Table II. Assessment of bidirectional associations between AA and migraine

Outcome	Events n	Events %	Incidence per 1000 PY	HR	95% CI	*P*	aHR*	95% CI	*P*	aHR†	(95% CI)	*P*
Risk for migraine												
Total						<.0001			<.0001			<.0001
Patients with AA	45	0.80	0.93	4.53	2.96-6.93		3.96	2.58-6.07		3.26	2.12-5.01	
Control individuals	40	0.18	0.21	1.00	Reference		1.00	Reference		1.00	Reference	
Male						.0074			.0265			.0766
Patients with AA	10	0.36	0.41	3.08	1.35-7.03		2.56	1.12-5.86		2.12	0.92-4.88	
Control individuals	13	0.12	0.13	1.00	Reference		1.00	Reference		1.00	Reference	
Female						<.0001			<.0001			<.0001
Patients with AA	35	1.25	1.45	5.23	3.17-8.64		4.59	2.78-7.60		3.83	2.31-6.37	
Control individuals	27	0.24	0.28	1.00	Reference		1.00	Reference		1.00	Reference	
Risk for AA												
Total						<.0001			<.0001			.0128
Patients with migraine	29	0.17	0.19	3.14	1.93-5.10		2.86	1.71-4.78		1.96	1.15-3.32	
Control individuals	37	0.06	0.06	1.00	Reference		1.00	Reference		1.00	Reference	
Male						.1651			.1915			.8031
Patients with migraine	6	0.13	0.14	2.00	0.75-5.33		1.99	0.71-5.59		1.15	0.39-3.36	
Control individuals	12	0.07	0.07	1.00	Reference		1.00	Reference		1.00	Reference	
Female						<.0001			.0001			.0067
Patients with migraine	23	0.19	0.21	3.68	2.09-6.49		3.24	1.79-5.88		2.33	1.26-4.30	
Control individuals	25	0.05	0.06	1.00	Reference		1.00	Reference		1.00	Reference	

AA, Alopecia areata; *aHR*, adjusted hazard ratio; *CI*, confidence interval; *HR*, hazard ratio; *PY*, person-years.
*Adjusted for age, sex, urbanization, income, and Charlson Comorbidity Index score.
†Adjusted for age, sex, urbanization, income, Charlson Comorbidity Index score, and annual outpatient visit.

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Melanomas and stress patterns on the foot: A systematic review and meta-analysis

To the Editor: Most melanomas are associated with UV radiation exposure.[1] However, melanomas can emerge on sun-shielded skin such as the plantar surfaces. The pathogenesis of these melanomas is largely unknown.[2] One hypothesis is that repetitive mechanical stress contributes to their formation. We performed a systematic review and meta-analysis to investigate the location of plantar and subungual melanoma lesions to examine a possible correlation with pressure areas of the foot.

We conducted a comprehensive search of MEDLINE, PubMed, and Embase up to April 2020

