of pigmentation-related genes with a median on target fold coverage of $>1000 \times$. 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.l103N) 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. 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. 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. 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. Furthermore, MAP2K1 mutations have been found in up to 6% of cases in a series of melanoma. Mosaic MAP2K1 variants have recently been described as a cause of arteriovenous malformations, 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.l103N) 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. We have recently reported the associations between partner bereavement (an extreme life stressor) and psoriasis, atopic eczema and melanoma. 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 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), emigration of 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 scores.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 (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

| Table 1 Association between partner bereavement and skin disorders, UK (1997–2017) and Denmark (1997–2016) |
|--------------------------------------------------|------------------|------------------|--------------------|--------------------|
| **UK**                                           | **Matched comparators** | **Denmark** | **Matched comparators** |
| **Time since index date**                        | **Bereaved cohort** | **Events** | **Person-years** | **Adjusted HR (95% CI)\textsuperscript{*}** | **Bereaved cohort** | **Events** | **Person-years** | **Adjusted HR (95% CI)\textsuperscript{*}** |
| 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                                      |                   | 7 704       | 7 135 3 31 0.31 0.08–1.28 |                   | 176             | 1 684 572     | NA                   |                |
| 0–365 days                                      | 20                | 150 221     | 214 1 376 313 0.88 0.56–1.40 |                   | 345             | 3 288 129     | 0.60 0.41–2.50      |                |
| 0–1095 days                                     | 85                | 388 765     | 846 3 542 326 0.93 0.74–1.16 |                   | 947             | 8 840 820     | 1.84 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                   |                   | 29              | 288 053       | NA                   |                |
| 0–90 days                                       | b 40 793         | 35 384 648 | 0.24 0.03–1.74    |                   | 88              | 856 229       | NA                   |                |
| 0–365 days                                      | 8                 | 155 369     | 105 1 470 901 0.69 0.34–1.42 |                   | 347             | 3 333 059     | NA                   |                |
| 0–1095 days                                     | 26                | 401 742     | 247 3 779 874 0.91 0.60–1.37 |                   | 953             | 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     | 34 24 178 445 1.05 0.74–1.49 |
| 0–30 days                                       | b 13 925         | b 131 873   | 0.63 0.08–4.83   |                   | 29              | 288 077       | NA                   |                |
| 0–90 days                                       | 5                 | 41 110      | 39 390 610 1.32 0.52–3.37 |                   | 88              | 856 303       | NA                   |                |
| 0–365 days                                      | 23                | 156 584     | 177 1 493 648 1.30 0.84–2.02 |                   | 347             | 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 |                   | 953             | 8 958 460     | 0.59 0.29–1.21      |                |

HR, hazard ratio; CI, confidence interval; NA, not applicable.\textsuperscript{*}Adjusted for Charlson Comorbidity Index scores.\textsuperscript{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.
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. 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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High and discordant prevalences of clinical and sonographic enthesitis in patients with hidradenitis suppurativa

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 HS 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 enthesal 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 enthesal 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...