EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Personalized analysis of pain–weather associations: a pilot study

Gábor TUBOLY[1], Gyöngyi HORVÁTH[2], Kamilla NAGY[3], Edit NAGY[4]

[1]Department of Neurology, Albert Szent-Györgyi Health Centre, School University of Szeged
[2]Department of Physiology, Albert Szent-Györgyi Medical School, University of Szeged
[3]Department of Pediatrics and Pediatric Health Center, Albert Szent-Györgyi Health Centre, University of Szeged
[4]Department of Physiotherapy, Faculty of Health Sciences and Social Studies, University of Szeged

| English | https://doi.org/10.18071/isz.77.0077 | www.elitmed.hu

Correspondent:
Dr. Gyöngyi HORVÁTH, Department of Physiology, Albert Szent-Györgyi Medical School, University of Szeged; 6720 Szeged, Dóm tér 10.
Phone: +36-62-544971, e-mail: horvath.gyongyi@med.u-szeged.hu; https://www.orcid.org/0000-0002-6025-4577

Érkezett:
2023. augusztus 8.
Elfogadva:
2023. november 24.

Background and purpose – It is a well-known belief that weather can influence human health, including pain sensation. However, the current data are controversial, which might be due to the wide range of interindividual differences. The present study aimed to characterize the individual pain–weather associations during chronic pain by utilizing several data analytical methods.
Methods – The study included 3-3 patients with (P1, P3, and P4) or without (P2, P5, P6) diabetes mellitus and signs of trigeminal neuralgia or low back pain. Subjective pain scores (0–10) and 12 weather parameters (terrestrial, geomagnetic, and solar) were recorded for one month repeated three times daily. Nonparametric Spearman's correlation (Sp), multiple regression (Mx), and principal component (PCA) analyses were performed to evaluate associations between pain and meteorological factors obtained at the day of recorded pain value, 2 days before and 2 days after the recorded pain, and the changes in these parameters (5 × 12 parameters). Complex scores were calculated based on the results of these analyses.
Results – While the temperature had the highest effects on the pain levels in most of the participants, huge interindividual differences in the degree and the direction of the associations between pain and weather parameters could be obtained. The analytic methods also revealed subject-specific results, and the synthesis of different statistical methods as total scores provided

Egyénre szabott fájdalom-időjárás kapcsolatelemzés: pilóta tanulmány
Tuboly G, MD, PhD; Horváth Gy, MD, DSc; Nagy K, MD; Nagy E, PT, PhD

Háttér és cél – A betegek beszámolója alapján jól ismert a fájdalom és az időjárás lehetséges összefüggése. Az eredmények azonban ellentmondóak, ami feltehetően az egyének közötti nagy érzékenységbeli különbségeknek köszönhető. Jelen tanulmány célja, hogy egyénre szabott módon jellemezze a fájdalom és az időjárás lehetséges kapcsolatait többféle statisztikai elemzés alkalmazásának kombinálásával.
Módszerek – A tanulmányban hat krónikus fájdalom szindrómás beteg vett részt (trigeminus neuralgia, illetve derékfájdalom tüneteivel). Három páciensben a tünetek diabeteses neuropathiához kapcsolódtak (P1, P3, P4), míg három betegben ugyanezek a szindrómák voltak megfigyelhetők cukorbetegség nélkül (P2, P5, P6). A szubjektív fájdalomskálát (0–10) és 12 időjárás-paramétert regisztráltunk egy hónapon keresztül napi három alkalommal. Spearman korrelációs (Sp), többszörös regressziós (Mx) és fő komponens (PCA) elemzéseket végeztünk összehasonlítva a fájdalom- és időjárás-paramétereket az adott napon, 2 nappal a mérés előtt és után, illetve a változások mértékét (5 × 12 paraméter). Az analízisekkel kapott adatokból egy komplex értéket számoltunk, és analizáltuk.
Eredmények – Bár a hőmérséklet fejtette ki a legnagyobb hatást a fájdalomérzetre, az egyéni különbség igen nagy volt. A fájdalom-időjárás összefüggés nemcsak az időjárás-paraméterektől, hanem az elemzés fajtájától is függött, így egyénenként különböző mintá-

a personalized map for each patient, which showed disparate patterns across the study participants. Thus, Participants 2 and 5 had higher scores for Mx compared to Sp; furthermore, certain factors showed opposite direction in their associations with the pain level depending on the type of analysis (Sp vs Mx). In contrast, P3 had a lower score for Mx compared to Sp, which might suggest a low level of weather sensitivity on the association between the different weather parameters in this subject. Furthermore, participants P4 and P6 had a very high level of weather sensitivity, while P1 had an opposite pattern. Regarding the time point-related effects on the pain level, most patients were sensitive to parameters obtained at the same day or two days before, except the P1 subject, who had the highest sensitivity to weather parameters detected two days after.
Conclusion – The present study highlights the importance of integrating different data analysis approaches to elucidate the individual connections between pain and most of the weather parameters. In conclusion, complex personalized profiling should be considered for the characterization of pain–weather associations by applying different data analytical approaches, which may provide feedback to physicians and patients.

Keywords: complex analysis, neuropathy, pain, weather

zatot adtak mind az egyes analízisek, mind a komplex értékek. A P2 és P5 beteg nagyobb pontszámot ért el az Mx-, mint az Sp-elemzéssel, sőt az összefüggés iránya is sok esetben ellentétes volt a két elemzésben. A P3 egyénben az Sp-elemzéssel kaptunk magasabb értéket, ami felveti, hogy az egyes időjárás-paraméterek egymásra kevésbé gyakoroltak hatást. A P4 és P6 beteg nagyon érzékeny volt az időjárás-paraméterekre, míg a P1-es egyén ellenkező mintázatot mutatott. A vizsgált időpontok tekintetében azt tapasztaltuk, hogy a legtöbb beteg az aznapi és az azt két nappal megelőző időjárás-paraméterekre volt a legérzékenyebb, kivéve a P1-es egyént, akinek a fájdalomszintje a két nappal későbbi időjárás-paraméterekkel mutatott legnagyobb összefüggést.
Következtetés – A jelen tanulmány eredményei felhívják a figyelmet arra, hogy számos környezeti paraméter adatainak integrált elemzése megvilágíthatja a fájdalom és az időjárás összefüggését egyéni szinten. Ezen adatok összetett, egyénre szabott elemzése segíthet a hatékonyabb fájdalomterápia megtervezésében.

