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Review

Pain and weather associations – Action mechanisms; personalized profiling

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ABSTRACT

It is a well-known hypothesis that weather can influence human health, including pain sensation. The primary meteorological factors are atmospheric pressure, wind, humidity, precipitation, and temperature, which vary from the climate and seasons, but the parameters of space weather (e.g., geomagnetic and cosmic ray activities) also may affect our body condition. Despite a significant number of experimental studies, reviews, and meta-analyses concerning the potential role of weather in pain sensitivity, the findings are heterogeneous and lack consensus. Therefore, rather than attempting a comprehensive analysis of the entire literature on the effects of weather on different pain types, this study highlights the potential action mechanisms of the meteorological factors, and the possible causes of the controversial results. The few data available about the individual evaluations are discussed in detail to reveal the significance of the personalized analysis of the possible relationships between the most available weather parameters and the pain scores. The use of special algorithms may enable the individual integration of different data for a precise outcome concerning the link between pain sensitivity and weather parameters. It is presumed that despite the high level of interindividual differences in response to meteorological parameters, the patients can be clustered in different groups based on their sensitivity to the weather parameters with a possible disparate treatment design. This information may help patients to control their daily activities and aid physicians to plan more valuable management for patients with pain states when the weather conditions change.

1. Introduction

It is a well-known presumption that weather affects human health. We are consistently affected by changes in meteorological factors (both terrestrial and space weather), which might cause alterations in several body parameters, including musculoskeletal, cardiovascular, somatic- and autonomic nervous systems (both the afferent and efferent pathways and centers), higher functions of the brain (behavior, mood, cognition), immune and endocrine systems. Thus, it appears that all of our cells can react to the weather parameters directly and/or indirectly.

Several types of pain conditions were found to be dependent, at least partially, on meteorological parameters. The most commonly examined conditions were headaches, musculoskeletal system-related pain states (e.g., acute/chronic low-back pain [LBP], rheumatoid arthritis [RA], osteoarthritis [OA], fibromyalgia [FM], gout-induced arthritis) and neuropathic pain (e.g. caused by cancer and/or diabetes mellitus) (Schultz et al., 2020, p. 202; Stovner et al., 2007; Yimer et al., 2022).

The major meteorological factors include atmospheric pressure, wind, humidity, precipitation and temperature, parameters depending on climate and seasons. However, space weather activity is also linked to human pathology, morbidity and mortality (Milojević, 2016; Stoupel, 2015; Wahbeh et al., 2021). Thus, all these elements, acting on the whole body, might greatly affect the pain sensation, promoting deterioration of the quality of life of the patients. The PubMed search on February 15th, 2023, with “pain and weather” presented more than 11 000 articles and close to 550 reviews. Despite a great number of experimental studies, reviews, and meta-analyses concerning the potential role of weather in pain sensitivity, the results are heterogeneous and lack consensus. A recent excellent review by Beukenhorst et al. (2020) identified and synthetized studies regarding the connection between pain and weather, and they outlined the difficulties with the methodologies of these studies. However, there is no review available

Abbreviations: FM, fibromyalgia; IL, interleukin; LBP, low-back pain; OA, osteoarthritis; RA, rheumatoid arthritis; TRP, Transient Receptor Potential.

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regarding the possible action mechanisms and the potential significance of the personalized evaluation in this aspect. Therefore, the aim of this study was not to obtain all data regarding the connection between weather and pain, but, after a brief analysis of the main results concerning the weather effects on different pain types, we summarized data about the potential mechanisms of effects of multiple meteorological factors and outcomes linked to the individual evaluations of pain sensitivity.

We searched PubMed and Scopus from the earliest available date to March 15, 2023. We also checked the Embase and Web of Science sources, but they provided a huge amount of irrelevant publications for our topics. Therefore, we also applied at least one weather-related parameter too (pressure and/or humidity, solar or geomagnetic), which decreased significantly the number of the articles. The search strategy applying combined terms related to weather are shown in Table 1., which indicates that the exploration in Pubmed provided more studies compared to Scopus. Identified records were screened by HG according to the eligibility criteria. Studies that were not observational (i.e. letters, conference abstracts), or in other languages than English were excluded. Articles were first screened for eligibility based on their title, abstract, and then, if needed, based on full text. Since the search for the criteria for the main objectives of this study provided only few studies, all of them were discussed in details in the 4. and 5. sections ("4. The possible action mechanism of weather parameters on sensitivity" and "5. Personalized characterization of weather sensitivity").