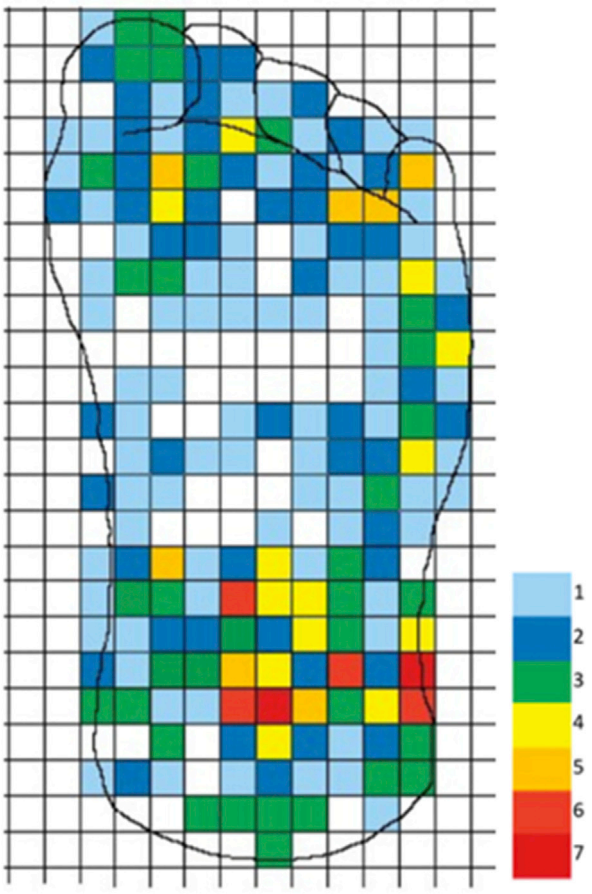

Fig 1. Density of lesion per pixel on the pooled plantar foot map.

using the terms "acral melanoma," "acral lentiginous melanoma," "hand melanoma," "foot melanoma," "plantar melanoma," "nail melanoma," "nail apparatus melanoma," and "nail complex melanoma." Two reviewers (KKC, YMF) extracted data including the location and number of melanoma lesions. Studies including images of melanoma sites were digitally adjusted to 24 cm and merged to create foot maps of the pooled locations. Study quality was assessed by using published critical appraisal tools. A random effects model was used to calculate the event rate (ER) (Supplemental Methods; available via Mendeley at https://doi.org/10.17632/y6kxmmz9x9.1).

The search yielded 5746 articles, with 18 studies (n = 1275) ultimately included in the meta-analysis (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/y6kxmmz9x9.1). Six studies included figures indicating melanoma site. The quality of all but 1 study was high (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/y6kxmmz9x9.1).

Two plantar foot maps were created: the first showing the locations of each melanoma

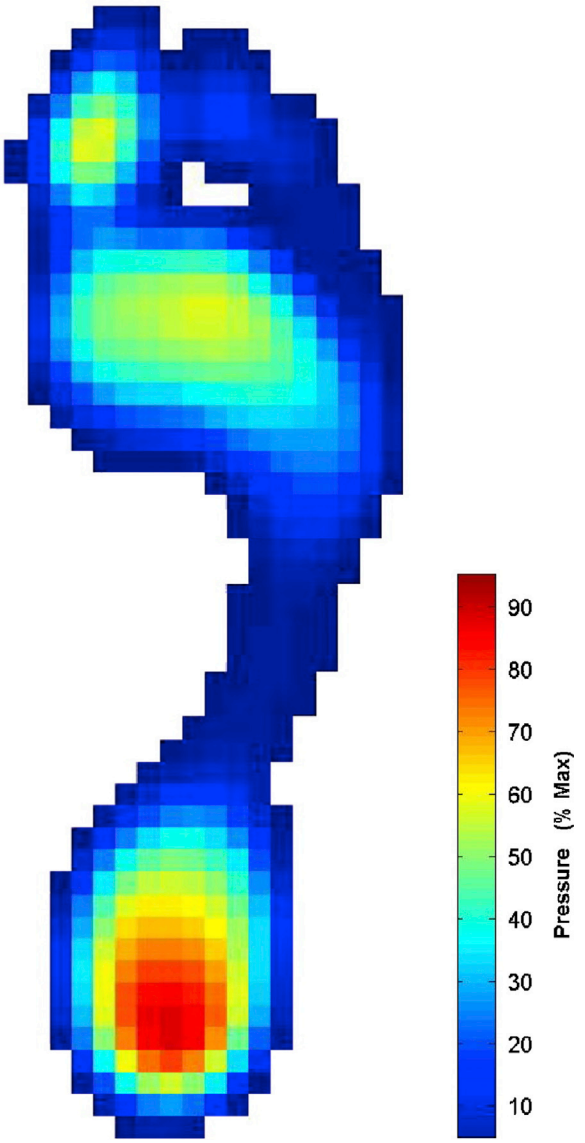

Fig 2. Mean foot pressure image analysis using a pixel-level approach. Reprinted from *Journal of Biomechanics*, 41/9. Pataky et al, New insights into the plantar pressure correlates of walking speed using pedobarographic statistical parametric mapping (pSPM), 1987-94, (2008), with permission from Elsevier.

