagnosis of the relevant outcome prior to the index date. We followed cohorts from the index date until the earliest of: diagnosis of a specific outcome, last data collection date from practice (U.K.), transfer out of the practice of either of the couple (U.K.), emigration of either of the couple (Denmark), death or the study end date. If a person in the comparison cohort experienced bereavement, he or she was censored 1 day before bereavement and was subsequently included in the bereaved cohort (Fig. S1; see Supporting Information).

Covariates

For members of the bereaved and comparison cohorts, we identified comorbidities, deprivation and lifestyle covariates. We defined comorbidity burden on the index date using the Charlson Comorbidity Index (CCI),[39] which we categorized into low (0 points), intermediate (1–2 points) and high (≥ 3 points). In the U.K. we used the quintiles of Index of Multiple Deprivation as a measure of socioeconomic deprivation, while in Denmark we used educational-level data as a proxy for socioeconomic status, categorized as short (7–10 years), medium (11–12 years) or long (≥ 13 years). In the U.K. we included lifestyle data on body mass index (according to World Health Organization guidelines), alcohol consumption (current, ex-drinker, nondrinker) and smoking (current, ex-smoker, nonsmoker) (Appendix S2; see Supporting Information).

We also determined whether bereavement was expected or unforeseen (risk of partners' deaths) using an age-adjusted CCI score for the partner who died based on comorbidity recorded up to 1 month before their death (Appendix S2). As an alternative measure, we identified records for terminal disease before the date of death (Appendix S2).

Statistical analysis

We used Cox regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs), stratified by matched sets for all models. We first fitted an 'unadjusted stratified model', implicitly adjusted for age and sex and general practice (U.K.) and also county of residence (Denmark). In sequential models, we adjusted for study participants' CCI in the 'adjusted model' and then additionally adjusted for deprivation status (U.K.), educational level (Denmark) and lifestyle variables (U.K.) in the 'fully adjusted model'. Due to incomplete lifestyle data (U.K.), we investigated patterns of missing data using conditional logistic regression. As lifestyle data are highly unlikely to be missing at random and we lacked data on probable predictors of missingness, we concluded that imputation techniques would not be appropriate to correct potential biases. We therefore used a simpler complete-case approach.[40]

As we hypothesized that the effect of bereavement would be highest in the short term following a partner's death,[26] we examined the association by time since the index date (0–30, 0–90, 0–365 and 0–1095 days). We first separately conducted the analyses for the U.K. and Denmark, and then pooled the results (from adjusted models) in a random-effects meta-analysis, using the DerSimonian and Laird method to pool variances.[41] We assessed the assumption of proportional hazards for the overall study period, and for each specific time period, by visual inspection of log–log plots. Because of evidence of nonproportionality (Fig. S2; see Supporting Information), we further evaluated whether the HRs changed over time by stratifying follow-up since bereavement into several periods (0–30, 31–90, 91–365, 366–1095 and > 1095 days) and performed likelihood ratio tests to analyse effect modification.

In each setting, we estimated HRs in subgroups defined by age, sex and risk of partners' deaths (by terminal disease and age-adjusted CCI of the partner who died) and performed likelihood ratio tests to explore possible effect modification by

these characteristics. We performed several sensitivity analyses to explore the robustness of our results (Table S1; see Supporting Information). We specified all analyses a priori unless otherwise stated. Study reporting is consistent with the RECORD statement (Table S2; see Supporting Information).[42] We performed analyses using Stata/MP 15·1 (StataCorp, College Station, TX, U.K.) and SAS 9·4 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Patient characteristics

Figure 1 presents a flowchart for inclusion in the study. The median age was 74 years in the U.K. and 71 years in Denmark, and approximately 66% of individuals were women in both settings (Tables 1 and 2). More individuals under 50 years were included in Denmark in both the psoriasis and atopic eczema analyses. In both analyses, bereaved individuals were more likely than nonbereaved individuals to have a higher CCI score and more deprivation (U.K.) (Table 1) and a lower educational level (Denmark) (Table 2).

Psoriasis

The pooled HR (adjusted for study participants' CCI) for the association between partner bereavement and psoriasis was 1·01 (95% CI 0·98–1·04) (Fig. 2). Similar HRs in fully adjusted models were observed (Table 3). We observed no evidence of higher HRs (with 95% CIs) for psoriasis within 0–30 days (0·96, 0·68–1·35), 0–90 days (1·07, 0·88–1·29), 0–365 days (1·02, 0·91–1·14) or 0–1095 days (1·02, 0·97–1·07) after bereavement (Fig. 2).