2. Weather and different pain types

Headache is among the most prevalent disorders, affecting 50%–75% of adults at least once a year (Stovner et al., 2007). Migraine and tension-type headaches are very common forms of headaches. Both the meteorological conditions and the geomagnetic activity were presumed to be triggers in the different types of headaches (De Matteis et al., 1994; Hoffmann and Recober, 2013; Kuritzky et al., 1999; Milojević, 2016). Studies on headache diaries and patient interviews indicate atmospheric pressure as a likely migraine trigger (Maini and Schuster, 2019), while other data suggest that high wind velocity, relative humidity and low ambient temperature might also be linked to the advancement of episodic migraine attacks (Akgün et al., 2021; Buoite Stella et al., 2022; Hoffmann and Recober, 2013). The collection of 63 million pain-related messages for 3 years did not indicate significant increases in Twitter rates during an intensive geomagnetic storm, and no substantial correlation with the peaks of geomagnetic activity was observed (Milojević, 2016). Thus, the outcomes of these studies are inconsistent regarding their directionality and fail to establish a strong association.

Regarding the analysis of the connection between weather and different musculoskeletal pain conditions, a recent meta-analysis involving 43 studies indicated that most studies discovered at least one association between a weather variable and pain levels, but the significant variables differed (e.g., warm, and cold temperature, or barometric pressure) (Beukenhorst et al., 2020). A cohort study analyzing the relationship between pain intensity and weather conditions over 6 months deduced that temperature and atmospheric pressure may impact LBP intensity (McGorry et al., 1998). Another study found that higher wind speed and wind gusts augmented the frequency of pain onset in this pain type (Steffens et al., 2014). In contrast, the degree of pain during the acute LBP episodes was not influenced by the weather parameters, including precipitation, temperature, relative humidity, and air pressure (Duong et al., 2016). The findings of a recent investigation of more than 7000 patients with ankylosing spondylitis for five years asserted that high humidity facilitated delayed increases in outpatient visits (Xin et al., 2021). Pain scores of RA patients also indicated positive correlations with humidity, mean temperature, and sunshine duration, while the negative correlation with atmospheric pressure (Cay et al., 2011; Patberg and Rasker, 2004; Smedslund and Hagen, 2011; Strusberg et al., 2002). Several data imply a moderate relationship between the weather changes and OA-induced pain with contentious results (Cay et al., 2011; Guedj and Weinberger, 1990; Peultier et al., 2017). Cay et al. (2011) discovered that pain scores in OA patients had negative correlations with mean temperature and sunshine duration, while positive correlations with atmospheric pressure, precipitation and wind speed. The evaluation of pain perception with OA, RA, and FM revealed an association between temperature, rain, and barometric pressure in persons with OA, while barometric pressure and temperature were linked to pain in patients with RA, and only barometric pressure was correlated with pain in persons having FM (Guedj and Weinberger, 1990). Acute gouty arthritis, characterized by intermittent episodic flares, is one of the most prevalent forms of inflammatory arthritis. Multiple linear regression analysis of data showed that only change in mean temperature between neighboring days was significantly associated with the number of episodes of acute, painful gouty arthritis (Park et al., 2017), while others suggested the effects of humidity and barometric pressure, as well (Wu et al., 2022). Thus, both positive and negative correlations were observed in the different studies between the pain level and ambient temperature, atmospheric pressure, or humidity.

The weather-related pain sensitivity modifications after traumatic injury might also be significant, since it appears that scar tissues react distinctively to different weather conditions (Shulman et al., 2016). Thus, pain in the immediate postoperative period is dominated primarily by acute tissue injuries, however, at the later phase of recovery barometric pressure, temperature, and humidity may also impact on the pain levels.

Regarding neuropathic pain, a prospective diary-based analysis of 89 patients with neuropathic pain over six-month period revealed that contrary to the patients' belief, Chinook winds appeared to be protective against exacerbations in neuropathic pain, but days with cold temperatures (≤ -14 °C) were linked to exacerbation, and no effects of precipitation or humidity were observed (Ngan and Toth, 2011).

