

Research letter

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

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DEAR EDITOR, The pathogenesis 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). To identify partners, in the UK we used the Clinical Practice Research Data-link, with a previously developed algorithm;^{3,4} in Denmark we used data from the Civil Registration System, 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 nonbereaved 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; and 0–182 days, 0–365 days and 0–1095 days for chronic urticaria as its definition required two codes recorded 6 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/MP 15.1 (StataCorp, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA), using the DerSimonian and Laird random-effects model.

Overall median follow-up was 4 years in the UK and 6 years in Denmark. 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. 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 (data available on request). 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 harmonized 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 to enable 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>.

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		Bereaved cohort		Matched comparators		Adjusted HR (95% CI) ^a	
	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years		
Chronic urticaria										
Entire follow-up	269	875 386	2483	7 615 764	0.96 (0.84–1.09)	67	2 778 742	646	23 908 253	0.93 (0.72–1.20)
0–182 days	^b	78 004	^b	713 353	0.31 (0.08–1.28)	^b	176 120	^b	1 684 577	NA
0–365 days	20	150 221	214	1 376 313	0.88 (0.56–1.40)	^b	345 359	^b	3 288 129	0.60 (0.14–2.50)
0–1095 days	85	388 765	846	3 542 326	0.93 (0.74–1.16)	10	947 459	148	8 840 820	0.64 (0.34–1.22)
Alopecia areata										
Entire follow-up	49	901 811	525	8 087 071	0.81 (0.60–1.10)	48	2 793 638	417	24 175 497	1.00 (0.74–1.36)
0–30 days	^b	13 817	^b	129 863	NA	^b	29 816	^b	288 053	NA
0–90 days	^b	40 793	35	384 648	0.24 (0.03–1.74)	^b	88 713	^b	856 229	NA
0–365 days	8	155 369	105	1 470 901	0.69 (0.34–1.42)	^b	347 651	^b	3 333 059	NA
0–1095 days	26	401 742	247	3 779 874	0.91 (0.60–1.37)	16	953 497	129	8 957 716	1.20 (0.71–2.02)
Vitiligo										
Entire follow-up	87	910 002	972	8 215 110	0.84 (0.67–1.05)	36	2 793 919	314	24 178 445	1.05 (0.74–1.49)
0–30 days	^b	13 925	^b	131 873	0.63 (0.08–4.83)	^b	29 817	^b	288 077	NA
0–90 days	5	41 110	39	390 610	1.32 (0.52–3.37)	^b	88 717	^b	856 303	NA
0–365 days	23	156 584	177	1 493 648	1.30 (0.84–2.02)	^b	347 669	^b	3 333 348	0.16 (0.02–1.15)
0–1095 days	54	404 936	449	3 838 367	1.18 (0.89–1.57)	8	953 555	128	8 958 460	0.59 (0.29–1.21)

HR, hazard ratio; CI, confidence interval; NA, not applicable. ^aAdjusted for Charlson Comorbidity Index scores. ^bIn accordance with the confidentiality rules of the Clinical Practice Research Datalink/Danish registries, we have not presented results where numbers of events are less than five.

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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 Funding sources and conflicts of interest statements.

Funding sources and conflicts of interest can be found in Appendix S1 (see Supporting Information).

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