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US ASSOCIATION FOR THE STUDY OF PAIN

PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 22, No 5 (May), 2021: pp 473–486
Available online at www.jpain.org and www.sciencedirect.com

Critical Review

A Systematic Review Into the Influence of Temperature on Fibromyalgia Pain: Meteorological Studies and Quantitative Sensory Testing

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Abstract: **Fibromyalgia syndrome (FMS) is a chronic widespread pain condition of unknown aetiology. The role of temperature in FMS pain has not been reviewed systematically. The goal of this study was to review the influences of temperature on pain in FMS, from meteorological and quantitative sensory testing (QST) studies.**

The review was registered with Prospero: ID-CRD42020167687, and followed PRISMA guidance. Databases interrogated were: MEDLINE (via OVID), EMBASE, PubMed, Web of Science, ScienceDirect, CINAHL, and ProQuest (Feb'20). Exclusion criteria were: age <18, animal studies, non-English, and noncontrolled articles.

Thirteen studies pertaining to ambient temperature and FMS pain were identified; 9 of these found no uniform relationship. Thirty-five QST studies were identified, 17 of which assessed cold pain thresholds (CPTs). All studies showed numerically reduced CPTs in patients, ranging from 10.9°C to 26.3°C versus 5.9°C to 13.5°C in controls; this was statistically significant in 14/17. Other thermal thresholds were often abnormal.

We conclude that the literature provides consistent evidence for an abnormal sensitization of FMS patients' temperature-sensation systems. Additional work is required to elucidate the factors that determine why a subgroup of patients perceive low ambient temperatures as painful, and to characterize that group.

Perspective: ***Patients often report increased pain with changes in ambient temperature; even disabling, extreme temperature sensitivity in winter. Understanding this phenomenon may help clinicians provide reassurance and advice to patients and may guide research into the everyday impact of such hypersensitivity, whilst directing future work into the pathophysiology of FMS.***

Key words: *Fibromyalgia, pain, temperature, quantitative sensory testing, meteorological observational studies.*

Background

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition of uncertain aetiology and may be viewed as pain state with central amplification.[13,14,74] However, there is also mounting evidence of peripheral abnormalities including small fiber polyneuropathy with abnormal nociceptor function,[25,33,51,73] abnormal thermoregulatory peripheral innervations,[1] and even peripherally binding pain-sensitizing IgG autoantibodies.[31] FMS is characterized

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflicts of interest: The authors have no conflicts of interest to disclose.
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1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2020.12.005

by widespread pain and a constellation of other symptoms, most markedly fatigue, sleep disturbance and cognitive problems.[14,90] Prevalence is estimated at 2% worldwide with a strong female preponderance.[7] Symptom intensity fluctuates on a daily basis, as well as over weeks, months, and years.[3,87]

In our clinical experience, many patients report increased pain when ambient temperatures fall, and even disabling extreme temperature sensitivity through winter,[54] resulting in increased use and costs of household heating. In summer, symptoms improve. These prominent clinical observations suggest a profound effect of ambient temperature on spontaneous or evoked FMS pain, highlighting a potential target for clinical intervention and social support. To our knowledge, however, temperature sensitivity in FMS, either in relation to ambient temperature or experimental skin stimuli, has not been systematically compiled.

Historically, *weather* has been highlighted as a significant aggravating factor in the pain experienced by FMS patients[4,10,71,92] with 25% of patients reporting symptom flares secondary to fluctuations thereof.[86] However, as with a number of rheumatological conditions, study results have been conflicting.[18,34,56,72]

Independently, the observation that FMS patients display *experimental* hypersensitivity to sensory stimuli, both noxious and innocuous, is well-established.[12] Skin sensory profiles can be interrogated through quantitative sensory testing (QST), whereby a quantifiable skin stimulus is used to measure perception. Sensory and pain perception thresholds ("when can I feel the stimulus" or "when does it become painful," respectively) to stimulus modalities may thus be determined.[2]

The theory of abnormal temperature regulation leading to pain[1,25] provides a potential link between temperature-sensing and pain. Aberrations in temperature sensation may be amplified through a dysfunctional thermoregulatory system, such as the arteriolar venous shunt (AVS),[1] leading to further tissue hypoxia and pain. In this systematic review, therefore, we aim to assimilate the current literature focusing on the role of temperature as a factor affecting spontaneous or stimulus-evoked pain in FMS. We investigate both meteorological studies assessing temperature as a solitary factor, and studies involving thermal QST to assess whether abnormalities in temperature-sensing explain this clinical phenomenon.

Methods

Search Strategy

An electronic literature systematic review was performed in accordance with the PRISMA guidelines,[57] to answer the question: "do adult patients with FMS show increased pain in response to changes in ambient temperature?" The systematic review was registered on PROSPERO (CRD: 42020167687). The review was performed in 2 parts. In Part 1, studies examining the influence of meteorological temperature on pain intensity were identified; and then in Part 2, QST studies examining the thermal sensitivity thresholds in FMS were identified. The primary outcome in Part 1 was to find evidence of a relationship between ambient temperature and pain in patients with FMS, measured through differences in mean pain scores or qualitative review. In Part 2, the primary outcome was to find evidence of a difference in the thermal thresholds in patients with FMS, compared to healthy participants, measured through differences in warmth detection threshold, cold detection threshold (CDT), heat pain threshold (HPT), or cold pain threshold (CPT), in °C or z-scores. Databases interrogated were: MEDLINE (via OVID), EMBASE (via Scopus), PubMed, Web of Science, ScienceDirect, CINAHL, and ProQuest. The searches were limited to the English language from inception and conducted in February 2020.