Atopic eczema

The pooled HR (adjusted for study participants' CCI) for the association between partner bereavement and atopic eczema was 0·97 (95% CI 0·84–1·12) (Fig. 2). Estimates from fully adjusted models were similar (Table 3). We did not find any evidence of a higher HR for atopic eczema within 0–30 days (1·09, 95% CI 0·86–1·38). However, we found evidence for higher HRs for atopic eczema following partner bereavement within 0–90 days and 0–365 days (HR 1·18, 95% CI 1·04–1·35 and HR 1·14, 95% CI 1·06–1·22, respectively), and some evidence within 0–1095 days (HR 1·07, 95% CI 1·02–1·12) (Fig. 2).

Subgroup analyses

Figure 3 and Tables S3–6 (see Supporting Information) show the results of subgroup analyses by age, sex and risk of partners' deaths for the entire follow-up and for 90 days. We found evidence to suggest that HRs for psoriasis differed by

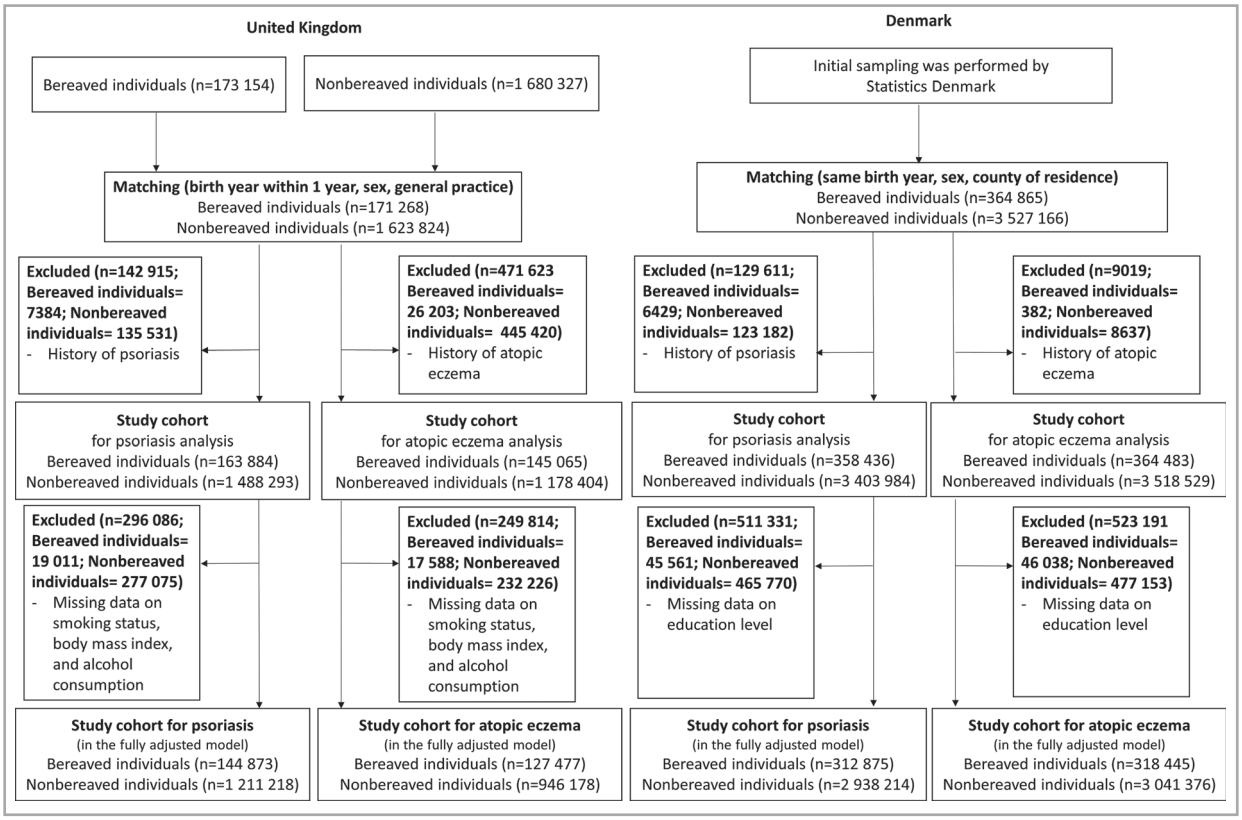

Fig 1. Flowchart for inclusion in the U.K. and Denmark cohorts.

