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

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**Abstract (200)**

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, non-controlled 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-26.3°C vs. 5.9°C-13.5°C in controls; this was statistically-significant in 14/17. Other thermal thresholds were also often abnormal.

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

**Perspective (50)**

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.

**Background**

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition of uncertain aetiology and may be viewed as pain state with central amplification13, 14, 74. However, there is also mounting evidence of peripheral abnormalities including small fibre polyneuropathy with abnormal nociceptor function25, 33, 51, 73, abnormal thermoregulatory peripheral innervations1, and even peripherally binding pain-sensitising IgG autoantibodies31. FMS is characterised by widespread pain and a constellation of other symptoms, most markedly fatigue, sleep disturbance and cognitive problems14, 90. Prevalence is estimated at 2% worldwide with a strong female preponderance7. Symptom intensity fluctuates on a daily basis, as well as over weeks, months and years3, 87.

In our clinical experience, many patients report increased pain when ambient temperatures fall, and even disabling extreme temperature sensitivity through winter54 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 patients4, 10, 71, 92 with 25% of patients reporting symptom flares secondary to fluctuations thereof86. However, as with a number of rheumatological conditions, study results have been conflicting18, 34, 56, 72.

Independently, the observation that FMS patients display *experimental* hypersensitivity to sensory stimuli, both noxious and innocuous, is well-established12. 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 determined2.

The theory of abnormal temperature regulation leading to pain1, 25 provides an important 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), 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 guidelines57, 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 two 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 (WDT), 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: (a) related ambient temperature to pain (i.e. Part 1) or assessed thermal thresholds from QST (i.e. Part 2); (b) confirmed diagnosis with the then current diagnostic criteria (Smythe77, Yunus94, American College of Rheumatology (ACR)90, 91, 93); and (c) were reported as full-text publications. Studies were excluded if they: (a) were not in humans, (b) were not in adults aged >18 years, (c) were not reported in English, and (d) 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. & 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 inFigure 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 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 addresses external and internal validity of the selected studies. 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 (NOS))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, 4-6 was moderate risk and 7 was high risk of bias. The QST studies were assessed with the NOS which again assigns points for section, comparability and exposure/outcome to a maximum of 9. A score of 0-3 is considered very high risk, 4-6 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.

**[Figures 1]**

**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 *(Tables 1)*. Three self-reported symptom studies associate pain with temperature23, 35, 93, 94 *(Figure 2)*. Temperature-dependent pain intensity was first highlighted by Yunus *et al.* (1981)*,* who reported that 92% of patients (n=50) found their symptoms were aggravated by “cold or humid” weather94 using Smythe’s77 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 diagnostic93. 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: -0.062; p<0.001, n=5149]23. Over all 140,432 tweets there was no uniform trend, however.

***[Figure 2 & Table 1]***

***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 temperature using Yunus criteria17, 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 influence34, 35. More recently, two Norwegian studies28, 75 were again unable to correlate these parameters using American College of Rheumatology (ACR) 1990 criteria93. Again, these studies did not stratify for patient reported temperature sensitivity; one measured pain daily at 2pm when symptoms may be minimal28 and one thrice daily via a web-based diary without record of indoor periods75. 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 analysis8, although no uniform trend. Measuring using the Brief Pain Inventory, Kim *et al. w*ere unable to identify a link between symptoms and meteorological temperature, although the drop out rate was high (37/67) and temperature measurement was non-contemporaneous (5-7pm)43*.* Recently, Fagerlund *et al.* (2019)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 (e.g. depression) are affected by weather and then, in turn, modulate pain intensity27.

Evidence of an association between temperature and FMS pain comes from three observational studies8, 54, 81. A prospective single-blinded Argentinean study, found a negative correlation between daily pain scores and local meteorological data (i*ncreased 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=2596)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: 0.74, 95% CI: 0.66-0.83) or chronic widespread pain (prevalence ratio: 0.40, 95% CI: 0.34-0.48) 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 Cold Pain Threshold***

The cold pain threshold (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 (*i.e. 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*)5, 6, 11, 15, 24, 26, 30, 37, 42, 44-46, 64, 65, 68, 69, 76, 82, 83, 85 but two study populations were shared between five37, 68, 69, 82, 83, so these were included only once 37, 83 giving 17 distinct populations. All studies indicate numerically lower CPTs in FMS vs. controls, and in 14/17 (82%) the difference is statistically significant, indicating cold pain hypersensitivity5, 6, 15, 24, 26, 30, 37, 42, 45, 46, 64, 65, 76, 83. The CPT data is plotted in Figure 3 to convey the spread of CPTs which ranged between 10.9°C-26.3°C and 5.9°C-13.5°C, in controls*.* Taken together, the evidence from QST indicates unambiguously that cold-pain sensitivity in FMS is increased (i.e. diminished CPTs).

***[Figure 3]***

***Reduced Heat Pain Threshold***

The heat pain threshold (HPT) represents the temperature upwards from which a thermal stimulus is felt as *painfully* hot. A *diminished* HPT represents increased sensitivity to heat *(i.e. feeling heat pain from a lower temperature).* We analysed the QST evidence of altered HPTs in FMS. Thirty three studies assessed the HPT5, 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, five sharing two study populations37, 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 non-significant trend towards a numerical reduction *(Supplementary Table S2)*11, 26, 44, 64, 85.