Search terms were developed iteratively and approved by senior author A.G. Searches were conducted by R.B. For Part 1, search terms included: "(fibromyalgia **OR** fibromyositis **OR** fibrositis **OR** muscular rheumatism **OR** chronic widespread pain **OR** CWP) **AND** (temperature **OR** ambient **OR** weather **OR** meteorological) **AND** (pain **OR** tenderness **OR** tender point count **OR** VAS)." For Part 2, search terms included: "(fibromyalgia **OR** fibromyositis **OR** fibrositis **OR** muscular rheumatism **OR** chronic widespread pain **OR** CWP) **AND** quantitative sensory testing **OR** QST **OR** thermal **OR** thresholds **OR** cold **OR** heat." All the search results were combined using Endnote and duplicates were removed by R.B. Reference lists of the primary and secondary literature were manually browsed to identify any additional studies.

Inclusion and Exclusion Criteria

Studies were included that: 1) related ambient temperature to pain (ie, Part 1) or assessed thermal thresholds from QST (ie, Part 2); 2) confirmed diagnosis with the then current diagnostic criteria (Smythe,[77] Yunus,[94] American College of Rheumatology [ACR][90,91,93]); and 3) were reported as full-text publications. Studies were excluded if they: 1) were not in humans, 2) were not in adults aged >18 years, 3) were not reported in English, and 4) did not have a QST control population (Part 2 only). There were no publication cut-off dates to capture all relevant literature.

All article titles and abstracts were then screened by two reviewers (R.B. and S.S.) independently, and articles meeting the inclusion criteria were selected for full-text analysis. Irrelevant articles were then removed following screening and a shortlist of articles was compiled for full-text eligibility analysis. Full-texts were obtained and R.B. and S.S. decided whether to include or exclude articles via consensus with input from senior author A.G. The selection and screening process is detailed in Fig 1.

Data Extraction and Quality Assessment

Study characteristics, methodology data and results from studies were extracted independently by R.B. and S.S. Extraction of the first author, study name and country, sample size, age, sex, diagnostic criteria used, and

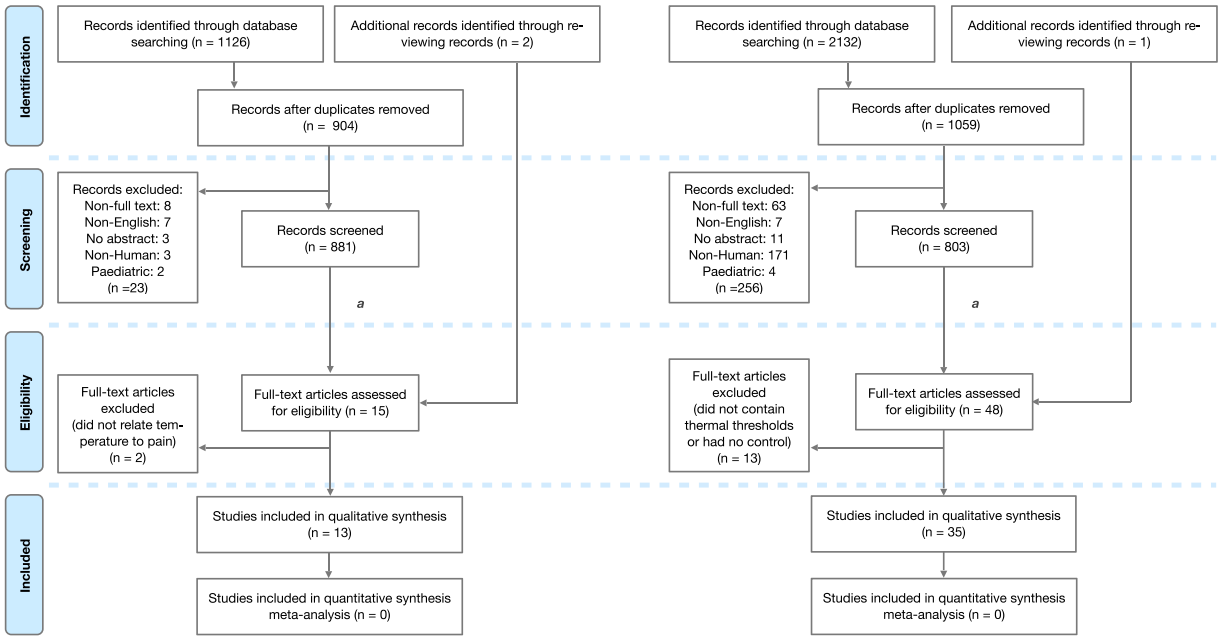

Figure 1. Study protocol: (a) Observational studies, (b) Quantitive sensory testing. The Prisma guidelines were adhered to for the search protocol design. The full study protocol is published on Prospero: (CRD:42020167687). [a]Studies excluded between screening and eligibility stages were deemed irrelevant to the research question by 2 reviewers (R.B. and S.S.), independently, based on the criteria set out in the study protocol.

results (correlation between temperature and pain or thermal thresholds) with significance values were obtained independently, and confirmed. Where relevant, study temperature ranges and method of QST measurement were also obtained.

The articles were appraised by risk of bias tools to address their external and internal validity. Independently, R.B. and S.S. appraised each article with tools for prevalence (Hoy et al)[36] and case control/cohort studies (Newcastle Ottawa Scale)[88] This was overseen by A.G. For prevalence studies (most studies in Part 1) the Hoy et al tool was used, which comprises of 10 questions mandating a "yes" or "no" answer. A point was given for each "yes" and a total score between 0 and 3 was considered low risk, 4 to 6 was moderate risk and 7 was high risk of bias. The QST studies were assessed with the Newcastle Ottawa Scale which again assigns points for section, comparability, and exposure/outcome to a maximum of 9. A score of 0 to 3 is considered very high risk, 4 to 6 high risk, and >6 low risk. As a meta-analysis was not conducted, the authors chose not to exclude the few potentially biased studies from the review, but all of these studies (which did not score as low risk of bias by one or both reviewers [R.B., S.S.]), are clearly noted in the review and scores are available in the supplementary tables. Any discrepancies in the risk of bias were put forward to the senior author A.G.