3. The possible causes of controverting results

As can be inferred from the above-mentioned data, a huge level of inconsistency could be observed in the association between weather and different pain states, which might be caused by several factors. It should be mentioned that the analysis of these dynamic, nonlinear systems with multi-fold parameters is extremely difficult. The large level of interindividual differences might be a major factor leading to the controverting results (see Section 5). The low number of participants and/or the low frequency of sample taking and/or the short period of the investigation might also have led to the mixed data. Furthermore, a great number of factors might impact the results, including the sex, age, day of the week, etc. Additionally, the pathophysiologic mechanisms of the different forms of pain differ significantly, facilitating disparate sensitivities to the meteorological factors, too. As weather circumstances exhibit seasonal patterns as well, the altered pain sensitivity might also be due to modifications in vitamin D levels, in the proportion of physical activity,

Table 1
The number of identified records with different terms in the obtained sources.

Term	PubMed	Scopus
Pain weather humidity pressure subgroup	9	2
Pain weather humidity pressure individual	191	0
Pain weather humidity pressure personalized	57	0
Pain weather humidity mechanism	14	5
Pain weather pressure mechanism	251	15
Pain weather pressure mechanism brain	40	4
Pain weather pressure mechanism sensory	69	1
Pain weather solar subgroup	0	0
Pain weather solar individual	28	1
Pain weather solar personalized	26	0
Pain weather solar mechanism	3	0
Pain weather geomagnetic	3	3

sleep and other patterns of daily life or mood (McNally et al., 2009; Yamaguchi et al., 2021). Thus, a recent analysis showed that distinct parameters have considerable effects on pain sensitivity in RA patients in winter when compared to summer, but there was no link between meteorological parameters and pain for all seasons (Azzouzi and Ichchou, 2020). The pain measurement techniques are also very diverse, i.e., several studies evaluated the spontaneous pain sensation in multiple chronic pain states, while others assessed the experimental pain tolerance to different types of stimuli (mechanical, chemical or heat). Furthermore, some studies applied questionnaires, while others use diaries which necessitate a description of pain states every day (Cay et al., 2011). Additionally, the pain degree might also be influenced by expectations, and the weather-mood relationship, as well, thus, patients may believe in the influence of specific weather conditions, irrespective of its real relevance (Keller et al., 2005). At last, but not at least, it is well-known that the pain level is also determined by several other factors including genetics, sex, health condition (e.g. sleep quality, diet, and psychological state), medical history, age, culture, and environment (including geographical locations) (Mogil, 2021).

It might also be essential to analyze the weather parameters before or after a few days of the pain sensitivity changes as well, but the outcomes are also inconsistent in this aspect (Cay et al., 2011; Li et al., 2020; Xin et al., 2021). Yamaguchi et al. (2021) found no change in the number of patients with night-time headaches 3 days before and after typhoons landing in Japan, while Cay et al. (2011) observed that the previous day's mean temperature significantly contributed to the symptom score in an OA group. Another study detected a significant increase in the number of patients attending the hospital several days after the development of high humidity or changes in environmental temperature (Xin et al., 2021). Therefore, the effect of weather on pain may vary depending on the current and/or the preceding weather and/or the changes in the different meteorological parameters.

Furthermore, it has to be claimed that the meteorological factors may act on homeostasis not only by themselves, but also in combination (Edefonti et al., 2012; Hollander and Yeostros, 1963; Schultz et al., 2020). The findings of a smartphone study of more than ten thousand subjects with chronic pain determined the importance of specific combinations of the different weather parameters (Schultz et al., 2020), i.e., the high incidence of pain across the population was characterized by a below-normal pressure, above-normal humidity, higher precipitation rate and stronger wind. In contrast, the daily weather with a low number of pain sensations was linked to above-normal pressure, below-normal humidity, lower precipitation rate, and weaker wind.

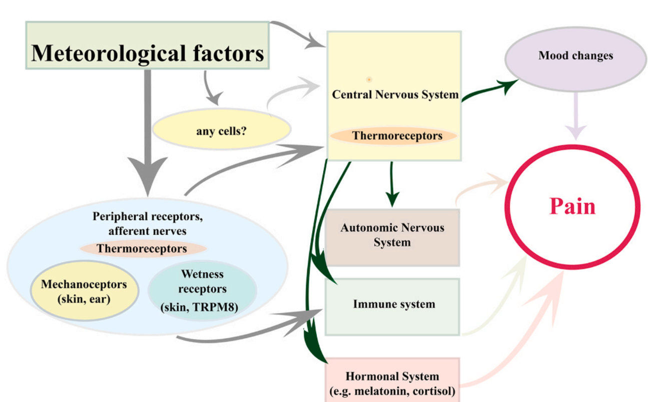

Fig. 1. The possible mechanisms for meteorological factors to influence pain sensation.