Kulcsszavak: komplex analízis, neuropathia, fájdalom, időjárás

Chronic pain is a devastating disease with significant deteriorating effects on the quality of life of patients and their surrounding relatives. The link between pain perception and weather parameters, including temperature, barometric pressure, humidity, and precipitation, is widely recognized[1–5]. In this context, studies have investigated several chronic pain conditions including headache[6–9] and musculoskeletal pain[1, 3–5, 10], with controversial results.

Neuropathic pain, a destructive condition affecting the somatosensory nervous system, commonly occurs as chronic pain with major impact on quality of life. Examples of neuropathic pain include trigeminal neuralgia (TN) and low back pain (LBP), which might be the signs of polyneuropathy[11]. In addition, diabetic polyneuropathy (DN), a common complication of diabetes, may appear as a chronic pain condition that is increasingly concerning in parallel with the rapidly increasing prevalence of diabetes.

While the effects of the different weather parameters on several physiological and pathophysiological factors are well-known[10, 12–16], few studies have examined the effects of weather on neuropathic pain, including DN. *Ngan* et al. analyzed the prospectively collected diary-based data of 89 patients with neuropathic pain over a 6-month period[17] and found that contrary to the patients' belief, Chinook winds were protective against acute exacerbation in neuropathic pain. The authors also reported that days with cold temperature were associated with greater risk of neuropathic pain exacerbation, while precipitation or humidity did not enhance the pain level. Another study found that extreme humidity was a crucial trigger for painful DN, providing further evidence of the adverse effects of extreme weather in this patient group[18]. TN, a form of neuropathy with intense craniofacial pain attacks, can be triggered by various factors[19]. Although mechanical stimulus is one of the most common triggers of TN, atypical triggers such as cold temperatures, strong wind,

Table 1. *Demographic and clinical characteristics of the study participants*

	1	2	3	4	5	6	Mean (SD)
Dg	DN_TN	LBP	DN_LBP	DN_LBP	TN	TN	
Age	65	74	38	52	69	33	55 ± 17.0
Duration of pain (month)	10	14	18	108	24	42	36 ± 37.0
Mean VAS	4	7	7	8	4	7	6 ± 1.7
BDI	2	9	6	14	8	7	8 ± 3.9
SF36 Physical functioning	40	35	50	30	90	90	56 ± 27.3
SF36 Physical limitations	100	0	25	0	50	100	46 ± 45.9
SF36 Emotional limitations	100	0	67	0	0	0	28 ± 44.4
SF36 Vitality	75	30	55	35	55	75	54 ± 19.1
SF36 Mental health	84	68	68	56	80	56	69 ± 11.7
SF36 Social functioning	88	88	63	75	63	75	75 ± 11.2
SF36 Bodily pain	70	23	35	33	45	70	46 ± 19.9
SF36 General health	45	15	30	15	25	55	31 ± 16.3

BDI: Beck depression inventory, Dg: diagnosis, DN_TN: diabetic polyneuropathy with trigeminal neuralgia, DN_LBP: diabetic polyneuropathy with low back pain, LBP: low back pain, Mean VAS: mean pain value based on a visual analog scale during the study period, SD: standard deviation, SF-36: short-form 36, TN: trigeminal neuralgia

and certain foods are observed in a significant proportion of affected patients[20, 21]. Similarly, LBP is a major cause of morbidity with a very diverse group of background[22, 23]. A cohort study investigating the relationship between pain intensity and weather conditions over 6 months concluded that temperature and atmospheric pressure might influence LBP level[24], whereas other studies found that only wind speed had significant effects on LBP intensity[25, 26].

These studies illustrate the contradictory findings and the lack of consensus on the relationship between neuropathic pain and specific weather conditions, which might be due to interindividual differences. Precision and personalized medicine aims at the prevention and treatment of diseases by considering interindividual variations[27]. The few studies, which have assessed differences in sensitivity to various meteorological factors at individual level[28, 29], suggest that the association between weather and pain might have clinical relevance at the individual level due to interindividual variations in sensitivity to the meteorological factors.

In the present pilot study, we aimed to examine the association of several meteorological factors with the level of reported pain at the individual level in patients with chronic pain conditions. Based on an earlier study[28], we included data of terrestrial weather, geomagnetic, and solar activities. To evaluate anticipatory and reactive responses toward the weather changes, we analyzed not only the real-time pain–weather associations (day 0) but also the weather parameters two days before (day −2) and two days after (day +2) the real-time pain–weather observations. We also compared changes between days −2 and 0 (D+2) and between days 0 and +2 (D-2) to assess the potential effects of weather changes on pain perception. Thus, we evaluated individual pain sensitivity based on a total of 60 weather variables. Nonparametric Spearman's correlation (Sp), multiple regression (Mx) analyses, and principal component analysis (PCA) were performed to evaluate associations between pain and meteorological factors, and complex scores were also calculated based on the results of various analytic methods to provide special maps for each participant.

Methods

Subjects

Seven female participants with chronic pain were recruited in the present study. One patient did not appropriately perform the required data collection; therefore, the final analyses included the data of six subjects. The study population included three participants with DN accompanied with TN or LBP, one participant with LBP, and two participants with TN. Information on demographic, physical, and psychological characteristics of the participants were obtained using health-related quality of life (short-form-36 [SF-36]) and short-form Beck depression inventory (BDI) questionnaires performed at the start of the study **(Table 1)**[30]. All participants provided written informed consent to be included in the study. The study was approved by the University of Szeged Ethics Committee for Human Participants (approval no. 156/2020-SZTE).