(Supplemental Fig 2; available via Mendeley at https://doi.org/10.17632/y6kxmmz9x9.1) and the second showing the density of lesions per pixel (Fig 1). The locations of the lesions correlated with pressure areas of the foot (Fig 2).

Plantar melanomas were most often found in the hindfoot (ER, 49%), followed by the forefoot (ER, 27%) and midfoot (ER, 19%) (Supplemental Fig 3; available via Mendeley at https://doi.org/10.17632/y6kxmmz9x9.1). Subungual melanomas disproportionately affected the nail of the hallux (big toe) (ER, 75%; 95% confidence interval [CI], 65-83];

$I^2 = 69.16\%$; $P = .001$) compared to nail 2 (ER, 5%; 95% CI, 3-8; $I^2 = 65.22\%$; $P = .002$), nail 3 (ER, 5%; 95% CI, 3-8; $I^2 = 0.00\%$; $P = .83$), nail 4 (ER, 5%; 95% CI, 3-8; $I^2 = 0.00\%$; $P = .74$), and nail 5 (ER, 7%; 95% CI, 3-17; $I^2 = 73.02\%$; $P = .001$) (Supplemental Fig 4; available via Mendeley at https://doi.org/10.17632/y6kxmmz9x9.1). Regarding melanomas of individual toes, the distributions were as follows: hallux: ER, 40%; 95% CI, 25-57; $I^2 = 0.00\%$; $P = .53$); second toe: ER, 17%; 95% CI, 8-33; $I^2 = .00\%$; $P = .83$); third toe: ER, 24%; 95% CI, 13-38; $I^2 = 0.00\%$; $P = .91$); fourth toe: ER, 16%; 95% CI, 7-33; $I^2 = 0.00\%$; $P = .65$); and fifth toe: ER, 21%; 95% CI, 9-41; $I^2 = 9.39\%$; $P = .36$). Egger's regression analysis showed no evidence of publication bias.

Studies suggest that inflammation is a contributing factor to the development of several malignancies.[3] A 2020 meta-analysis exclusively in the Asian population found that areas of plantar pressure were associated with a higher number of melanomas.[4] Previous research suggests that the first toe, including the subungual surface, also has a greater tendency for trauma and repetitive sheer force.[5] Our systematic review and meta-analysis included study populations from all ethnic background and supports the hypothesis of repetitive mechanical stress as a risk factor for plantar melanoma carcinogenesis, with melanoma locations correlating with pressure areas of the feet. Future research exploring distributions of plantar melanoma and biomechanical stress patterns within the same patient population may provide further evidence for this hypothesis.

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Long-term treatment with apremilast in hidradenitis suppurativa: A 2-year follow-up of initial responders

To the Editor: In a previously published randomized controlled trial (RCT) among hidradenitis suppurativa (HS) patients with Hurley stage 1 and 2, we showed that the Hidradenitis Suppurativa Clinical Response (HiSCR) was met in 53.3% (8/15) of patients receiving apremilast 30 mg twice daily for 16 weeks compared with 0% (0/5) in the control group.[1] Responders continued treatment through a compassionate use program, and after 2 years of follow-up, we aimed to assess the longer-term clinical efficacy of apremilast in HiSCR responders from the initial RCT.

After study completion, 100% (8/8) of the responders, all female, chose to continue treatment. Apremilast became available through a compassionate use program 3 to 4 months after the end of the RCT, and patients were assessed approximately every 3 months during routine clinical visits. Three patients reported an increase in symptoms while waiting for the compassionate use program.

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