4. Possible action mechanisms of weather parameters on pain sensitivity

Concerning the action mechanism of the different environmental factors, some hypotheses and/or data are accessible (Fig. 1). It appears that nociceptive nerve fibers, which are more sensitive in arthritic patients (due to the high level of inflammatory mediators), may be affected by low pressure, stiffness, or small movements influenced by changes in temperature and pressure (Schaible et al., 2009). Thus, fluctuations in atmospheric pressure may impair the joints' structure and change the intracapsular fluid flow, resulting in augmented pain (Wingstrand et al., 1990). It has also been proposed that the cold and damp weather has different effects on the expansion and contraction of different tissue types with diverse densities, which can induce micro-trauma and pain (Wingstrand et al., 1990; Xin et al., 2021). Therefore, the peripheral tissue changes in different weather conditions might be substantial in the action mechanism of meteorological parameters.

Animal studies can offer a good tool to reveal the action mechanisms of different weather parameters, however, only a few studies are available in this respect. Sato's laboratory in Japan demonstrated the significant impact of the meteorological factors on nociception in multiple pain models (Funakubo et al., 2011, 2010; Messlinger et al., 2010; Sato, 2003; Sato et al., 2019, 2011, 1999; Takahashi et al., 2003). They have determined that the low barometric pressure within the natural weather range can elevate the pain sensitivity in neuropathy models (Funakubo et al., 2011; Sato et al., 2011, 1999). Low barometric pressure boosted the activity of neurons that received corneal and dural, but not meningeal, inputs in the trigeminal nucleus caudalis of rats (Messlinger et al., 2010). The possible mechanism that facilitates the occurrence may involve the inner ear, since barometric pressure changes modify the vestibular neuronal activity in the superior vestibular nucleus in a separate neuron group (Sato et al., 2019). It was implied that the pressure changes induced a pressure difference between the perilymph and endolymph inducing the stimulation of the vestibular pathway. While no similar system has been observed in humans, rapid and large pressure changes during diving or flight can induce vertigo (Lundgren and Malm, 1966; Molvaer and Albrektsen, 1988). Since the effect of autonomic nerve activities on nociceptive afferents is well-known, it can be presumed that vestibular neuronal activation influenced by low pressure increases pain via sympathetic nerve activities (Sato, 2003; Sato et al., 2019, 2001). Furthermore, vestibular neural activities projecting to the hypothalamus may induce hormonal changes (Markia et al., 2008), through the modulation of the hypothalamic-pituitary-adrenal axis. Since several chronic-pain conditions are linked to this axis, it can be presumed that hormones of the adrenal cortex have roles in response to low pressure stimulation (Sato, 2003). The circulating hormones (e.g., cortisol, catecholamines) might directly stimulate the peripheral nociceptive fibers and/or induce vasoconstriction, augmenting pain, and enhanced responses in nociceptive fibers (Drummond, 2014; Pertovaara, 2013; Sato and Perl, 1991).

It is well-known that temperature-sensitive ion channels, including transient receptor potential (TRP) ones, are major receptors in the temperature sensitivity both centrally and peripherally. Six temperature-sensitive TRP ion channels are distinguished (Caterina, 2007; Caterina and Pang, 2016). TRPA1 (active below 17 °C) and TRPM8 (active below 28 °C) are the cold sensitive channels, while the heat-sensitive channels are TRPV1 (active above 42 °C), TRPV2 (active above 52 °C), TRPV3 (active between 31 °C-39 °C) and TRPV4 (active between 25 °C-42 °C). It has been revealed that the reduced expression of TRPM8 receptors may hinder the progression of migraine attacks (Gavva et al., 2019). Furthermore, rapid cold stimuli increased the expression of TRPV3, but not TRPV1, TRPV2, TRPV4, TRPA1 and TRPM8 genes in posterior hypothalamic neurons (Kozyreva et al., 2018). However, another study showed that the peripheral TRPA1 receptors contributed to the cold-weather-induced changes in pain sensitivity and articular blood flow during chronic joint inflammation

(Fernandes et al., 2016). Therefore, both the central and peripheral thermosensitive receptors can be implicated in the weather-related pain sensitivity changes.