Pain diaries

For the subjective perception of pain, the participants were instructed to use a visual analog scale (VAS) rang-

Table 2. *Definitions, abbreviations and units for the obtained weather parameters*

Parameter	Definition	Abbreviation	Unit
Terrestrial			
Temperature	Temperature at 2m height.	TEMP	°C
Apparent temperature	The measure of the human thermal comfort at 2m height.	TEMP_A	°C
Surface pressure	The pressure exerted by the air.	PRESS	hPa
Humidity	The concentration of water vapor at 2m height.	HUM	%
Total cloud cover	The fraction of the sky covered by all the visible clouds.	CC_T	%
Effective cloud cover	The fraction of the sky covered by all the clouds including not visible thin clouds as well.	CC_E	%
Precipitation	All liquid and solid water particles that fall from clouds and reach the ground.	PREC	mm/h
Geomagnetic			
Planetary A index	Daily average level of geomagnetic activity.	AP	Score
Planetary K index	Characteristic of the magnitude of geomagnetic storms, derived by weighted average of K-indices from a network of 13 geomagnetic observatories at mid-latitude locations.	KP	Score
Solar			
Solar Radio Flux	The indicator of solar activity at 10.7 cm, as F10.7 cm radio emissions, originates high in the chromosphere and low in the corona of the solar atmosphere.	RF	Units
Sunspot number	Dark areas at the Sun's photosphere as a result of intense magnetic flux pushing up from further within the solar interior.	SP_Nr	Nr
Sunspot area	The sum of the corrected area of all observed sunspots, in units of millionths of the solar hemisphere.	SP_A	Units

ing from 0 to 10, to describe pain intensity. The participants completed a 28-day pain diary between May and October 2021 by recording the intensity of perceived pain three times a day (6 AM, 12 PM, and 6 PM) for a total of 78–84 observations per participant.

Weather parameters

Terrestrial weather parameters **(Table 2)** obtained three times/day (6 AM, 12 PM, and 6 PM) were provided by the Swiss Meteomatics AG based on the GPS coordinates of the residence of the participants. The corresponding mean daily geomagnetic and solar parameters were downloaded from the National Oceanic and Atmospheric Administration database **(Table 2)**.

Statistical analyses

In the present study, three types of data analyses were performed for all parameters. In the first step, nonparametric univariate Spearman's correlation analysis was performed to evaluate the relationships between the 60 distinct weather parameters (5 × 12) and a p value of <0.001 was considered to indicate statistical significance. Furthermore, this analysis was performed to explore the association between the pain score and all weather parameters. Multiple regression analysis was applied where the dependent variable was VAS whereas the regressors' dataset contained the 12 weather parameters on days 0, +2, and −2, and the differences between days −2 and 0 (D-2) and between days +2 and 0 (D+2), separately (5 data set).

Principal component analysis was performed to emphasize individual patterns of pain sensitivity in order of importance of different weather parameters. For this analysis, the following four pain categories were created: 0, VAS score of 0; 1, VAS score of 1–4; 2, VAS score of 5–7; 3, VAS score of 8–10. The order of importance was performed separately for all 60 parameters and for the five datasets (12 × 5).

In the next step the scoring process was performed. The following classification with three categories was obtained based on the significant correlations identified with regression and correlation analyses, depending on the direction of the relationship **(Table 3)**. The PCA results were also classified **(Table 3)**. Based on these categorizations, total scores were calculated for each weather parameter by determining the sum of the absolute values of all four analyses at both the study cohort and individual levels. The possible maximum total score was 8 for a single parameter (Tot_single), 96 for all weather parameters in one time point (Tot_Time) and 480 for all 60 parameters (Tot_all).

Table 3. *Scoring method for the Sp, Mx and PCA analyses*

Score	Sp	Mx	PCA60	PCA12
			Importance order	
0	NS	NS	11–60	3–12
–1	p < 0.05	p < 0.05		
+1	p < 0.05	p < 0.05	5–10	2
–2	p < 0.001	p < 0.001		
+2	p < 0.001	p < 0.001	1–5	1

Explanation: –1 and –2, negative; +1 and +2, positive relationships in Sp and Mx analyses.

Finally, z-scores were calculated by subtracting the mean of all participants to each individual value and dividing the results by the standard deviation of the study population, based on a recent study [31]. Thus, the distribution of the z-scores were determined for the number of significant relationships obtained by Sp (Sp_Z), Mx (Mx_Z), sum of them (Sum_Z), and total score (Tot_all_Z) for each participant.

All of the analyses were performed with Statistica software (TIBCO Statistica®, 14.01.25; Arlington, VA, USA).

Results

Correlations among the weather parameters

First, we determined the associations among the weather parameters and found that the temperature and the apparent temperature at each time point exhibited strong correlation ($r > 0.8$; same day, 2 days before and after; **Figure 1**). Furthermore, the temperature parameters exhibited inverse correlations with PRESS, CC_T, CC_E, and HUM (see abbreviations in **Table 2**). Surprisingly, the precipitation parameters were not correlated with the other parameters. The geomagnetic and solar parameters, which were significantly correlated with few of the other weather parameters, exhibited significant correlations between each other.

Analysis of pain–weather relationship at the group level

In the overall cohort, the mean number of VAS scores was 82 (489 the total data number) and the mean pain score was 6 ± 0.1 **(Table 1)**. The BDI score indicated that one participant (participant 4; P4) harbored low level depression, whereas the SF-36 indicated high degree of interindividual differences in quality of life. The correlation analysis revealed a significant inverse correlation between the mean VAS score and emotional health ($p < 0.05$) only.

