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

Dear Editor,

The pathogeneses of skin diseases are not fully understood. Psychological stress has been proposed to be associated with skin diseases, but the epidemiological evidence is limited [1, 2]. We have recently reported the associations between partner bereavement (an extreme life stressor) and psoriasis, atopic eczema and melanoma [3, 4]. In this study, we further investigated whether partner bereavement was associated with urticaria, alopecia areata, or vitiligo.

We conducted two cohort studies using data from the UK (1997-2017) and Denmark (1997-2016). In the UK, we used the Clinical Practice Research Datalink Gold to identify partners using a previously developed algorithm [3, 4]. In Denmark, we used the data from the Civil Registration System to identify partners with an algorithm developed by Statistics Denmark [3, 4]. Among eligible couples, we defined bereaved people (exposed) if their partner died and matched each with up to 10 non-bereaved partners on age, sex, and, county of residence within Denmark, or general practice in the UK on the bereavement date. We followed participants from bereavement until the first of: diagnosis of specific outcomes (urticaria, alopecia areata, or vitiligo), 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. We used stratified Cox regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for each outcome, adjusting for participants' Charlson Comorbidity Index (CCI) [5]. In the fully-adjusted model, we additionally adjusted for education duration (Denmark), Index of Multiple Deprivation quintile (UK), body mass index (UK) and lifestyle variables (UK). As we hypothesized that the effect of bereavement would be most pronounced in the short-term, we further examined the associations by time since bereavement (0–30 days, 0–90 days, 0–365 days, and 0–1095 days for alopecia areata and vitiligo; 0–182 days, 0–365 days, and 0–1095 days for chronic urticaria, as its definition required two codes recorded six weeks apart). 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 conducted analyses separately for the UK and Denmark, and combined the main results (from the adjusted models) in Stata using DerSimonian and Lairds' random-effects model.

The overall median follow-up was 4 years in the UK and 6 years in Denmark. The overall pooled HRs (adjusted for participants' CCI scores) for associations between partner bereavement and chronic urticaria, alopecia areata, and vitiligo were 0.95 (95% CI, 0.85–1.07), 0.90 (95% CI, 0.73–1.12) and 0.90 (95% CI, 0.74–1.10), respectively (Supporting information). We found similar results for chronic urticaria in analyses by time since bereavement (Table 1). Event rates for alopecia areata and vitiligo were low, specifically in early time periods. Similar results were seen in fully adjusted models (Table 1). For subgroup

analyses, some evidence suggested that the HR for vitiligo differed by sex (lower HR among men) in the UK. No substantial differences were observed across other subgroups for other outcomes.

This study investigated associations between partner bereavement and chronic urticaria, alopecia areata, and vitiligo in population-based cohorts in settings with universal healthcare (UK and Denmark), using harmonised methodology. Previous studies have been limited by small sample size, difficulty in measuring stress, and potential misclassification of adverse life events due to recall bias [6-8]. We undertook our study in two similar cohorts enabling replication, and used partner bereavement as a proxy for acute severe stress with specific onset date. Limitations include a lack of information on the level and duration of stress arising from bereavement, individual responses to bereavement, social support, potential misclassification of partnership status, possible delay between disease onset and diagnosis, overrepresentation of severe cases in the Danish hospital setting, and absence (Denmark) and missingness (UK) of body mass index and lifestyle covariates. People with mild skin conditions may be less likely to seek medical advice immediately after bereavement, which may have led to underestimation during short-term follow-up and an overrepresentation of the most severe skin diseases. In conclusion, this large study showed no evidence of associations between partner bereavement and chronic urticaria, alopecia areata, or vitiligo. Despite a large study population, precision was limited by low event rates for alopecia areata and vitiligo, especially in early time periods.

Details of the methods, additional and sensitivity analyses, and discussion of results can be found via: https://doi.org/10.17037/PUBS.04656104

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Table 1. Association between partner bereavement and skin disorders, UK (1997–2017) and Denmark (1997–2016).

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

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

[a]Adjusted for Charlson Comorbidity Index scores.

[b]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.

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