Statistical Analysis

A formal meta-analysis was not performed due to the small study numbers and heterogeneity of the studies in terms of study protocols and form of data. The results are presented descriptively with the use of simple statistical analysis for a narrative synthesis.

Results

Part 1: Pain and Meteorological Studies

Patients Report a Temperature Influence

Studies investigating patient reported symptoms often present a positive influence of temperature on pain (Table 1). Three self-reported symptom studies associate pain with temperature[23,35,93,94] (Fig 2). Temperature-dependent pain intensity was first highlighted by Yunus et al, who reported that 92% of patients (n = 50) found their symptoms were aggravated by "cold or humid" weather[94] using Smythe's[77] criteria. Wolfe et al then showed that cold, as a "modulating factor" in FMS symptomatology, was 79.3% sensitive but only 52.5% specific, for detecting FMS, suggesting cold sensitivity was widely experienced but poorly diagnostic.[93] Delir Haghighi and colleagues took an original approach invoking big data. In a worldwide Twitter analysis, evidence of a very weak negative correlation between ambient temperature and negative "sentiment scores," indicative of symptoms such as pain, was found in California (Pearson rank correlation coefficient: −.062; $P < .001$, n = 5,149).[23] Over all 140,432 tweets there was no uniform trend, however.

Observational Meteorological Studies Find Little Evidence of a Uniform Correlation Between Pain and Temperature

The majority of these studies find no uniform correlation between reported pain and meteorological temperature. Three early studies from the Netherlands, Israel and the USA have failed to demonstrate an association between FMS pain intensity and meteorological

Table 1. Observational Studies Into FMS Pain and Meteorological Temperature

Author	Year	Location	FMS:HC	Female/Male	Temperature mean ± SD (range)	Diganosis of FMS*	Result	Bias	
Yunus et al[94]	1981	North America	50:50	43/7	NA	Smythe [77]	*92% of patients reported aggravation of symptoms by cold/humid weather.*	3/10 (H)	4/10
Wolfe et al[93]	1990	North America	293:265	260/33	NA	"Clinician's method"	*Patients reported cold as a modulating factor of symptoms. This discriminator was 79.3% sensitive and 52.5% specific for diagnosing FMS.*	7/9 (N)	6/9
Guedj et al[34]	1990	Israel	11:0	Not disclosed	(8.0°C−27.0°C)	Yunus[94]	*No significant association found using ($P < .05$) between morning pain score (0 = no pain, 1 = pain, 2 = extreme pain) and meteorological temperature.*	6/10 (H)	6/10 ¶
de Blécourt et al[17]	1993	Netherlands	32:0	24/3	6.2°C (−9.0 to 15.0°C)	Yunus[94]	*Mean temperatures from local meteorological stations did not correlate with daily pain score in patients reporting weather sensitive symptoms.*	4/10 (H)	6/10 e
Hagglund et al[35]	1994	North America	84:0	Not disclosed	Not disclosed	Yunus[94]	*88% reported temperature affected pain, but no correlation was found between myalgic score‡ and tender point count (as per ACR 1990) and mean pain scores on Wednesdays at 12 noon.*	5/10 (H)	5/10 ¶
Strusberg et al[81]	2002	Argentina	17:32	17/0	Not disclosed	ACR[93]	*In patients with FMS, spontaneous daily pain was negatively correlated with temperature ($r = -.255$; $P < .001$).*	5/9 (N)	6/9
Fors et al[28]	2002	Norway	55:0	55/0	Not disclosed	ACR[93]	*Single weather variables (including temperature), or various composite weather parameters were not predictors of spontaneous pain measured on a 0 to 100 VAS at 2 PM daily.*	3/10 (H)	4/10
Macfarlane et al[54]	2010	UK	381:0	1462/1020	Not disclosed	Self reported CWP as per ACR[93]	*Survey respondents completing the form ($n = 2,761$) on a day with an average temperature >17.5°C were significantly less likely to report 'pain today' (PR = .74, 95% CI: .66, .83) or CWP (PR = .40, 95% CI: .34, .48) compared with those who completed the questionnaire on days with an average temperature of <5°C. Even after adjusting for exercise frequency, sleep problems and levels of reported monotony 'pain today' and CWP relationships were remained, with a lower likelihood of pain on high-temperature days (>17.5°C; PR = .86, 95% CI: .77, .97 and PR = .57, 95% CI: .48, .69, respectively.*	2/10 (H)	3/10

(continued on next page)

Table 1. Continued

Author	Year	Location	FMS:HC	Female/Male	Temperature mean ± SD (range)	Diganosis of FMS*	Result	Bias		
Bossema et al[8]	2013	Netherlands	333:0	333/0	13.7°C ± 4.4°C	ACR[90]	*Multilevel regression modelling was employed to identify subgroups of patients based on pain levels and temperature. Groups were defined by Pearson correlation coefficients large (>.5), moderate (>.3), small (>.1) or very small (<.1). They found a spread of correlations both positive and negative, which the authors attribute to a heterogeneity in temperature sensitivity, possibly accounting for the lack of overall association.*	2/10 (H)	4/10	
Smedslund et al[75]	2014	Norway	42:0	42/0	Not disclosed	ACR[93]	*No association found between meteorological temperature and pain scores or psychological variables.*	4/10 (H)	5/10	¶
Kim et al[43]	2016	North America	67:0	67/0	Not disclosed	ACR[93]	*No significant effect of meteorological temperature (measured between 5 and 7 PM) on fibromyalgia symptoms with FIQR and BPI using ANCOVA.*	4/10 (H)	5/10 (H)	¶
DelirHaghighi et al[23]	2017	Worldwide	140,432:0	Not disclosed	NA	Self nominated: #fibromyalgia, #fibro, & #spoonie †	*Tweets from California (n = 5,149) indicated a negative correlation between local meteorological temperature and negative sentiment scores§ (Pearson correlation coefficient: −.062, P < .001). No correlation from other regions with 1,000+ tweets (Colorado, Florida, Georgia, Minnesota, New York, Ohio, and Texas). No overall association.*	5/10 (H)	7/10	¶
Fagerlund et al[27]	2019	Norway	48:0	45/3	−1.9°C ± 5.0°C (−18.2 to 27.4°C)	ACR[90]	*Temperature was not correlated with pain intensity unpleasantness or affective measures.*	3/10 (H)	4/10	