The pain–weather associations evaluated by different analytical approaches revealed a higher number of significant pain–weather associations with the Sp compared to the Mx analyses (27 vs 17; **Figure 2A**). Furthermore, the effects of weather parameters on pain parameters at different time points revealed that the weather parameters on days 0 and −2 had the highest impact on the pain level, whereas the changes in weather parameters (D+2 and D-2) had the lowest effect **(Figure 2B)**. Thus, Sp and/or Mx analyses showed that TEMP, TEMP_A, PRESS, HUM, SP_Nr, and SP_A were correlated with VAS values on days 0, −2, and +2. Furthermore, RF influenced pain sensation two days later (day +2) whereas SP-Nr was negatively correlated with the VAS score two days before scoring (day −2); the changes in SP-Nr also had a significant influence on pain sensation **(Figure 3)**. PCA showed, in agreement with the Sp and Mx results, that TEMP and TEMP_A had the highest level of importance, and precipitation and KP had the lowest level of importance. Regarding the changes in TEMP, TEMP_A, and CC_E, no significant relationships could be detected by Sp and Mx, but the PCA analyses revealed their importance. No significant sensitivity with any methods to the KP was detected at the study cohort level. The Tot_all was 100 out of a possible maximum of 480, indicating that only approximately 20% effects could be detected by all types of analysis, with highest values for the temperature parameters **(Figure 4)**.

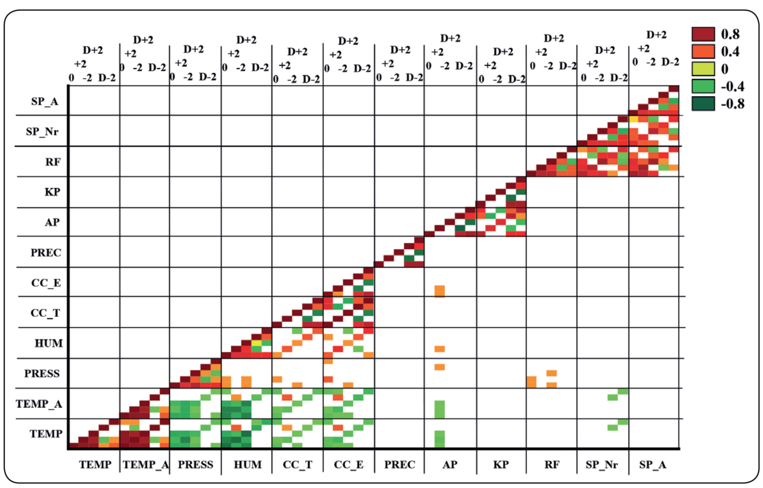

Figure 1. *Correlations between the different weather parameters at different time points related to the pain level determination and their changes. The abbreviations for weather parameters see Table 2. 0, same day of pain observation; +2, 2 days after the pain observation; −2, two days before the pain observation; D+2, difference between the day of pain observation and two days later; D-2, difference between the day of pain observation and two days earlier*

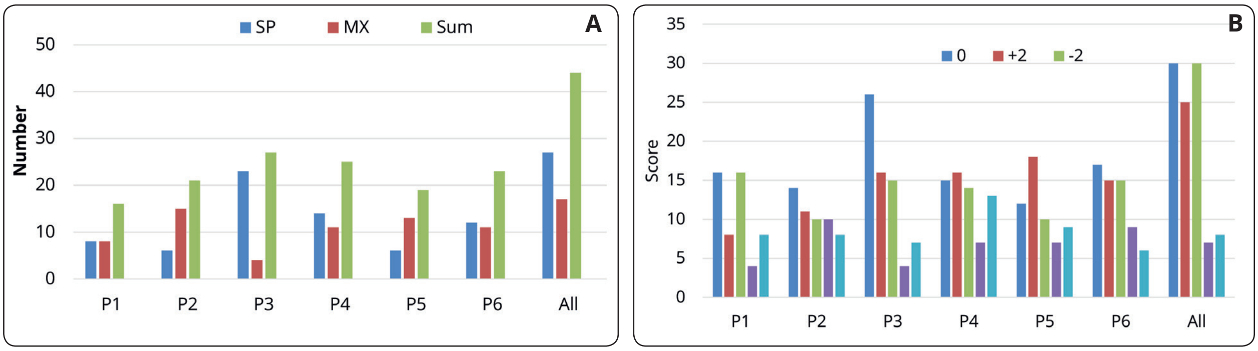

Figure 2. A *Distribution of the number of significant correlations determined using Spearman's correlation (Sp), multiple regression (Mx), sum of Sp and Mx (Sum) for each participant (P1-P6) and the whole group (All).* **B** *Distribution of the Tot_time scores (max: 96) for all 12 weather parameters detected at indicated time points 0, same day of pain observation; +2, 2 days after the pain observation; −2, two days before the pain observation; D+2, difference between the day of pain observation and two days later; D-2, difference between the day of pain observation and two days earlier*

Analysis of pain–weather relationship of individual participants

The analysis of individual pain profiles of the participants by the four analytic approaches revealed important distinctive features of the participants, displaying different sensitivities to the various parameters **(Figures 2–4)**. The majority of the participants were sensitive not only to the terrestrial but also some of the geomagnetic and solar parameters.

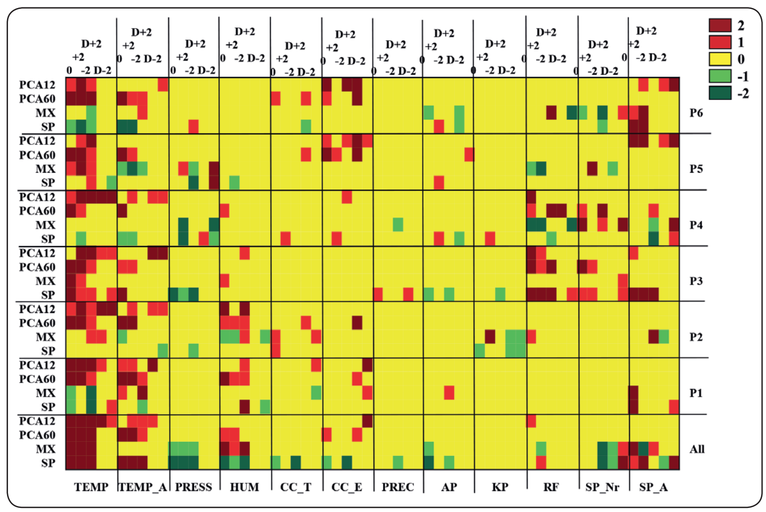

Figure 3. *Distribution of significance of different parameters obtained with different analytic methods at indicated time points for the whole group (All) and for each participant (P1-P6). The abbreviations for weather parameters see Table 2. 0, same day of pain observation; +2, 2 days after the pain observation; −2, two days before the pain observation; D+2, difference between the day of pain observation and two days later; D-2, difference between the day of pain observation and two days earlier*