Table 1 Characteristics of the bereaved cohort and the matched comparison cohort, U.K. 1997–2017

	Psoriasis		Atopic eczema	
	Bereaved cohort	Comparison cohort[a]	Bereaved cohort	Comparison cohort[b]
Total	163 884 (9·9)	1 488 293 (90·1)	145 065 (11·0)	1 178 404 (89·0)
Age at index date (years)				
Range	31·9–101·4	31·4–100·4	31·9–101·4	31·4–100·4
Median (IQR)	74·6 (66·8–80·8)	73·8 (66·3–79·9)	74·3 (66·6–80·6)	73·4 (65·8–79·5)
< 50	2994 (1·8)	28 437 (1·9)	2731 (1·9)	23 831 (2·0)
50–59	15 301 (9·3)	148 055 (10·0)	14 011 (9·7)	124 042 (10·5)
60–69	37 667 (23·0)	361 687 (24·3)	34 109 (23·5)	296 968 (25·2)
70–79	61 614 (37·6)	585 139 (39·3)	54 631 (37·7)	462 374 (39·2)
≥ 80	46 308 (28·3)	364 975 (24·5)	39 583 (27·3)	271 189 (23·0)
Sex				
Female	107 475 (65·6)	977 819 (65·7)	94 891 (65·4)	770 534 (65·4)
Male	56 409 (34·4)	510 474 (34·3)	50 174 (34·6)	407 870 (34·6)
Comorbidity burden[c]				
Low	71 961 (43·9)	684 789 (46·0)	65 411 (45·1)	561 217 (47·6)
Intermediate	60 087 (36·7)	534 239 (35·9)	52 652 (36·3)	417 890 (35·5)
High	31 836 (19·4)	269 265 (18·1)	27 002 (18·6)	199 297 (16·9)
Smoking status				
Nonsmoker	59 789 (36·5)	589 185 (39·6)	53 122 (36·6)	471 023 (40·0)
Ex-smoker	66 186 (40·4)	614 171 (41·3)	57 296 (39·5)	471 448 (40·0)
Current smoker	35 216 (21·5)	264 591 (17·8)	32 096 (22·1)	218 062 (18·5)
Missing	2693 (1·6)	20 346 (1·4)	2551 (1·76)	17 871 (1·5)
Alcohol consumption				
Nondrinker	19 259 (11·8)	158 969 (10·7)	17 159 (11·8)	127 203 (10·8)
Ex-drinker	21 173 (12·9)	171 885 (11·6)	18 461 (12·7)	133 949 (11·4)
Current drinker	110 602 (67·5)	1 054 171 (70·8)	97 492 (67·2)	830 080 (70·4)
Missing	12 850 (7·8)	103 268 (6·9)	11 953 (8·2)	87 172 (7·4)
Body mass index (kg m^{-2})				
< 18·5	4097 (2·5)	26 489 (1·8)	3528 (2·4)	20 460 (1·7)
18·5–24·9	55 915 (34·1)	508 746 (34·2)	49 100 (33·9)	397 340 (33·7)
25–29·9	56 763 (34·6)	548 587 (36·9)	50 242 (34·6)	434 394 (36·9)
≥ 30	34 255 (20·9)	307 143 (20·6)	30 338 (20·9)	244 068 (20·7)
Missing	12 854 (7·8)	97 328 (6·5)	11 857 (8·2)	82 142 (7·0)
Index of Multiple Deprivation				
1 (least deprived)	38 286 (23·4)	372 476 (25·0)	33 358 (23·0)	286 681 (24·3)
2	34 097 (20·8)	322 582 (21·7)	30 008 (20·7)	252 586 (21·4)
3	35 357 (21·6)	321 404 (21·6)	31 641 (21·8)	258 947 (22·0)
4	31 904 (19·5)	273 268 (18·4)	28 621 (19·7)	223 338 (19·0)
5 (most deprived)	24 240 (14·8)	198 563 (13·3)	21 437 (14·8)	156 852 (13·3)
Follow-up (years)				
Total	869 475	7 559 995	764 045	6 032 538
Median (IQR)	4·3 (1·8–8·0)	4·1 (1·8–7·5)	4·3 (1·7–8·0)	4·2 (1·8–7·6)

The data are presented as n (%) unless stated otherwise. Information on educational level was not available in the U.K. IQR, interquartile range. [a]In the U.K. comparison cohort, 18·8% (15·3% of unique individuals) experienced bereavement after the end of their follow-up. [b]In the U.K. comparison cohort, 19·0% (15·6% of unique individuals) experienced bereavement after the end of their follow-up. [c]Comorbidity burden was measured by the Charlson Comorbidity Index score defined at the index date and categorized as low (0 point), intermediate (1–2 points) or high (≥ 3 points).

age (with a greater HR among the youngest) and partner death following terminal disease in the U.K. We observed a greater hazard of atopic eczema among those whose partners had terminal disease in the U.K. The HR for atopic eczema also differed by sex, with a greater hazard of atopic eczema among men during the entire follow-up, and among women during shorter follow-up of 90 days (U.K. only). No substantial differences were observed for either psoriasis or atopic eczema by characteristics (age, sex or risk of partner's death) in Denmark. Meaningful comparisons were hampered by low power leading to wide CIs during 90-day follow-up in both settings.