Regarding the sensation of humidity and wetness, particularly invertebrate insects (but not mammals including humans) have special hygroreceptors for humidity sensation, where humidity changes are remodeled into mechanical and/or thermal cues (Merrick and Filingeri, 2019; Tichy et al., 2017). Alternative strategies for sensing wetness in humans might be a combination of thermal and tactile inputs, but the visual and auditory information is also significant in this aspect (Ackerley et al., 2012). Some recent studies revealed that the TRPM8 receptor might also be a peripheral mediator of human skin wetness perception (Buoite Stella et al., 2022; Rivera et al., 2020; Typolt and Filingeri, 2020). Intriguingly, migraine patients have no disparities in overall thermal sensations, but they reported an increased sensitivity to skin wetness on the forehead area only, where pain attacks occur (Buoite Stella et al., 2022).

The pain sensation may also depend on the weather-related changes in the various syndromes/conditions. Thus, global trends on the occurrence of renal colic and kidney stone diseases seem to be influenced by seasonal variation preferring warmer periods with the stone production inducing to painful attacks (Geraghty et al., 2017). Regarding the gout, it was indicated that the physiochemical changes linked to weather parameters may facilitate the formation of monosodium urate crystals leading to gout flare-ups with pain (Park et al., 2017). Furthermore, the occurrence of intervertebral disc disease emerged more frequently in dogs during colder temperatures (Barandun et al., 2020).

The level of the inflammatory processes can also be influenced by the weather followed by altered pain sensation. Since several types of pain are linked to inflammatory processes, the sensitivity of immune cells to various meteorological factors also might contribute to the observed changes in pain sensitivity (Maes et al., 1994; Maes and De Meyer, 2000). Thus, the activation of skin thermoreceptors may considerably impact the immune responses, including the antigen binding and the antibody production (Kozyreva and Khramova, 2020). Local tissue edema, as an major sign of inflammation, is a key contributor to stiffness and pain, and the degree of edema depending on the weather may also have some role in the enhanced pain. It has been shown that both the low and high ambient temperatures with high relative humidity can boost the expression of different inflammatory substances (e.g., vascular endothelial growth factor; interleukin-1 [IL-1]) in the joints, which augmented the degree of cartilage damage and the pain level in a rat model of RA (Bai et al., 2012). Some hormone levels might also influence the changes in pain sensitivity via the action on the immune system. Thus, melatonin contributes to regulation of both cellular and humoral immunity and its regulatory function varies seasonally (Srinivasan et al., 2008). Melatonin can stimulate the production of natural killer cells, monocytes, leukocytes and the T-helper cells' responses, which increases the production of cytokines such as interleukin IL-2, IL-6, IL-12 and interferon-gamma. This fact may partly account for the melatonin-induced seasonal changes in the pain sensation, primarily in patients with RA.

It is noteworthy that the observed links between meteorological variables and pain tolerance could be due to changes in the state of regions of the brain that are implicated in pain-processing (Cay et al., 2011; Lee et al., 2018; Mizoguchi et al., 2011). The weather might influence people's mental status (including cognition) and mood, thus, the weather changes induced depression could also influence the pain sensitivity (Keller et al., 2005).

Regarding the action mechanisms of space weather on cell functions, the leading factors include solar activity, geomagnetic activity, cosmic ray activity and high energy proton flux (Stoupel, 2015). It is assumed that neutrons at the earth's surface are transforming into protons and they affect the function of different cells in the whole body (Stoupel, 2015). It was presumed that these parameters may also influence psychophysical processes affecting people in different ways depending on their personal sensitivity and health condition. Several studies have highlighted a wide range of influences of solar and geomagnetic field effects on human health and behavior (e.g., heart rate variability or myocardial infarctions), but few data indicate a moderate role of space weather in pain sensation (De Matteis et al., 1994; Kuritzky et al., 1987; Milojević, 2016; Stoupel, 2015; Wahbeh et al., 2021). The examination of heart rate variability indicated that the daily autonomic nervous system activity depended on changes in geomagnetic and solar activity, which lasted over varying time periods (Alabdulgader et al., 2018). A recent study revealed that the pain sensation changes after energy medicine treatment (a branch of integrative medicine that studies the science of therapeutic applications of subtle energies, e.g. Reiki or healing touch) had a mild positive relationship only with the interplanetary magnetic field (Wahbeh et al., 2021).