Participant 1

Participant 1 with DN and TN, relatively good SF-36 and BDI scores and low pain levels, had the same number of significant connections obtained by Sp and Mx (8 and 8), and inverse correlations were detected between some temperature parameters and the pain level **(Figure 2A, 3)**. The weather parameters on days 0 and −2 had the highest influence on pain values, whereas the changes in weather parameters two days later (D+2) had the lowest effect **(Figure 2B)**. The participant had no sensitivity to PRESS, PREC, KP, RF, or SP_Nr, and only a small number of AP and SP_A parameters had significant associations with the pain level. PCA revealed that besides the temperature parameters, the HUM and cloud conditions had an important role in the VAS score, whereas the geomagnetic and solar parameters had no significant effect **(Figure 3)**. Therefore, the Tot_single scores were high for the temperature parameters whereas almost all the geomagnetic and solar parameters had 0 T_single score, and the Tot_all value was 52 **(Figure 4)**. All types of z-scores (Sp_Z, Mx_Z, Sum_Z, and Tot_all_Z) indicated that the level of connections between the weather parameters and pain levels was lower in this participant compared to that observed at the study cohort level and that this phenomenon was observed for all types of scores **(Figure 5)**.

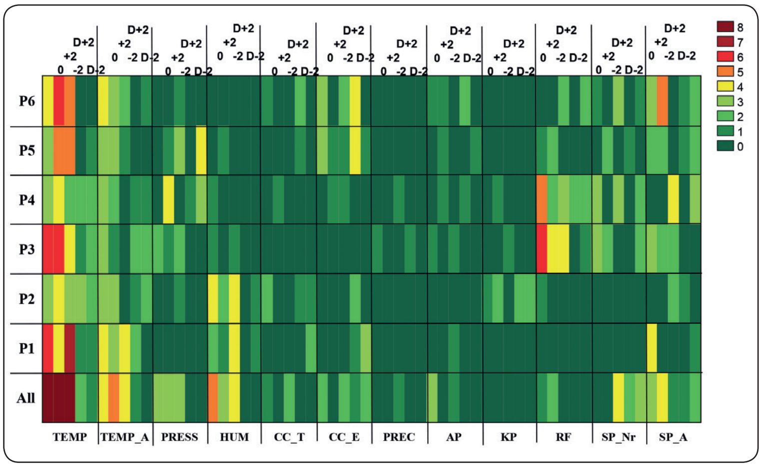

Figure 4. *Distribution of the Tot_single score (max. 8) of different weather parameters for the whole group (All) and for each participant at indicated time points. The abbreviations for weather parameters see Table 2. 0, same day of pain observation; +2, 2 days after the pain observation; −2, two days before the pain observation; D+2, difference between the day of pain observation and two days later; D-2, difference between the day of pain observation and two days earlier*

Figure 5. *Distribution of the z-scores for Spearman's correlation analysis (Sp_Z), multiple regression analysis (Mx_Z), sum of them (Sum_Z), and for the total score (Tot_all_Z) collected from all the weather parameters in each participant (P1–P6)*

Participant 2

Participant 2, with LBP, slightly impaired SF-36 and BDI scores and high pain levels, had a higher number of significant effects by Mx than with Sp (15 vs 6; **Figure 2A**). The weather parameters on day 0 had the highest influence on the pain values, whereas changes in weather parameters (D+2 and D-2) had the lowest one **(Figure 2B)**. She had no significant sensitivity to PREC, AP, and SP_Nr, whereas few significant effects were detected with PRESS, CC_E, RF, and SP_A parameters **(Figure 3)**. Furthermore, TEMP_A, PRESS, HUM, KP, and SP_A exhibited inverse correlations with the pain level. PCA indicated that temperature parameters and HUM had a significant influence on the pain level. The Tot-all score was relatively low (53) in this participant **(Figure 4)**. The examination of z-scores showed that the level of connections between the weather parameters and VAS values was lower in this participant compared to that observed at the study cohort level for Sp_Z and Tot_all_Z, but higher for Mx_Z values **(Figure 5)**.

Participant 3

Participant 3 with DN and LBP had slightly altered SF-36 and BDI scores and high pain levels. In contrast to that observed at the study cohort level, the detected number of significant effects was much higher with Sp than with Mx (23 vs 4), which included the solar parameters as well **(Figures 2A, 3)**. The weather parameters on day 0 had the highest influence on the pain values, whereas changes in weather parameters (D+2 and D-2) had the lowest effect **(Figure 2B)**. None of the cloud conditions and few PRESS, HUM, PREC, AP, and KP parameters had an impact on pain scores. PCA revealed the significant influence of not only temperature parameters, but also the HUM, RF, SP-Nr, and SP_A parameters on the pain level. Therefore, the Tot_single scores were relatively high for the RF and SP besides the temperature parameters, and the Tot-all score was also relatively high (68) **(Figure 4)**. The examination of z-scores indicated that the level of connections between the weather parameters and pain levels was lower in this participant compared to that observed at the study cohort level for Mx_Z only **(Figure 5)**.

Participant 4

Participant P4 with DN and LBP had relatively good SF-36 and BDI scores and low pain levels. In this participant, the number of significant connections detected by

Sp and Mx were comparable (14 and 11, respectively; **Figure 2A**). The weather parameters detected at different time points had similar influence, except the changes two days later (D+2), which had the lowest number of significant relationships **(Figure 2B)**. The pain levels showed inverse correlations with several parameters **(Figure 3)**, and only few of the HUM, cloud, PREC, AP, and KP parameters had significant relationship with pain level. PCA revealed the importance of not only the temperature but also the solar parameters; therefore, the Tot_single scores were relatively high for these parameters, and the Tot_all score was also high (65) **(Figure 3, 4)**. Furthermore, the level of connections between the weather parameters and pain levels was higher in this participant compared to that observed at the study cohort level for all types of z-scores **(Figure 5)**.