Additional and sensitivity analyses

In the U.K., missingness of lifestyle data was dependent on each outcome, conditional on bereavement status and other covariates (Table S7; see Supporting Information). However, HRs for

Table 2 Characteristics of the bereaved cohort and the matched comparison cohort, Denmark 1997–2016

	Psoriasis		Atopic eczema	
	Bereaved cohort	Comparison cohort[a]	Bereaved cohort	Comparison cohort[b]
Total	358 436 (9·5)	3 403 984 (90·5)	364 483 (9·4)	3 518 529 (90·6)
Age at index date (years)				
Range	16·5–100·3	16·1–100·7	16·5–100·3	16·1–100·7
Median (IQR)	71·4 (62·6–78·9)	70·9 (62·2–78·2)	71·4 (62·6–78·9)	71·0 (62·3–78·2)
< 50[c]	24 495 (6·8)	241 834 (7·1)	24 692 (6·8)	245 478 (7·0)
50–59	46 176 (12·9)	454 364 (13·3)	46 874 (12·9)	467 861 (13·3)
60–69	91 802 (25·6)	900 974 (26·5)	93 531 (25·7)	934 857 (26·6)
70–79	119 295 (33·3)	1 156 594 (34·0)	121 520 (33·3)	1 198 904 (34·1)
≥ 80	76 668 (21·4)	650 218 (19·1)	77 866 (21·4)	671 429 (19·1)
Sex				
Female	239 227 (66·7)	2 269 590 (66·7)	243 250 (66·7)	2 345 321 (66·7)
Male	119 209 (33·3)	1 134 394 (33·3)	121 233 (33·3)	1 173 208 (33·3)
Comorbidity burden[d]				
Low	254 543 (71·0)	2 485 139 (73·0)	258 225 (70·8)	2 561 298 (72·8)
Intermediate	86 334 (24·1)	768 017 (22·6)	88 208 (24·2)	798 899 (22·7)
High	17 559 (4·9)	150 828 (4·4)	18 050 (5·0)	158 332 (4·5)
Educational level				
Short	162 465 (45·3)	1 396 665 (41·0)	165 112 (45·3)	1 442 105 (41·0)
Medium	108 041 (30·1)	1 092 620 (32·1)	110 134 (30·2)	1 133 158 (32·2)
Long	42 943 (12·0)	548 745 (16·1)	43 779 (12·0)	569 309 (16·2)
Missing	44 987 (12·6)	365 954 (10·8)	45 458 (12·5)	373 957 (10·6)
Follow-up (years)				
Total	2 737 250	23 357 938	2 791 720	24 138 608
Median (IQR)	6·7 (3·0–11·6)	5·7 (2·5–10·4)	6·8 (3·1–11·7)	5·7 (2·5–10·4)

The data are presented as n (%) unless stated otherwise. Information on smoking status, alcohol consumption, body mass index and Index of Multiple Deprivation was not available in Denmark. [a]In the Danish comparison cohort, 22·7% (17·0% of unique individuals) experienced bereavement after the end of their follow-up. [b]In the Danish comparison cohort, 21·4% (16·0% of unique individuals) experienced bereavement after the end of their follow-up. [c]For psoriasis, 7660 patients (2·1%) and 75 471 patients (2·2%) aged < 40 years were in the bereaved and comparison cohorts, respectively. For atopic eczema, 7679 patients (2·1%) and 75 864 patients (2·2%) aged < 40 years were in the bereaved and comparison cohorts, respectively. [d]Comorbidity burden was measured by the Charlson Comorbidity Index score defined at the index date and categorized as low (0 point), intermediate (1–2 points) or high (≥ 3 points).

the whole cohort and complete-case cohort were similar in unadjusted and adjusted models in both settings (Table S8; see Supporting Information). We investigated changes in HRs during several stratified follow-up periods (Table S9; see Supporting Information) and observed differences in HRs for atopic eczema in the U.K., with the highest HR during 31–90 days of follow-up (HR 1·23, 95% CI 1·05–1·44).

In a sensitivity analysis in which the matched cohort was redefined (without replacement) in the U.K., the adjusted HR for atopic eczema was of lower magnitude during 0–90 days than in the main analysis (HR 1·06, 95% CI 0·86–1·29) (Table S10; see Supporting Information). All other sensitivity analyses yielded findings similar to those of the main analysis (Tables S11–18; see Supporting Information).

Discussion

In this large matched-cohort study, we found increased risk of atopic eczema up to 3 years following partner bereavement. It peaked during the first 3 months, supporting the role of acute stress in triggering onset or relapse of atopic eczema episodes in the short term. However, we observed no evidence for overall long-term increased risk of psoriasis or atopic eczema following partner bereavement.

The death of a partner is extremely stressful, yet coping mechanisms and life circumstances might vary between individuals. While we could not measure the level and duration of stress arising from bereavement, we examined associations in certain subgroups as proxies. It is possible that young partners find partner bereavement more stressful or more unexpected than older individuals; we observed an increased risk of psoriasis among bereaved persons aged < 50 years in the U.K. Specific types of stress, such as the partner's disease process leading up to death, may also be of importance.