All living organs are consistently exposed to electromagnetic influences, which differ in amplitude and frequency, too. Sferics are oscillating electromagnetic pulses with low frequency band and intensities caused by distant meteorological events (e.g. thunderstorm) (Panagopoulos and Balmori, 2017). Few data suggested that these pulses may be related to altered pain sensitivity, i.e., correlations were shown between the sferic frequency and migraine attacks (Vaitl et al., 2001; Walach et al., 2001). Regarding the possible action mechanisms of sferics, it is indicated that the electric field can induce changes in membrane potential leading the enhanced permeability to different ions and larger molecules (Cifra et al., 2021; Panagopoulos and Balmori, 2017).

5. Personalized characterization of weather sensitivity

Personalized medicine is a special method for providing treatments that consider the individuals' distinctive physical, genetic and sociodemographic characteristics to apply individually planned treatments with feasible higher efficacy. The high level of interindividual variability in pain sensitivity may be due to differences between age, sex, ethnicity, genetics, and psychosocial variables, but also to the environmental factors, including the weather parameters (Fillingim, 2005). Therefore, the large individual heterogeneity in the weather sensitivity might intricate the characterization of the associations between weather and pain (Smedslund and Hagen, 2011). Only a few reports are available on the detailed individual evaluation of pain responses to meteorological parameters (Edefonti et al., 2012; Smedslund et al., 2009), while some studies clustered the subjects in subgroups based on their response to multiple weather parameters after superficial individual analyses of the data (Table 2) (Bossema et al., 2013; Fagerlund et al., 2019; Gorin et al., 1999; Guedj and Weinberger, 1990; Hollander and Yeostros, 1963; Yimer et al., 2022).

Smedslund et al. (2009) assessed the associations between joint pain in patients with RA ($n = 36$) and a large number (13; see Table 2) of meteorological and solar variables on the same day of the reported pain and one day before. Weather sensitive patients were characterized as one having a great correlation with at least 3 parameters. The bivariate individual analyses yielded several significant relationships in 61% of the patients, but they differed in the variables they responded to and in which direction.

Edefonti et al. (2012) evaluated the individual pain level in 7 patients with chronic masticatory muscle pain procured hourly pain level and three meteorological parameters (temperature, pressure and humidity; Table 2) (Edefonti et al., 2012). While this was a pilot study including only a few subjects, the hourly collection of pain scores presented about 300 pain reports for all patients. The separate generalized least squares regression models demonstrated the high level of disparity in the perception of chronic pain, including the severity and the direction of observed values, therefore, this study also suggested that the effect of one meteorological factor on pain perception depends on other meteorological factors. The outcomes also proved that the weather changes may reliably predict changes in pain perception.

Table 2
Summary of results from studies investigated weather-related pain responses at individual or subgroup levels.