Participant 5

Participant 5 with TN had moderately lower SF-36 and BDI scores and high pain levels. The number of significant effects determined with Mx was higher than that determined with Sp (13 vs. 6; **Figure 2A**). The weather parameters obtained two days after VAS recording had the highest influence, whereas the other time points or changes between the days (D-2 or D+2) had a similar, but lower degree of influence on the pain level **(Figure 2B)**. Some of the temperature, PRESS, HUM, AP, RF and SP_Nr parameters exhibited inverse correlations with the pain levels, whereas no sensitivity could be observed to the PREC and KP parameters **(Figure 3)**. The Tot_single scores were relatively low for most of the parameters, except for the temperature parameters; therefore, the Tot_all score was also low (56; **Figure 4**). The analysis of z-scores indicated that the level of connections between the weather and pain parameters was lower in this participant compared to that observed at the study cohort level for Sp_Z and Tot_all_Z scores but higher number for Mx values **(Figure 5)**.

Participant 6

Participant 6 with TN had relatively normal SF-36 and BDI scores, but high pain levels, and a similar number of significant connections were found by Sp and Mx analyses (12 and 11, respectively; **Figure 2**). Regarding the effects of the weather parameters detected at different time points, changes in weather parameters (D+2 and D-2) had the lowest influence on the pain level **(Figure 2B)**. She had no sensitivity to any of the HUM, PREC and KP parameters, whereas some of the temperature, CC_T, AP, RF and SP-Nr parameters were inversely correlated with the pain level **(Figure 3)**. PCA revealed the importance of the temperature, cloud, and SP_A parameters. The distribution of the Tot-single scores revealed high values for the temperature and SP_A parameters, and the Tot_all score was also relatively high (62; **Figure 4**). The examination of z-scores indicated that all four z-scores were closest to the mean z-scores of the study cohort **(Figure 5)**.

Discussion

The present study including the collection and analyses of a wide array of data from six participants with chronic pain conditions revealed the significant interrelationships between several weather parameters and pain levels, with high level of interindividual differences in the direction, in their time-point-related connection and also depending on the analytical method. The temperature parameters had a high impact in most participants, while the precipitation had the lowest level of influence on pain sensitivity. The majority of the participants were also sensitive to the terrestrial magnetic and solar factors, suggesting that the most available types of parameters may be important for the characterization of pain–weather associations. Not only the real-time data on day 0 but also those from two days before and after the evaluation of pain levels revealed several relationships, whereas the calculated changes in weather parameters (D-2 or D+2) showed moderate effects. Participants 2 and 5 had higher scores for Mx compared to Sp; furthermore, certain factors showed opposite direction in their associations with the pain level depending on the type of analysis (Sp vs Mx). In agreement with earlier studies[29], our findings suggest that the multiple connections among the different weather parameters might have high impact, thus, the effect of one meteorological factor on pain perception depends on other meteorological factors in some subjects. In contrast, P3 had a lower score for Mx compared to Sp, which might suggest a low level of sensitivity on the association between the different weather parameters in this subject. Furthermore, participants (P4 and P6) with only positive z-scores may indicate a very high level of weather sensitivity, while P1 had an opposite pattern. Regarding the time point-related effects on the pain level, most patients were sensitive parameters obtained at the same day or two days before, except the P1 subject, who had the highest sensitivity to weather parameters obtained two days after. Surprisingly, the changes in the weather parameters had low impact in most cases.

Personalized medicine considers individuals' distinctive physical, genetic, and sociodemographic characteristics to develop and implement individually planned feasible treatments with efficacy. The high level of interindividual variability in pain sensitivity may be due to not only differences in age, sex, ethnicity, genetics, and psychosocial variables but also environmental factors, including weather parameters[2, 32]. The large heterogeneity in the weather sensitivity might complicate the characterization of the associations between weather and pain[33], but only few studies have conducted detailed individual evaluation of pain responses to meteorological parameters[28, 29]. *Smedslund* et al. assessed the associations between pain and 13 weather variables the day before and the day of the reported pain in 36 patients with rheumatoid arthritis[28]. In agreement with our results, the individual level analyses revealed several significant relationships in most patients; however, the patients differed in the variables they responded to and in the direction of the relationship. Another study evaluated the individual pain level in seven patients with chronic masticatory muscle pain based on hourly evaluated pain level and three meteorological parameters (temperature, pressure, and humidity)[29]. In spite of the few investigated parameters, they also observed high level of individuality in the weather-pain associations. We suggest that our paradigm, performing four types of analyses with a high number of weather parameters at different time points, might provide a complex individual pattern of pain-weather relationship.

Some studies clustered subjects in subgroups based on their response to weather parameters after preliminary individual analyses[34–39]. One study, in which 333 patients were clustered in subgroups based on their correlation parameters, indicated that the symptoms of patients were, to a minimal extent, differentially influenced by weather conditions including temperature, sunshine duration, precipitation, pressure, and humidity[38]. The analyses in two subgroups of 48 patients with fibromyalgia involving 3 meteorological parameters (temperature, pressure and humidity) revealed that increased pressure was associated with decreased pain levels in 83% of the patients. Furthermore, stress levels did not change in parallel with increased pressure in this subgroup, whereas the subgroup of patients with the opposite response to pressure reported increased stress in parallel with elevated pressure[36]. These results suggest that individual factors related to emotional status might be associated with responsiveness to changes in barometric pressure. The latest analysis of 6850 participants with chronic pain, obtaining four weather parameters (temperature, pressure, wind speed and humidity) found that most participants (72.5%) could be categorized as weather-sensitive based on the presence of sensitivity to a single weather parameter with highly distinct degree and direction[34].