Abbreviations: PR, prevalence ratio; CWR, chronic widespread pain, BPI, Brief Pain Inventory; FIQR, Fibromyalgia Impact Questionnaire revised.
Meteorological studies identified in Part 1 of the search protocol. Bias scores from 2 independent reviewers included where (H) indicates a prevalence tool[36] (high risk for bias: >4−6/10) and (N) indicates The Newcastle Ottawa Scale[88] (high risk for bias: <5/9).
*See Supplemental Figure S1 for the diagnostic criteria.
†The term "spoonie" is used commonly in tweets referring to both FMS and other chronic illnesses associated with prominent fatigue. It derives from the inability of the individual to carry out daily tasks.
‡"Myalgic score" is a summation of dolometric values 0 to 9 at 6 sites on the right body side. The score ranges from 0−54.
§"Sentiment" is a computer generated entity derived from textual analysis using an opinion lexicon. It takes account of positive, neutral and negative terms and phrases. A negative score is indicative of negative statements, which the authors attribute to severe symptoms, such as pain.
¶Indicates authors deemed overall high risk of bias.

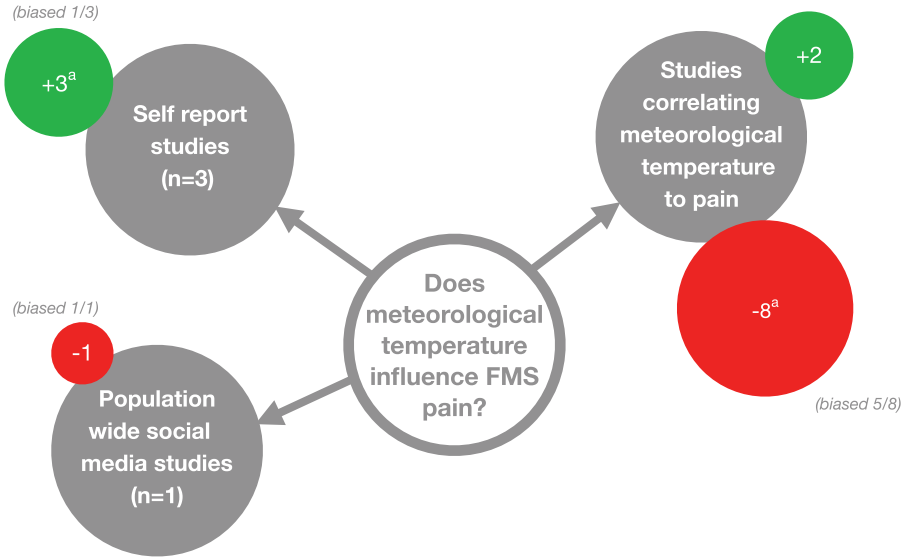

Figure 2. Does ambient temperature influence FMS pain? The green circles represent supportive studies that find a correlation and the red circles represent those that found no correlation. The area of the circle is proportional to the number of studies not the size of studies. One study (Hagglund et al[35]) has been included twice because it presented both self-reported relationships and meteorological correlations). Six of 9 of the negative studies are at risk of bias compared to 1/5 studies in support of an association (see Table 1).

temperature using Yunus criteria.[17,34,35] These were hampered, however, by a high drop out rate (73/135)[34] and (17/50),[17] limited data collection (recruitment day only)[35] and failure to stratify for self-reported temperature influence.[34,35] More recently, 2 Norwegian studies[28,75] were again unable to correlate these parameters using American College of Rheumatology 1990 criteria.[93] Again, these studies did not stratify for patient reported temperature sensitivity; one measured pain daily at 2 PM when symptoms may not be representative of the average[28] and one thrice daily via a web-based diary without record of indoor periods.[75] Interestingly, a larger study by Bossema et al, looking at 333 women with FMS, identified subgroups of patients with significant air temperature-related pain symptoms over a 28 day period with a multilevel regression analysis,[8] although they found no uniform trend. Measuring using the Brief Pain Inventory, Kim et al were unable to identify a link between symptoms and meteorological temperature, although the drop out rate was high (37/67) and temperature measurement was noncontemporaneous (5–7 PM).[43] Recently, Fagerlund et al were also unable to identify a uniform correlation between meteorological temperature and either pain intensity or affective measures; contesting the authors' hypothesis that mood states (eg, depression) are affected by weather and then, in turn, modulate pain intensity.[27]

Evidence of an association between temperature and FMS pain comes from three observational studies.[8,54,81] A prospective single-blinded Argentinean study, found a negative correlation between daily pain scores and local meteorological data (*increased pain in low temperatures*).[81] This study was conducted in a Mediterranean climate (Northern Argentina). The authors argue that this resulted in fewer discrepancies between true temperature exposure (co-influenced by indoor conditions) and external conditions: a particular issue in maritime and cold climates. Their study size was, however, small (n = 17). The substantial UK EpiFunD study (n = 2,596),[54] also makes an association between low meteorological temperatures and both FMS pain and immediate pain. Survey respondents completing the form on a day with an average temperature of at least 17.5°C were significantly less likely to report "pain today" (prevalence ratio: .74, 95% CI: .66–.83) or chronic widespread pain (prevalence ratio: .40, 95% CI: .34–.48) compared with those who completed the questionnaire on days with an average temperature of <5.0° C. Even after adjusting for exercise frequency, sleep problems, and levels of reported "monotony" this trend remained significant.

