of pigmentation-related genes[3] with a median on target fold coverage of > 1000 ×. A missense substitution at codon 203 in *MAP2K1* (c.607G>A, p.E203K) was identified within both melanomas (medial left thigh and left lateral foot) and also within the background NS-type CMN. Allele loads were 7% in the SSMM, 2% in the LMM and 1% in the NS-type CMN. A second variant in *MAP2K1* (c.308T>A, p.I103N) was also seen in the SSMM (7% allele load), but undetectable in the other melanoma and NS-type CMN. Targeted sequencing specifically excluded *HRAS*, *NRAS* and *BRAF* mutations in the NS-type CMN and melanomas.

NS-type CMN have previously been associated with specific mosaic variants in *NRAS*.[1,2,4] Our patient differs phenotypically from prior cases and has many small, dark naevi on the skin of the affected limb with no apparent café-au-lait pigmentation. These naevi were not present at birth, and continue to develop. NS-type CMN are a clinically heterogeneous entity, and our finding of a postzygotic mutation in *MAP2K1* adds to known existing drivers such as *NRAS*.[4] The *MAP2K1* E203K variant lies within the protein kinase domain of the MAP2K1 protein. This results in a gain of function at the protein level; E203K-mutated melanoma cell lines demonstrate constitutive phosphorylation of extracellular signal-regulated kinase, a downstream kinase in the Ras signalling pathway.[5] Importantly, similar mutations in the germline give rise to cardiofaciocutaneous syndrome, which has been associated with increased numbers of melanocytic naevi, adding support for the pathogenicity of this variant.[6] Furthermore, *MAP2K1* mutations have been found in up to 6% of cases in a series of melanoma.[5] Mosaic *MAP2K1* variants have recently been described as a cause of arteriovenous malformations,[3] but not previously in melanocytic lesions. Taken together, our findings suggest that our patient's NS-type CMN is driven by a postzygotic mutation in *MAP2K1*, predisposing to development of melanoma within the lesion. It is of interest that a second pathogenic variant in *MAP2K1* (p.I103N) was detected in one melanoma at an identical allele load. It hints at the possibility that biallelic mutations in *MAP2K1* are important to initiate melanoma formation in this birthmark. It would be of interest to determine if loss of heterozygosity of *MAP2K1* has occurred specifically in melanoma cells in this patient's remaining melanomas; however, technical issues relating to working with paraffin-embedded tissue prevent this from being demonstrated unequivocally. Our findings highlight the clinical and genetic heterogeneity in NS-type CMN. These data add evidence to the central role of Ras signalling in CMN and melanoma development, and the need for long-term follow-up of such patients.

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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 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

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

	UK					Denmark				
	Bereaved cohort		Matched comparators			Bereaved cohort		Matched comparators		
Time since index date	Events	Person-years	Events	Person-years	Adjusted HR (95% CI)[a]	Events	Person-years	Events	Person-years	Adjusted HR (95% CI)[a]
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. [a]Adjusted for Charlson Comorbidity Index scores. [b]In 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.

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 Datalink, 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.

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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).

S.A.J.S. and S.M.L. were senior authors.

High and discordant prevalences of clinical and sonographic enthesitis in patients with hidradenitis suppurativa

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Dear Editor, The prevalence of spondyloarthritis (SpA) reported among patients with hidradenitis suppurativa (HS) ranges from 2·3% to 28·2%, depending on the diagnostic method used.[1] A key feature of SpA and one of the European Spondyloarthropathy Study Group diagnostic criteria for this group of diseases is enthesitis: inflammation at the insertion of tendons, ligaments and capsules. However, pain at an entheseal site is nonspecific and does not always indicate inflammation. Objective assessment of the presence of enthesitis can be done using ultrasound.[2] Therefore, the aim of this cross-sectional study was to investigate the prevalence of clinical enthesitis among patients with HS and to correlate it with sonographic enthesitis.

Patients were selected randomly prior to their routine visit at the specialized HS outpatient clinic of a tertiary centre in the Netherlands between October 2018 and February 2019. The study was approved by the medical ethical committee of the Erasmus University Medical Center (MEC-2018-158). Patient characteristics were collected through the HiScreen Registry (MEC-2016-426) and patient charts.

Clinical enthesitis, defined as pain elicited by local pressure at the enthesis, was assessed bilaterally at eight entheseal points (total 16 sites) according to the Spondyloarthritis Research Consortium of Canada (SPARCC) criteria.[3] Ultrasound examination was performed according to the Madrid Sonographic Enthesitis Index at six bilateral entheses and