REF	DG	P NR	Age (Y)/ Females (%) DD (Y)	SD (D)/ SFR (NR/ D)/SNR	Data analysis	Pain-related parameters	Obtained weather parameters	Results						
(Hollander and Yeostros, 1963)	RA/ OA	12	ND/ND/ ND	14/4/ ~670	Multivariate REG	CI (joint pain/stiffnes/ analgesic dose): 0–100	TEMP_CH	NS						
							PRESS_CH	NS						
							HUM_CH	NS						
							Ionization_CH	NS						
							HUM↑+PRESS↓	S						
(Guedj and Weinberger, 1990)	RA/ IA/ OA/ FM	62	53/81/ ND	28/1/ ~1750	Univariate analysis/ Multivariate REG	VAS:0–2;	TEMP	**P (%) with S CORR at least 1 WP**						
							PRESS							
							HUM	RA:25; IA:64; OA:83:FM:78						
							PREC							
(Gorin et al., 1999)	RA	75	53/71/9	75/1/ ~5600	Multi-level random effects models	VAS:1–100	**Top 10% with highest sensitivity**							
							TEMP/same day	10 °C ↓= >2.39 mm ↑in pain						
							TEMP/1 day later	10 °C ↓= >2.64 mm ↑ in pain						
(Smedslund et al., 2009)	RA	36	50/69/15	84/1/ ~3000	Time-series analysis/ Autoregressive integrated moving averages/ Exponential smoothing/ Bivariate analysis	VAS 1–100	**P NR with S CORR**				**P % with S CORR at least 1 WP**			
							TEMP	4						
							HUM	2						
							DP. TEMP	4						
							WV PRESS	3						
							PRESS	0			61			
							PREC	7						
							SD	1						
							Cloud cover	4						
							WS	2						
							Sunspot NR	4						
							SRF	5						
							OI	3						
							UV index	7						
(Edefonti et al., 2012)	MP	7	27/100/1	30/12/ ~2100	Descriptive analysis/ GLS REG models	VAS 0–10		**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**
							TEMP						S	S
							PRESS				BL		S	
							HUM	BL			S			
							PRESS/HUM	BL			S			
							TEMP/PRESS						S	S
							TEMP/HUM		S	S			S	S
(Bossema et al., 2013)	FM	333	47/100/4	28/1/ ~9300	Multilevel REG modelling/ CORR	VAS:1–5	**P (%) with different CORR**							
								NO	**Small**		**Middle**		**Large**	
							TEMP	33	54		19		4	
							SD	32	52		14		2	
							PREC	33	50		15		3	
							PRESS	35	42		19		4	
							HUM	28	53		18		2	
(Fagerlund et al., 2019)	FM	48	49/94/ ND	30/3/ ~2700	Histograms/Linear mixed model/CORR	VAS:0–10	TEMP	NS						
							HUM	NS						
							PRESS	Pain↓/↑: 40/8						
(Yimer et al., 2022)	IA/ OA/ FM	6213	49/82/ ND	106/1/ ~660 000	Multilevel orbital probit model	VAS:1–5	**P (%) with different sensitivity**							
								NO		**low**		**high**		
							TEMP	6		5		89		
							PRESS	2		1		97		
							HUM	1		3		96		
							WS	1		2		97		

Abbreviations: BL:borderline; CH:changes; CI: clinical index; CORR: correlation; D: day; DD: disease duration; DG: diagnose;DP TEMP: dew point temperature; FM: fibromyalgia; FR: frequency; GLS: generalized least squares; HUM: relative humidity; IA: intflammatory arthritis; MP: myofascial pain; ND:no data; NO: no effects; NR: number; NS: non significant; OA:osteoarthritis; OI:oscillation index; P: patient; PREC: precipitation; PRESS: atmospheric pressure; RA: rheumatoid arthritis; REG: regression; S: significant; SD:sunshine duration; SDs: sampling duration; SNR: sample number; SFR: sampling frequency; SRF: solar radio flux; TEMP: tempreratrure; UD:undetermined;VAS: visual analog scale; WP: weather parameter; WS: wind speed; WV PRESS: water vapor pressure; Y: year.