Part 2: Thermal QST

Reduced CPT

The CPT is the temperature from below which a cold stimulus to the skin is perceived as painful. Patients reporting increased pain to ambient cold, might be expected to have a diminished (termed "*reduced*") CPT (*ie, need a smaller temperature change for a cold stimulus to be perceived as painful, compared to controls*). We identified 20 QST studies measuring CPTs (Supplementary Table S1) but 2 study populations were shared between 5,[37,68,69,82,83] so these were included only once [37,83] giving 17 distinct study populations. All studies indicate numerically lower CPTs in FMS versus controls, and in 14/17 (82%) the difference is statistically significant, indicating cold pain hypersensitivity.[5,6,15,24,26,30,37,42,45,46,64,65,76,83] The CPT data is plotted in Fig 3 to convey the spread of CPTs which ranged between 10.9°C and 26.3°C and 5.9°C to 13.5°C, in controls. Taken together, the evidence from QST indicates unambiguously that cold-pain sensitivity in FMS is increased (ie, diminished CPTs).

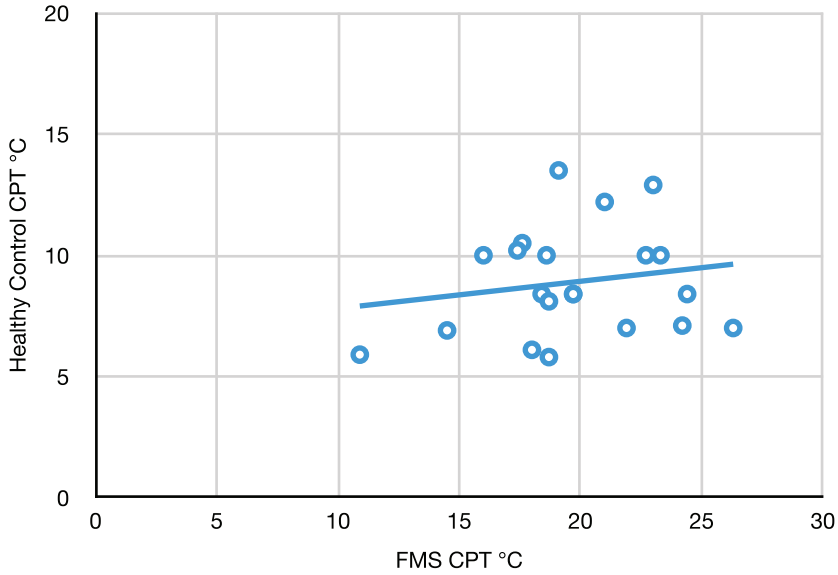

Figure 3. Scatter plot of QST study CPTs FMS vs HC. Fibromyalgia syndrome (FMS) cold pain thresholds (CPTs) range between 10.9°C to 26.3°C vs 5.9°C to 13.5°C, in healthy controls. Note: of the 15/18 studies that found a significant reduction in CPTs, data for only 13 were available. Only 10 of these are distinct populations. There are 21 data points as some studies measured multiple regions, or analyzed the same population. Data can be seen in Supplemental Table S1.

Reduced HPT

The HPT represents the temperature upwards from which a thermal stimulus is felt as *painfully* hot. A *diminished* HPT represents increased sensitivity to heat (*ie, feeling heat pain from a lower temperature*). We analyzed the QST evidence of altered HPTs in FMS. Thirty-three studies assessed the HPT,[5,6,9,11,15,20,24,26,29,30,37,42,44-46,49,50,52,59,62-69,76,78,82,83,85,89] 5 sharing 2 study populations.[37,68,69,82,83] Of the distinct study populations, 23/30 (77%) reported a statistically significantly lower threshold in FMS than controls (heat pain hypersensitivity).[5,6,9,15,20,24,29,30,37,42,45,46,49,50,52,59,62,63,65-67,76,83] For others there was a nonsignificant trend toward a numerical reduction (Supplementary Table S2).[11,26,44,64,85]

Unchanged CDTs

The CDT is the temperature at which a person can detect a stimulus as being innocuous cold. Pain severity is closely related to CDTs in other chronic pain conditions, such as diabetic neuropathy.[47] We hypothesized that FMS patients were hypersensitive to non-noxious cold stimuli (which is commonly termed "gain of function"[2]) and felt cold at temperatures below the HCs due to feeling tense. We investigated, therefore, the CDTs within the identified QST studies (Supplementary Table S2). Twelve out of 17 studies (70.6%) found that the CDTs were statistically unchanged compared to healthy controls.[5,6,15,19,24,26,30,37,44,45,64,83] Five (29.4%) found that they were significantly different.[16,46,49,65,85] They were elevated in three[16,65,85] (*ie, requiring a greater cold stimulus, from baseline, to feel cold*), termed hyposensitivity, and reduced in two[46,49] termed hypersensitivity. Although rarely noted in the above studies, CDTs are approximately 30°C.[24,49,65]

Heterogeneity in the FMS Population

A bimodal frequency distribution of CPTs was first demonstrated by Kosek et al Measuring over painful regions, they found most patients fell into 2 groups: 10°C to 14.9°C, (3/10) and 25°C to 25.9°C, (5/10).[45] Further studies have noted this. Hurtig et al[37] identified 2 subgroups of FMS patients based on HPTs and CPTs using nonhierarchical regression analysis (K-means algorithm).[37] Subgroup One (CPT: 13.6°C, HPT: 44.1°C, n = 11; distinguished from HC by CPTs [$P < .05$]) was less sensitive to thermal stimuli than Subgroup Two (CPT: 23.5°C, HPT: 39.2°C, n = 18); distinguished from HC by CPTs and HPTs ($P < .0001$). Regression analysis elucidated that: hand pain intensities (a surrogate for background pain levels), tender point score, and sleep quality were significant regressors, with Subgroup Two being more sensitive. A cluster analysis by the same group[68] in the same cohort saw the more sensitive group (CPT: 23.1°C, HPT: 39.1°C; n = 20) differed from the less sensitive group (CPT: 12.6°C, HPT: 43.4°C; n = 12) in psychometric coping measures with the sensitive group more "confrontative" in stress-coping and "attention diverting" in pain-coping. In the same population, they found differences in thermal thresholds in high versus low global pain groups.[69] Tampin et al confirmed that patients reporting regional temperature sensitivity on "painDetect" were indeed more cold pain hypersensitive (diminished CPTs).[82]