While there was no evidence that low risk of partner death (as a proxy for unexpected death) was associated with more pronounced risk in our study, those whose partners had a terminal disease had increased risk of both psoriasis and atopic eczema in the U.K. This may reflect the effect of chronic stress experienced while providing long-term care for a terminally ill partner. Notably, this could not be confirmed in our study as we did not have information on whether they took care of

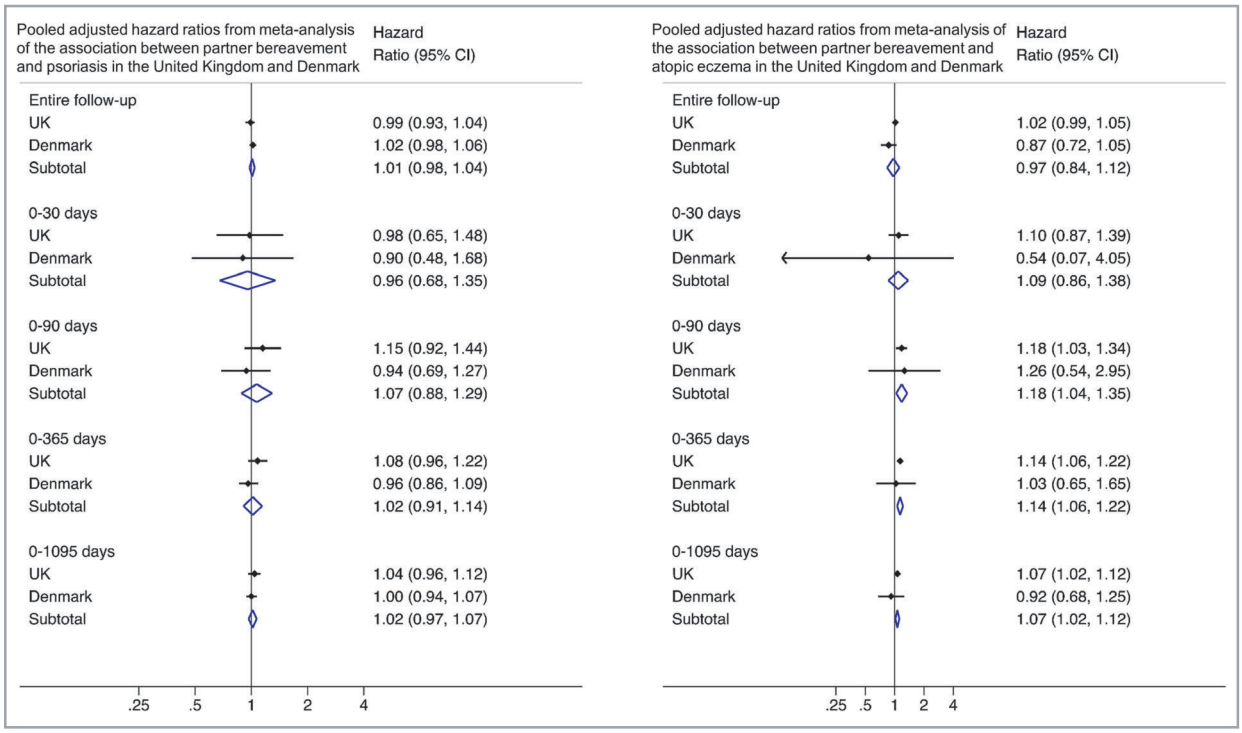

Fig 2. Pooled adjusted hazard ratios with confidence intervals (CIs) from the meta-analysis in the U.K. and Denmark. Hazard ratios were adjusted by Charlson Comorbidity Index score.

their partners, and if they did, what their stress level was while taking care of their partners who had terminal illness. Future research specifically investigating chronic stress is required to test this hypothesis. The U.K. study also revealed an overall increased risk of atopic eczema following partner bereavement in men but not in women; this requires further investigation.

While it is generally perceived that atopic eczema more commonly develops in children, a recent study reported that approximately 40% of individuals with atopic eczema had onset of symptoms in adulthood.[43] We may not have captured all historical records of psoriasis or atopic eczema. However, we obtained similar findings when a longer prebereavement follow-up period (3 years) was required. Our findings were also consistent in a post hoc sensitivity analysis that retained individuals with prevalent psoriasis or atopic eczema in order to examine the effects of bereavement on disease worsening. A short-term increased risk of atopic eczema could reflect poorer management of existing disease in the postbereavement phase. As this post hoc analysis was exploratory, it is important for future studies to investigate the role of stress in flare-ups.