Overall, these data indicate that given the large variation in personal sensitivity to meteorological parameters, the connection between weather and pain might have clinical relevance at the individual level. The weak correlations observed at the population level might be at least partially due to the sensitivity of subjects with opposite responses; however, the different degrees or types of pain states might also contribute to this phenomenon. Unfortunately, most studies conducted to date involved only a small number of weather parameters or evaluations at only one-time point performed the same day. Although we were not able to perform stratification of the patients based on the pain-weather relationship, due to the small cohort size, our findings suggest that future studies should integrate several data analysis models to obtain more reliable outcomes. More effective pain self-management can be developed with accurate predictive models. Although chronic pain cannot be cured, avoiding exposure to weather triggers can minimize the negative effect of pain on quality of life. For example, identifying the specific pain–weather associations two days before the pain event may aid in the planning of prompt therapeutic intervention whereas identifying the specific pain–weather associations two days after the pain event may offer predictions on changes in weather parameters. However, the weather forecast can provide information for at least the next two days, which can aid in the planning of improved approaches for pain therapy. These promising findings also propose new prospects for precision medicine in patients with chronic pain syndromes.

The main strength of this study is the application of a combination of different types of analyses to build a total score, which can be considered as a basis for the prediction of individual sensitivity to different weather parameters. However, several further environmental parameters could have been involved, including the air pollution, heatwaves or special wind conditions[15, 40]. The data were limited by the cohort size and the short study duration, which might have influenced the prediction performance. Unfortunately, it was very difficult to recruit patients with similar characteristics and appropriate activity for recording their pain levels three-times a day for four weeks. The present study was based on self-reports on pain intensity, which might have also dampened the reliability of the data. There is also room for improvement in handling the importance of variables. For example, different machine learning-based pattern recognition approaches should be considered as promising alternatives to traditional statistical methods.

Conclusion

The effect of meteorological factors on pain sensitivity raises important questions regarding optimizing medical resources. In agreement with earlier studies, the findings of the present study confirm the importance of personalized analysis of special weather triggers, which can facilitate the reliable prediction of pain exacerbation. The detailed and complex personalized analyses of data may provide feedback to physicians and patients for providing weather-dependent therapy. The present study also highlights the importance of integrating different data analysis approaches to elucidate the individual connections between pain and most of the weather parameters.

STATEMENTS AND DECLARATIONS – No specific financial support was available for this study. Declarations of interest: none.

References

1. *Cay HF, Sezer I, Firat MZ, Kaçar C.* Which is the dominant factor for perception of rheumatic pain: meteorology or psychology? Rheumatol Int 2011;31:377-85. https://doi.org/10.1007/s00296-009-1279-7
2. *Horvath G, Nagy K, Tuboly G, Nagy E.* Pain and weather associations - Action mechanisms;personalized profiling. Brain Res Bull 2023;200:110696. https://doi.org/10.1016/j.brainresbull.2023.110696
3. *Patberg WR, Rasker JJ*. Weather effects in rheumatoid arthritis: from controversy to consensus. A review. J Rheumatol 2004;31:1327-34.
4. *Strusberg I, Mendelberg RC, Serra HA, Strusberg AM.* Influence of weather conditions on rheumatic pain. J Rheumatol 2002;29:335-8.
5. *Xin L, Liu J, Zhu Y, Fang Y*. Exposure-lag-response associations between weather conditions and ankylosing spondylitis: a time series study. BMC Musculoskelet Disord 2021;22:641. https://doi.org/10.1186/s12891-021-04523-y
6. *Milojević S.* Revisiting the connection between Solar eruptions and primary headaches and migraines using Twitter. Sci Rep 2016;6:39769. https://doi.org/10.1038/srep39769
7. *De Matteis G, Vellante M, Marrelli A, Villante U, Santalucia P, Tuzi P, et al.* Geomagnetic activity, humidity, temperature and headache: is there any correlation? Headache 1994;34:41-3. https://doi.org/10.1111/j.1526-4610.1994.hed3401041.x
8. *Kuritzky A, Zoldan Y, Hering R, Stoupel E*. Geomagnetic activity and the severity of the migraine attack. Headache 1987;27:87-9. https://doi.org/10.1111/j.1526-4610.1987.hed2702087.x
9. *Hoffmann J, Recober A.* Migraine and triggers: post hoc ergo propter hoc? Curr Pain Headache Rep 2013;17:370. https://doi.org/10.1007/s11916-013-0370-7
10. *Beukenhorst AL, Schultz DM, McBeth J, Sergeant JC, Dixon WG*. Are weather conditions associated with chronic musculoskeletal pain? Review of results and methodologies. Pain 2020;161:668-83. https://doi.org/10.1097/j.pain.0000000000001776
11. *Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al.* The Revised IASP definition of pain: concepts, challenges, and compromises HHS Public Access. Pain 2020;161:1976-82. https://doi.org/10.1097/j.pain.0000000000001939
12. *Boussoussou N, Boussoussou M, Nemes A*. Az orvosmeteorológia történeti áttekintése - új horizont a preventív medicina területén. Historical overview of medical meteorology - the new horizon in medical prevention. Orvosi Hetilap 2017;158:187-91. https://doi.org/10.1556/650.2017.30655
13. *Kérdő I.* Időjárás és vegetatív idegrendszer. Időjárás 1951;55:136-44.
14. *Fülöp A, Mika J, Dúll A.* Survey of Kérdő's weather sensitivity test and an attempt for its improvement. Légkör 2014;59:74-7.
15. *Bobvos J, Málnási T, Rudnai T, Cserbik D, Páldy A*. The effect of climate change on heat-related excess mortality in Hungary at different area levels. Idojaras 2017 at <https://www.semanticscholar.org/paper/The-effect-of-climate-change-on-heat-related-excess-Bobvos-M%C3%A1ln%C3%A1si/b804844ec18ed-b9aa96877c3e4058fe0dafbd07e>
16. *Madaras K, Orményi I.* The effect of weather fronts on the development of periostitis of dental origin. Fogorv Sz 1974;67:366-9.
17. *Ngan S, Toth C*. The influence of Chinook winds and other weather patterns upon neuropathic pain. Pain Med 2011;12:1523-31. https://doi.org/10.1111/j.1526-4637.2011.01227.x
18. *Xin L, Zhu Y, Zhao J, Fang Y, Xie J*. Association between short-term exposure to extreme humidity and painful diabetic neuropathy: a case-crossover analysis. Environ Sci Pollut Res Int 2023;30:13174-84. https://doi.org/10.1007/s11356-022-23095-5
19. *Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al*. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019;160:53-9. https://doi.org/10.1097/j.pain.0000000000001365
20. *Koh W, Lim H, Chen X*. Atypical triggers in trigeminal neuralgia: the role of A-delta sensory afferents in food and weather triggers. Korean J Pain 2021;34:66-71. https://doi.org/10.3344/kjp.2021.34.1.66
21. *Symonds T, Randall JA, Hoffman DL, Zakrzewska JM, Gehringer W, Lee JY.* Measuring the impact of trigeminal neuralgia pain: the Penn Facial Pain Scale-Revised. J Pain Res 2018;11:1067-73. https://doi.org/10.2147/JPR.S152958
22. *Deyo RA, Weinstein JN*. Low back pain. N Engl J Med 2001;344:363-70. https://doi.org/10.1056/NEJM200102013440508
23. *Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, et al, Lancet Low Back Pain Series Working Group.* Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet 2018;391:2368-83. https://doi.org/10.1016/S0140-6736(18)30489-6
24. *McGorry RW, Hsiang SM, Snook SH, Clancy EA, Young SL.* Meteorological conditions and self-report of low back pain. Spine (Phila Pa 1976) 1998;23:2096-2102;. https://doi.org/10.1097/00007632-199810010-00011
25. *Duong V, Maher CG, Steffens D, Li Q, Hancock MJ.* Does weather affect daily pain intensity levels in patients with acute low back pain? A prospective cohort study. Rheumatol Int 2016;36:679-84. https://doi.org/10.1007/s00296-015-3419-6
26. *Steffens D, Maher CG, Li Q, Ferreira ML, Pereira LSM, Koes BW, Latimer J.* Effect of weather on back pain: results from a case-crossover study. Arthritis Care Res (Hoboken) 2014;66:1867-72. https://doi.org/10.1002/acr.22378
27. *Goetz LH, Schork NJ*. Personalized medicine: motivation, challenges, and progress. Fertil Steril 2018;109:952-63. https://doi.org/10.1016/j.fertnstert.2018.05.006
28. *Smedslund G, Mowinckel P, Heiberg T, Kvien TK, Hagen KB*. Does the weather really matter? A cohort study of influences of weather and solar conditions on daily variations of joint pain in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:1243-7. https://doi.org/10.1002/art.24729
29. *Edefonti V, Bravi F, Cioffi I, Capuozzo R, Ammendola L, Abate G, et al.* Chronic pain and weather conditions in patients suffering from temporomandibular disorders: a pilot study. Community Dent Oral Epidemiol 2012;40 Suppl 1:56-64. https://doi.org/10.1111/j.1600-0528.2011.00667.x