Risk of Bias

Six of the 13 meteorological studies were deemed to have a high risk of bias.[17,23,34,35,43,75] This was usually due to the selection of participants for none generalizable populations, the exclusion of males, and the lack of independent verification of diagnosis. Of the QST studies, 10/35 (28.6%) were noted to be of high risk of bias

(4−6/9) for the same reasons.[6,19,29,30,42,44,46,68,69,85] None were deemed very high risk of bias.

Discussion

We conducted a systematic review of the literature regarding temperature sensitivity in patients with FMS finding inconsistent evidence from meteorological studies of increased pain in the cold, but consistent evidence from psycho-physical studies, that patients are hypersensitive to cold pain.

Both anecdotal clinical experience and epidemiological evidence[54] suggest that FMS patients find low ambient temperatures aggravate their pain. Such observations are supported by the results from early studies assessing patient-reported outcomes[35,93,94]; however, we found that observational studies interrogating the relationship between meteorological temperatures and pain inventories provide no consistent evidence of a relationship between ambient temperature and pain intensity.[17,27,28,34,35,43,75] In contrast, QST studies consistently indicate heightened thermal sensitivities in FMS, most impressively for the perception of pain with the application of cold skin stimuli (Fig 3, Supplemental Table S1). Skin HPTs are also often *diminished* in FMS[5,6,9,15,20,24,29,30,37,42,45,46,49,50,52,59,62,63,65-69,76,82,83] (*ie, patients perceive heat as painful at lower temperatures)* indicating "heat-pain hypersensitivity"; here, differences compared to healthy subjects are smaller and the shift occurs at 40°C to 50°C, above the usual ambient temperatures in temperate climates These changes we assume to be less relevant to patients' day-to-day experiences for this reason; studies in tropical climates would be needed to examine this.

Meteorological studies correlate weather variables against patients' spontaneous pain intensities, whereas QST studies correlate distinct skin stimuli with patients' sensory perceptions. The incongruence between these results may, of course, be explained in part by study limitations.

With regards to meteorological studies, we suggest that the existing research may not provide a reliable means of elucidating whether ambient temperature affects FMS pain, due to a number of limitations (listed below); this is also born out by the high risk of bias noted in these studies.[17,23,34,35,43,75]

1. There are basic methodological limitations of studies using meteorological data which, by necessity, neglect compensation measures, such as artificial heating and clothing, which present significant confounders in cold temperate climes.
2. There are limitations due to variabilities between these existing studies; including: the examined patient cohorts (geographical or genetical dissimilarities and gender discrepancies), study-parameters such as diagnostic criteria (eg, American College of Rheumatology 1990[93]/2010[90]: see Supplemental Fig S1) typical temperature ranges in the studied areas (eg, −18.2°C to 27.4°C)[27] and study designs, with some relying on patient-recall[93,94] and others local meteorological station data (Tables 1 and S3).[8,17,27,28,34,35,54,75,81] Other meteorological parameters such as barometric pressure, relative humidity, and wind speed are additional potential confounders which can be challenging to control for. It is also likely that there are genetically determined temperature sensitivities, which would further confound comparison of studies. For example, cold sensing is primarily determined by the transient receptor potential melastatin member 8 (TRPM8) calcium channel. The TRPM8 allele frequency differs globally (5%−88%)[53] and thus genetic heterogeneity between studies, conducted in different countries, is likely important. There are also confounders such as psychosocial stress[15] which are currently unmeasured and, therefore, do not allow fair study comparison.
3. Most studies are too small to permit robust conclusions. Due to high attrition (see bias analysis), many observational meteorological studies may have suffered attrition-bias. Interestingly, however, we note that the second largest study (n > 300) by MacFarlane et al[54] does find a temperature pain association. Although it must be noted that the largest by Delir Haghighi[23] did not. This latter study was somewhat hampered by a loose approach to inclusion criteria and the inherent confounders of a global Twitter analysis.

With regards to QST studies, these, too, are not without flaws. Some QST studies were deemed of high risk of bias[6,19,29,30,42,44,46,68,69,85] though none were deemed very high risk of bias.

1. Lautenbacher et al highlighted that pain thresholds, as elicited by brief noxious stimuli, are an over-reduction of the endogenous pain network and, therefore, conclusions from such data should be guarded.[49]
2. Differences in study protocols, particularly around: the stimulus ramping protocol, device type and location, contact area and the measurement of QST parameters, all vary between different QST protocols (Supplementary Table S1). Measuring thermal thresholds with a superficial temperature probe is also imprecise; only the most superficial skin nerve endings receive the measured thermode temperature and afferent perception will be dependent upon both technical factors and spatial arrangement of nerve endings.
3. Furthermore, there are confounding factors altering the CPT, such as serotonergic medication, co-morbid depression,[39,55,76] or stress; for example: Crettaz et al found psychosocial stress reduced CPT by ∼2°C.[15]

At first sight, the robust cold pain hyperalgesia demonstrated by the QST studies appears to be consistent with the phenomenon of increased spontaneous pain in cold conditions, as reported by FMS patients. A fall in ambient temperature may induce skin nociceptive afferents to discharge when skin

temperature drops below the CPT. In humans, exposure to a cool ambient temperature, indeed, results in a fall in peripheral skin temperature. For example, an ambient temperature of 15°C induces a skin temperature of 30.1°C, and a core temperature of 36.3°C.[80] However, almost all of the reviewed FMS studies report patient CPT values <25°C (Fig 3) indicating that a more significant fall in ambient temperature (eg, *<15°C*) may be required to generate pain-signaling by skin afferents. Further, temperature drops in central body compartments are so small that a patient's report of increased *deep pain* in cold environments is unlikely *directly* related to a reduced CPT. We hypothesize that spatial summation of input from a large surface area from whole body exposure (*as opposed to a small region as measured in QST*) may be sufficient, on a background of chronic pain and established central sensitization, to reduce the CPT and generate the perception of cold pain at a higher temperature than measured in conventional QST. In support of this theory, HPTs have been reduced by spatial summation in *health* and *spinal injury*.[21,22] However, the evaluation of the effect of spatial summation of CPTs in FMS has not yet been conducted.