Similarly to our study, a nested case–control study using CPRD data found no evidence of an increased risk of psoriasis associated with stress disorder diagnosed within the previous year (adjusted odds ratio 1·23, 95% CI 0·83–1·82),[44] but the type of stress disorder was not specified. A systematic review[21] that pooled results from five case–control studies reported a threefold increase in risk of psoriasis onset associated with preceding stressful events.[44–48] Two additional case–control studies demonstrated an association between stressful life events and psoriasis.[49,50] However, several different types of stress were measured in these studies, including stress disorder and a combination of life events related to family, personal illness, school, work or hormonal changes. This might account for the large amount of heterogeneity found in the meta-analysis.

Unlike previous studies, we used partner bereavement as a proxy for stress, to minimize heterogeneity in exposure to different types of stress. A Swedish cohort study that used matching and sibling analyses found an increased risk of various autoimmune disorders, including psoriasis, associated with stress-related disorder.[51] Stress-related disorders and partner bereavement reflect different types of stress, in which the former is more long term and the latter is relatively short term. The Swedish study might lend support to the role of chronic stress in immune-mediated skin disorders. Future studies are warranted to elucidate the association between chronic stress and onset or worsening of skin disorders.

Regarding atopic eczema, our findings are consistent with a cohort study that examined the association between perceived stress and self-reported atopic eczema.[52] A seven-point stress score based on assessment of both intensity and frequency of stress was used to measure stress level. A dose–response effect of stress on atopic eczema was found, but the investigators did not indicate how the level of stress was categorized as

Table 3 Results of the main analysis for the associations between partner bereavement and skin disorders in different time intervals, for U.K. (1997–2017) and Denmark (1997–2016)

	Bereaved cohort			Matched comparators					
Time since index date	Number of events	Person-years at risk	Rate per 1000	Number of events	Person-years at risk	Rate per 1000	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
U.K.									
Psoriasis									
Entire follow-up	1524	869 475	1·75	13 789	7 559 996	1·82	0·99 (0·93–1·04)	0·99 (0·93–1·04)	0·97 (0·92–1·03)
0–30 days	26	13 357	1·95	240	121 532	1·97	0·98 (0·65–1·47)	0·98 (0·65–1·48)	0·94 (0·61–1·47)
0–90 days	88	39 431	2·23	705	359 967	1·96	1·15 (0·92–1·44)	1·15 (0·92–1·44)	1·14 (0·91–1·45)
0–365 days	299	150 129	1·99	2562	1 376 306	1·86	1·08 (0·96–1·22)	1·08 (0·96–1·22)	1·05 (0·93–1·20)
0–1095 days	741	387 992	1·91	6547	3 535 938	1·85	1·04 (0·97–1·13)	1·04 (0·96–1·12)	1·04 (0·96–1·13)
Atopic eczema									
Entire follow-up	5034	764 045	6·59	38 130	6 032 538	6·32	1·02 (0·99–1·05)	1·02 (0·99–1·05)	1·01 (0·98–1·04)
0–30 days	79	11 821	6·68	566	96 225	5·88	1·10 (0·87–1·40)	1·10 (0·87–1·39)	1·04 (0·80–1·34)
0–90 days	257	34 886	7·37	1734	285 081	6·08	1·19 (1·04–1·35)	1·18 (1·03–1·34)	1·16 (1·00–1·33)
0–365 days	959	132 689	7·23	6788	1 090 887	6·22	1·14 (1·07–1·22)	1·14 (1·06–1·22)	1·13 (1·05–1·21)
0–1095 days	2378	342 296	6·95	17 805	2 808 190	6·34	1·07 (1·03–1·12)	1·07 (1·02–1·12)	1·06 (1·01–1·11)
Denmark									
Psoriasis									
Entire follow-up	3339	2 737 250	1·22	28 724	23 357 938	1·23	1·02 (0·98–1·06)	1·02 (0·98–1·06)	1·02 (0·98–1·06)
0–30 days	11	29 300	0·38	115	278 260	0·41	0·90 (0·49–1·68)	0·90 (0·48–1·68)	0·82 (0·41–1·62)
0–90 days	47	87 183	0·54	475	827 167	0·57	0·96 (0·71–1·30)	0·94 (0·69–1·27)	0·92 (0·67–1·27)
0–365 days	301	341 647	0·88	2945	3 220 429	0·91	0·97 (0·86–1·09)	0·96 (0·86–1·09)	0·95 (0·84–1·08)
0–1095 days	1011	936 657	1·08	9416	8 655 697	1·09	1·00 (0·94–1·07)	1·00 (0·94–1·07)	1·01 (0·94–1·08)
Atopic eczema									
Entire follow-up	132	2 791 720	0·05	1325	24 138 689	0·05	0·88 (0·73–1·06)	0·87 (0·72–1·05)	0·89 (0·73–1·07)
0–30 days	[d]	29 795	[d]	[d]	287 620	[d]	0·50 (0·07–3·73)	0·54 (0·07–4·05)	0·58 (0·08–4·41)
0–90 days	6	88 650	0·07	48	854 945	0·06	1·24 (0·53–2·89)	1·26 (0·54–2·95)	1·51 (0·63–3·63)
0–365 days	20	347 403	0·06	186	3 328 093	0·06	1·06 (0·67–1·68)	1·03 (0·65–1·65)	1·05 (0·65–1·71)
0–1095 days	46	952 824	0·05	478	8 944 428	0·05	0·93 (0·69–1·26)	0·92 (0·68–1·25)	0·94 (0·68–1·28)