Some studies, outlined below, explored subgroups' sensitivity to the weather, with some degree of individual analysis as well. A very special experiment was conducted with 12 arthritic patients by Hollander and Yeostros in 1960 s (Hollander and Yeostros, 1963). It was shown in a climate chamber that pain-related signs increased greatly after rising humidity together with falling pressure, and the symptoms subsided when baseline climatic conditions were resumed (Table 2). The individual analysis of the RA patients revealed that seven of the eight subjects presented significant worsening of arthritis within a few hours after the onset of humidity rise with barometric fall in more than 50% of exposures to the combined cycles. Guedj and Weinberger (1990) disclosed the pain sensitivity of 62 patients with different forms of arthritis (Guedj and Weinberger, 1990). 25% of patients with RA, 83% with OA, 77% with FM, and 64% with inflammatory arthritis were sensitive to at least on one weather condition that altered the pain score. Gorin et al. (1999) evaluated RA patients (n = 62) at the group and individual levels for 75 consecutive days using a time-series methodology to contrast pain diaries with weather data (Gorin et al., 1999). Significant variability between patients in their weather sensitivity patterns was found, but even in patients with higher levels of pain showed more weather sensitivity (top 10% of patients), the weather variables accounted for only a small amount of change in pain scores (Table 2). The multilevel modeling technique using Pearson correlation was applied by Bossema et al. in 333 patients with FM on 28 consecutive days (Bossema et al., 2013). The patients were clustered in subgroups based on their correlation coefficients, i.e., correlation coefficients above the absolute values of 0.10, 0.30 and 0.50 were deemed to be small, moderate and large, respectively. In 20% of analyses, great differences between patients were found in the random effects of the weather variables, indicating that the symptoms of patients were, to a minimal extent, differentially influenced by some weather conditions. Significant small random effects of temperature levels on the same and prior days, of atmospheric pressure levels on the same day, of precipitation on the previous day, and of relative humidity levels on the same and previous days were discovered. Pain levels were negatively linked to a change in the sunshine, but positively associated with a change in relative humidity. For each weather-symptom combination, an equal number of patients had positive, negative or absent associations between the weather variable and the symptom. It was contended that the individual differences were not significant connection neither with demographic, functional or mental patient characteristics, nor by season or weather variation during the assessment period. The largely negative outcomes resulted in the conclusion that there is no support for or indication of, patients' characteristics explaining patient-specific influences of weather on daily symptoms of pain in patients with FM. Fagerlund et al. (2019) assessed individual differences in weather sensitivity (temperature, pressure and humidity) using a multilevel modeling framework in patients ($n = 48$) with FM, but the comprehensive analyses were conducted in two subgroups (Fagerlund et al., 2019). Both pressure and humidity had great impacts on the individual slopes for pain reports with 83% of patients reporting less pain with increased pressure, and this subgroup had no stress level changes parallel with increased pressure, whereas the subgroup with the opposite response to pressure reported increased stress when pressure was elevated. This outcome implies that individual factors in emotional status may be associated with responsiveness to changes in barometric pressure. The latest analysis of 6850 participants with chronic pain (Yimer et al., 2022) examined the possible connections between pain and weather parameters (temperature, atmospheric pressure and relative humidity, wind speed). Comparable to other studies, only a modest association was found between the weather and pain at the population level. To exposure effect heterogeneity of the patients, the participant-level weather-pain associations were identified, and the patients were clustered in three groups for each of the weather parameters: 2 distinct group (low-value or high-value sensitive, respectively) differed significantly, and a third group (undetermined) of participants who did not vary substantially from the members of the 2 distinct clusters. Most of the participants belonged to the undetermined cluster for all weather parameters, however, it was presumed that the lack of significance does not mean the absence of a connection. The size of the low- and high-value sensitive clusters varied by weather parameters. For example, there was a comparable proportion of participants for whom relatively lower temperature was linked to a higher level of pain (6.3%), as there were participants (4.7%) for whom the higher temperature was associated with an increase in their pain, resulting in a very modest overall effect of temperature. However, more participants (2.9% for relative humidity and 2.2% for wind speed) were sensitive to higher values of these weather parameters than to lower values (0.6% for both parameters). Similarly, proportionally more participants (1.6%) wee sensitive to low pressure than high pressure (0.7%). In summary, most of the participants (72.5%) categorized as weather sensitive possessed sensitivity to a single weather parameter with highly distinct degree and direction.

All these data indicate that given the large difference in the personal sensitivity to the meteorological parameters, the connection between weather and pain may have clinical relevance at the individual level. The weak correlations at the population level might be, at least partially, due to the sensitivity of subjects with opposite directions, however, the different level and or kind pain states may also contribute to this phenomenon.

6. Conclusions

In conclusion, the present study sought to claim the significance of the intensive evaluation of the impact of weather parameters on pain sensitivity, as an important factor of variation in pain states. The combinations of many mechanisms can outline the variations in weather associated pain sensitivity with a high level of individual differences, however, only a few studies examined the potential molecular action mechanisms of this phenomenon. This paper highlights the significance of undertaking in vivo and in vitro experiments to reveal the exact mechanisms of associations between pain and weather parameters, even at the individual level, too. Individual variation in sensitivity to weather parameters can influence vulnerability to different diseases and reactions to treatments, as well. It is presumed that during the treatment of several pain syndromes, effective recommendations and warnings about weather conditions can be made. This information can help patients with different pain states to regulate their daily living activities and can aid physicians to implement more valuable treatments with low levels of side effects for patients when the weather conditions change.

Declaration of Competing Interest

All of the authors claim that there's no financial/personal interest or belief that could affect our objectivity.

Data availability

No data was used for the research described in the article.

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