30. *Chibnall JT, Tait RC*. The short form of the Beck Depression Inventory: validity issues with chronic pain patients. Clin J Pain 1994;10:261-6.
https://doi.org/10.1097/00002508-199412000-00004
31. *Fouyssac M, Puaud M, Ducret E, Marti-Prats L, Vanhille N, Ansquer S, et al.* Environment-dependent behavioral traits and experiential factors shape addiction vulnerability. Eur J Neurosci 2021;53:1794-808. https://doi.org/10.1111/ejn.15087
32. *Fillingim RB*. Individual differences in pain responses. Curr Rheumatol Rep 2005;7:342-7. https://doi.org/10.1007/s11926-005-0018-7
33. *Smedslund G, Hagen KB.* Does rain really cause pain? A systematic review of the associations between weather factors and severity of pain in people with rheumatoid arthritis. Eur J Pain 2011;15:5-10. https://doi.org/10.1016/j.ejpain.2010.05.003
34. *Yimer BB, Schultz DM, Beukenhorst AL, Lunt M, Pisaniello HL, House T, et al.* Heterogeneity in the association between weather and pain severity among patients with chronic pain: a Bayesian multilevel regression analysis. Pain Rep 2022;7:e963.
https://doi.org/10.1097/PR9.0000000000000963
35. *Guedj D, Weinberger A*. Effect of weather conditions on rheumatic patients. Ann Rheum Dis 1990;49:158-9.
https://doi.org/10.1136/ard.49.3.158
36. *Fagerlund AJ, Iversen M, Ekeland A, Moen CM, Aslaksen PM*. Blame it on the weather? The association between pain in fibromyalgia, relative humidity, temperature and barometric pressure. PLoS ONE Edited by Luciano JV. 2019;14:e0216902.
https://doi.org/10.1371/journal.pone.0216902
37. *Gorin AA, Smyth JM, Weisberg JN, Affleck G, Tennen H, Urrows S, Stone AA.* Rheumatoid arthritis patients show weather sensitivity in daily life, but the relationship is not clinically significant. Pain 1999;81:173-7.
https://doi.org/10.1016/S0304-3959(99)00010-X
38. *Bossema ER, Middendorp H van, Jacobs JWG, Bijlsma JWJ, Geenen R.* Influence of weather on daily symptoms of pain and fatigue in female patients with fibromyalgia: a multilevel regression analysis. Arthritis Care Res (Hoboken) 2013;65:1019-25.
https://doi.org/10.1002/acr.22008
39. *Hollander JL, Yeostros SJ.* The Effect of simultaneous variations of humidity and barometric pressure on arthritis. Bulletin of the American Meteorological Society 1963;44:489-94.
https://doi.org/10.1175/1520-0477-44.8.489
40. *Kurcsics M, Horváth Á*. From Adriatic bora to Bakony-Balaton dewnslope wind. Légkör 2022;67:77-89.
https://doi.org/10.56474/legkor.2022.2.2