HR, hazard ratio; CI, confidence interval. [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 U.K.). [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 comparators cohorts presented in this table were calculated in the full cohort for the unadjusted and adjusted models only. The data were adjusted additionally for smoking status, body mass index, alcohol consumption and socioeconomic status in the U.K. For psoriasis, the total numbers of bereaved and comparison individuals were 144 873 and 1 211 218, respectively, after excluding patients with missing values of body mass index, alcohol consumption and smoking status. For atopic eczema, the total numbers of bereaved and comparison individuals were 127 477 and 946 178, respectively, after excluding patients with missing values of body mass index, alcohol consumption and smoking status. The data were adjusted additionally for education level in Denmark. For psoriasis, the total numbers of bereaved and comparison individuals were 312 875 and 2 938 214, respectively, after excluding patients with missing education level. For atopic eczema, the total numbers of bereaved and comparison individuals were 318 445 and 3 041 376, respectively, after excluding patients with missing education level. [d]Where there were fewer than five patients the exact number has been withheld in accordance with the confidentiality rules of the Clinical Practice Research Datalink and Danish registries.

low, medium or high based on the stress scores. Also, as data were lacking on atopic eczema at baseline, individuals with a history of atopic eczema were not excluded.

Our study is the first population-based study to investigate the association between partner bereavement and psoriasis and atopic eczema. Strengths include a large sample size and use of population-based data in settings with universal healthcare. Recording of deaths in the healthcare databases is of high quality; hence, partner bereavement was a reliable exposure with quite specific onset compared with other stressful life events. In addition, both psoriasis and atopic eczema are validated outcomes for epidemiological studies.[36–38] Importantly, we used data from different settings in the U.K. and Denmark to confirm our findings.