It is, of course, quite possible that there is no real association between ambient temperature and pain levels in FMS. One notable theory, explaining the disparity between patient-reported and experimentally-observed findings, focusses on cognitive biases. Cognitive psychologists have posited that patients may feel less helpless if they are able to relate their systems to some external influence, a sentiment expounded by Nyberg.[60] To further compound this, humans have a proclivity for perceiving correlations in random sequences where non exist.[70]

In this review, we have found that CDTs in FMS are elevated in some studies[16,46,49,65,85] but statistically unchanged in the majority.[5,6,15,19,24,26,30,37,42,44,45,64,83] In many there is a trend towards elevation,[5,6,19,24,37,42,44,45,64] however, no studies have been powered for this. FMS patients and controls perceive experimental *innocuous cold* (cold detection) at approximately 30°C.[24,49,65] Notwithstanding, a change in CDT, which we find little evidence of, is probably only small and, therefore, of minimal importance compared to the CPT. We suggest that a reduction in the CPT leads to a narrower window between innocuous cold detection and cold pain. This may compromise the normal homeostatic mechanisms which take place to mitigate temperature change such as, behavioral (eg, muscle tensing, shivering) or autonomic (eg, piloerection, vasoconstriction). In health, these start to take place at 20°C.[53] Indeed, the mechanism of "habituating" to cold afferentation is impaired in FMS.[76] In *health* continuous exposure to a cool environment causes suppression of thermal pain thresholds (ie, humans become *less* sensitive to thermal pain),[80] perhaps this is also impaired in FMS patients, thus rendering them more susceptible to feeling cold during prolonged cold exposure.

Pain in response to temperature changes in FMS may be caused by peripheral mechanisms or central ones. Peripheral mechanisms may be primary, as described above, through summation of cold nociception, or they may be secondary. One emerging secondary mechanism of pain, now gaining momentum, is the theory of nociceptor activation from tissue ischaemia.[1,25,40,41,58] According to this theory, abnormal control of blood flow is culpable for the malperfusion of deep tissues and results in ischemic pain. The early findings of Lapossy et al showed that cold-induced vasospasm at the nail bed is more prevalent in FMS.[48] This pointed to aberrant vasomotor control. Cutaneous arterioles and AVS, which have an important role in thermoregulation, have dense sympathetic and sensory innervation.[1] In a pertinent study, Albrecht et al examined the AVS innervation of glabrous skin of the hand in patients with FMS. They found increased vasodilatory peptidergic innervation of the cutaneous AVS but reduced intraepidermal nerve fiber density (IENFD) of thoracic, nonglabrous skin.[1] These authors hypothesize that abnormal shunting of blood may lead to deep tissue ischemia and contribute to pain. Very recently Üçeyler's group have taken this further, finding again reduced FMS dermal nerve fiber innervation of vasculature in non-glabrous skin, over the calf. These authors speculate that reduced dermal innervation of blood vessels impairs blood flow autoregulation and thermal tolerance, therefore.[25] Both studies point to a dysregulated system of thermoregulation in FMS, at both glabrous and non-glabrous sites. We have noted that detection threshold in FMS are not altered, suggesting that the afferent sensory pathway is intact, however, it may well be that the efferent pathway of automatic control is abnormal, as suggested by the nerve fiber studies above.

Possible too, is that cold sensation at, and below, these thermal thresholds is more intense or uncomfortable, provoking exaggerated behavioral responses, similar as shown previously for painful stimuli in FMS.[24,79] Since reduced innocuous sensory input in neuropathy impairs modulation of noxious input,[26,61] small fiber damage in FMS[26,32,85] may generate this effect by further augmenting the role of innocuous cold-sensation, especially, where small fiber pathology correlates with symptom severity.[26]

Regarding the mechanism underpinning the profoundly abnormal experimental CPT in FMS, our recent finding that most patients with severe FMS have temperature-pain sensitizing immunoglobulin G auto-antibodies point to a potential root-cause,[31] but neuropathic[33] or central mechanisms[13,14,74] likely contribute. Given that FMS patients can be classified for presence, absence, and degree of small fiber pathology[33] it is tempting to speculate that this feature might affect temperature sensitivity.

It is also pertinent that the here-reviewed studies only occasionally investigate FMS subgroups, but those which do find temperature sensitive subpopulations, both when using meteorological, and QST

methodologies.[8,37,45,68,69,82] Across all studies it is possible that results from less sensitive subgroups have diluted the effect of more sensitive ones.

Limitations

This review is limited by the heterogeneity of the study data. We also report only upon full text, adult, English articles, assessing ambient or experimental temperature, and may have missed some relevant findings, consequently. We attempted to mitigate this with reference analysis of the studies identified, however. Pain and discomfort are often difficult for patients to distinguish between and this may confound the studies we cite[84]; discomfort is influenced by fatigue from hot weather or stiffness from cold. No specific date exclusion was included in the search. The results encompass studies published over a number of decades using disparate, in part, now outdated diagnostic criteria.[77,90,91,93,94] We cannot exclude that the studied patient groups may differ between each other in their responses to ambient temperature as a result of how they were identified. It is also necessary to note that QST is designed to examine specific receptor pathways, however, natural stimuli rarely activate just one receptor and clearly summate over an entire body. Abnormal QST results are, therefore, only part of the picture but still suggestive of an abnormal temperature-sensing system.