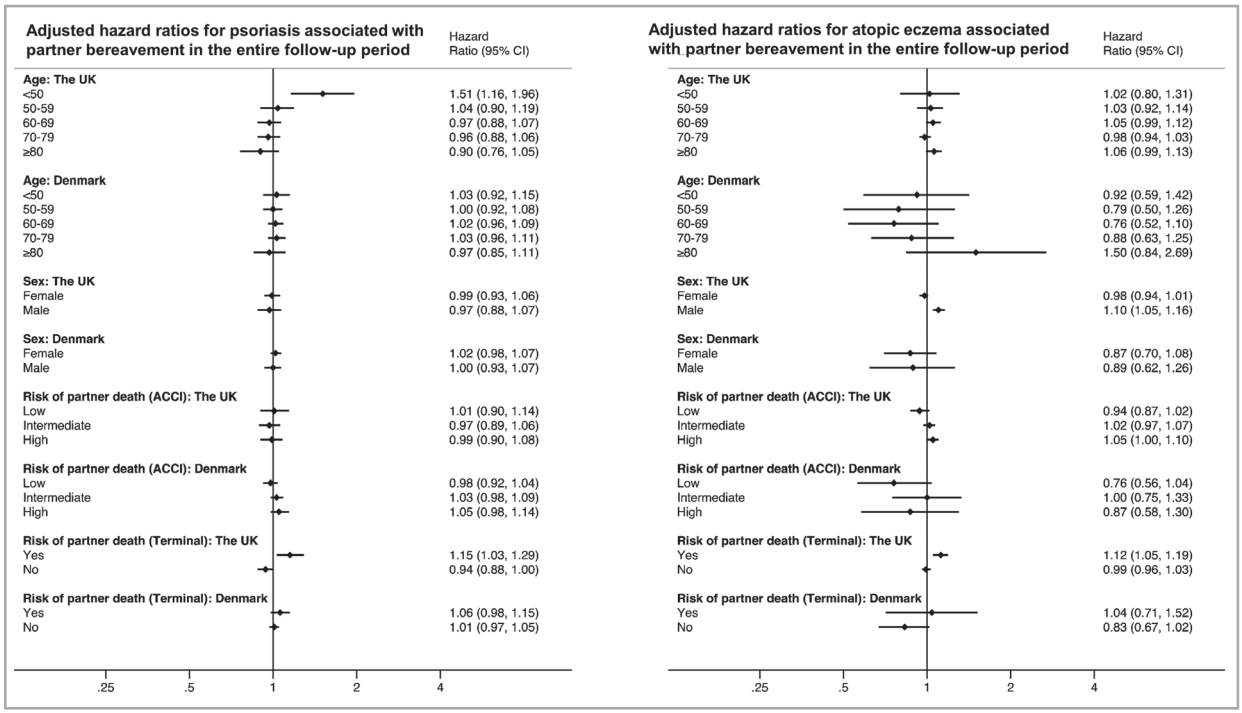

Fig 3. Adjusted hazard ratios with confidence intervals (CIs) for the association between partner bereavement and psoriasis and atopic eczema by characteristics in the U.K. and Denmark. Hazard ratios were adjusted by Charlson Comorbidity Index score. The risk of partner death was determined using the age-adjusted Charlson Comorbidity Index score (ACCI), categorized as low (0–3 points), intermediate (4–6 points), high (≥ 7 points) or terminal disease.

Although we were able to adjust for potential confounders, including deprivation status and lifestyle variables, residual confounding remains possible. Another concern is that we matched our cohort with replacement in the main analysis in both settings, which might have led to overconfidence in our estimates. Partnership status may have been misclassified, particularly in the U.K. where direct data on relationship status was unavailable. To minimize such misclassification we used relatively strict criteria for partner identification (e.g. acceptable age differences between partners), which has been successful in other contexts.[26,27,29,30] Detailed data on partnership, including the change in partnership status, were available in Denmark, which complement U.K. findings.

In the Danish study, skin disease outcomes were recorded in a hospital setting, resulting in a potential delay between actual disease onset and diagnosis in our study. Furthermore, they are more likely to represent severe cases. In contrast, mild-to-moderate cases diagnosed in primary care were included in the U.K. study. Moreover, as the data were captured since birth in the Danish setting, medical history of psoriasis or atopic eczema in a hospital setting during childhood might be more completely recorded compared with the U.K. Finally, partner bereavement may affect disease perception, health-seeking behaviour or heightened diagnostic efforts, and thus ascertainment of outcomes. Such bias may have led to short-term change in outcome detection and over-representation of the most severe skin diseases.

In conclusion, in this study we observed a modest increase in risk of atopic eczema within 3 years of partner bereavement, which peaked during the first 3 months (18% increase in risk). Underlying mechanisms may include the impact of acute stress on the immune system or on management of existing atopic eczema conditions immediately following bereavement.

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Supporting Information

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

Appendix S1 Details on data sources.

Appendix S2 Algorithms for identifying incident study outcomes, history of study outcomes and covariates.

Appendix S3 Code lists for defining partners' risk of death, outcomes and other covariates in Denmark.

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

Fig S2. Assessment of the assumption of proportional hazards.

Table S1 Sensitivity analyses for association between partner bereavement and risk of psoriasis and atopic eczema.

Table S2 The RECORD statement.

Table S3 Subgroup analysis for psoriasis in the entire follow-up: U.K. 1997–2017 and Denmark 1997–2016.

Table S4 Subgroup analysis for atopic eczema in the entire follow-up: U.K. 1997–2017 and Denmark 1997–2016.

Table S5 Post hoc subgroup analysis for psoriasis for the follow-up period of 90 days.

Table S6 Post hoc subgroup analysis for atopic eczema for the follow-up period of 90 days.

Table S7 Patterns of missing data on smoking status, body mass index and alcohol consumptions.

Table S8 Unadjusted and adjusted hazard ratios among the full cohort and complete-case cohort.

Table S9 Results of stratifying follow-up time since bereavement.

Table S10 Post hoc sensitivity analysis redefining the cohort using matching without replacement in the U.K.

Table S11 Sensitivity analysis identifying death dates using Clinical Practice Research Datalink data only to ascertain death of partners in the U.K.

Table S12 Sensitivity analysis restricting to patients with more than 3 years of registration history prior to the index date.

Table S13 Sensitivity analysis restricting patients eligible for linkage to Hospital Episode Statistics and Office for National Statistics in the U.K.

Table S14 Post hoc intention-to-treat analysis that did not censor follow-up on the day of experiencing partner bereavement, transfer out of practice of their partner after the index date (U.K.) or emigration of partner (Denmark).

Table S15 Post hoc sensitivity analysis retaining patients with prevalent psoriasis and atopic eczema.

Table S16 Post hoc sensitivity analysis censoring follow-up on the day of experiencing partner bereavement, end of partnership or emigration of partner in Denmark.

Table S17 Post hoc sensitivity analysis for psoriasis excluding those with any vitamin D derivate prescription prior to the index date in Denmark.

Table S18 Post hoc sensitivity analysis for atopic eczema changing the outcome definition to require at least two distinct inpatient or outpatient hospital contacts for the diagnosis to be fulfilled in Denmark.

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