Conclusions

In summary, the influence of ambient temperature on FMS pain remains unclear. The evidence from meteorological studies is conflicting. The strength of this evidence is poor and subgroup analyses are lacking. Evidence is mounting, however, that there are temperature-sensitive subgroups in FMS. QST studies demonstrate heightened thermal pain sensitivity in FMS. The degree of any concordance between

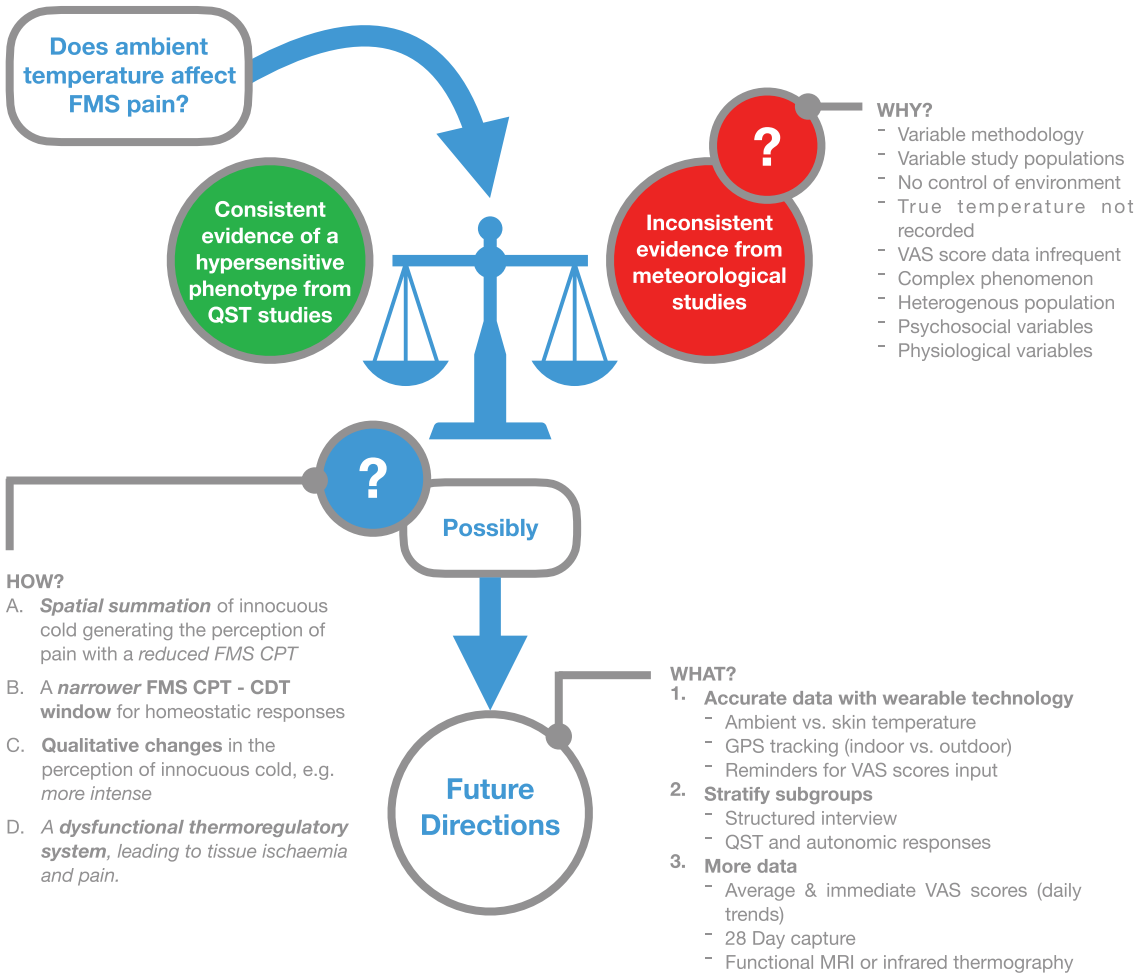

Figure 4. Summary of findings and future directions. The evidence from quantitative sensory testing (QST) is unambiguously in favour of a hypersensitive fibromyalgia syndrome (FMS) phenotype with respect to thermal thresholds. The evidence from observational meteorological studies, however, is less conclusive and hampered by biases. Some possible reasons for the observational studies failing to capture the phenomenon, should it exist, are listed. Three theories are presented for how an altered sensory phenotype might cause increased pain involving the cold pain threshold (CPT) and cold detection threshold (CDT). Future avenues of investigation to provide more robust data and conclusions are detailed.

environmentally-triggered temperature-related pain, and QST sensitivity remains challenging to ascertain based on current data due to the pervasive methodological flaws seen in the environmental studies. This is clearly a very complex phenomenon with multiple confounders, and detailed assessment of an FMS cohort by structured interview is warranted to fully comprehend temperature-sensitive subgroup proportions and characteristics, especially, we suggest, with reference to small fiber pathology and genetic heterogeneity (eg, TRPM8 allele). To provide 'objective' robust data, wearable technology tracking ambient temperature and acquisition of both immediate and average pain scores, in a cohort of FMS patients, controlling for other environmental factors (Fig 4) would be particularly instructive. Noting the historic nature of many studies investigating this phenomenon, newer technologies such as infrared thermography or functional MRI may provide illuminating new insights. A detailed understanding of this phenomenon may identify patient subgroups with differing biological mechanisms. We anticipate that elucidating the role of autonomic function during the reduced CPT - CDT window is also crucial. The symptoms of fibromyalgia are likely to persist for decades[38] and so information empowering clinicians to provide lifestyle advice and validate symptomatology is vitally important.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2020.12.005.

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