***Unchanged Cold Detection Thresholds***

The cold detection threshold (CDT) is the temperature at which a person can detect a stimulus as being innocuous cold. Pain severity is closely related to cold detection thresholds in other chronic pain conditions, such as diabetic neuropathy47. To ascertain whether FMS patients are hyposensitive to non-noxious cold stimuli (which is commonly termed ‘loss of function’2), we considered 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 controls5, 6, 15, 19, 24, 26, 30, 37, 44, 45, 64, 83. Five (29.4%) found that they were significantly elevated16, 46, 49, 65, 85 *(i.e. requiring a greater temperature change to feel cold),* termed hyposensitivity.

***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 two groups: 10°C-14.9°C, (3/10) and 25°C-25.9°C, (5/10)45. Further studies have noted this. Hurtig *et al.*37 identified two subgroups of FMS patients based on HPTs and CPTs using non-hierarchical regression analysis (K-means algorithm)37. Subgroup One (CPT: 13.6°C, HPT: 44.1°C, n=11; distinguished from HC by CPTs [p<0.05]) 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<0.0001]. 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 group68 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 vs. low global pain groups69. 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 bias17, 23, 34, 35, 43, 75. This was usually due to the selection of participants for none generalisable 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 evidence54 suggest that FMS patients find low ambient temperatures aggravate their pain. Such observations are supported by the results from early studies assessing patient-reported outcomes35, 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 intensity17, 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 *(Figure 3, Supplemental Table S1)*. Skin HPTs are also often *diminished* in FMS5, 6, 9, 15, 20, 24, 29, 30, 37, 42, 45, 46, 49, 50, 52, 59, 62, 63, 65-69, 76, 82, 83 (*i.e. 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-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 these17, 23, 34, 35, 43, 75 studies.

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 (e.g. ACR 199093/201090: see *Supplemental Figure S1*) typical temperature ranges in the studied areas (*e.g*. -18.2°C to 27.4°C)27 and study designs, with some relying on patient-recall93, 94 and others local meteorological station data *(Tables 1 & 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 stress15 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 Haghighi23 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 bias6, 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 guarded49.
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 depression39, 55, 76, or stress; for example: Crettaz *et al.* found psychosocial stress reduced CPT by ~2°C15.

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°C80. However, almost all of the reviewed FMS studies report patient CPT values <25°C *(Figure 3)* indicating that a more significant fall in ambient temperature (*e.g. <15°C*) may be required to generate pain-signalling 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 hypothesise that spatial summation of input from a large surface area from whole body exposure (*as opposed to a small region as in QST*) may be sufficient, on a background of chronic pain and established central sensitisation, to generate the perception of pain. In support of this theory, HPTs have been reduced by spatial summation in *health* and *spinal injury*21, 22. Evaluation of the effect of spatial summation of CPTs in FMS has not been done, however.

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 Nyberg60. To further compound this, humans have a proclivity for perceiving correlations in random sequences where non exist70.

In this review, we have found that CDTs in FMS are elevated in some studies16, 46, 49, 65, 85 but statistically unchanged in the majority5, 6, 15, 19, 24, 26, 30, 37, 42, 44, 45, 64, 83. In many there is a trend towards elevation5, 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 (noted specifically in these studies24, 49, 65). Notwithstanding, a change in CDT which may, or may not, exist 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, behavioural (e.g. muscle tensing, shivering) or autonomic (e.g. piloerection, vasoconstriction). In health, these start to take place at 20°C53. Indeed, the mechanism of “habituating” to cold afferentation is impaired in FMS76. In *health* continuous exposure to a cool environment causes suppression of thermal pain thresholds (i.e. 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.

One emerging peripheral theory of FMS pain is that of nociceptor activation from tissue ischaemia1, 25, 40, 41, 58. According to this theory, abnormal control of blood flow is culpable for the malperfusion of deep tissues and results in ischaemic pain. The early findings of Lapossy et al. showed that cold-induced vasospasm at the nail bed is more prevalent in FMS48. This pointed to aberrant vasomotor control. Cutaneous arterioles and arteriolar venous shunts (AVS), which have an important role in thermoregulation, have dense sympathetic and sensory innervation1. 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, non-glabrous skin1. These authors hypothesise that abnormal shunting of blood may lead to deep tissue ischaemia and contribute to pain. Very recently Üçeyler’s group have taken this further, finding again reduced FMS dermal nerve fibre 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, therefore25. Both studies point to a dysregulated system of thermoregulation in FMS, at both glabrous and non-glabrous sites.

Possible too, is that cold sensation at, and below, these thresholds is more intense or uncomfortable, provoking exaggerated behavioural responses, similar as shown previously for painful stimuli in FMS24, 79. Since reduced innocuous sensory input in neuropathy impairs modulation of noxious input26, 61, small fibre damage in FMS26, 32, 85 may further augment the role of innocuous cold-sensation, especially, where small fibre pathology correlates with symptom severity26.

Regarding the mechanism underpinning the profoundly abnormal experimental CPT in FMS, our recent finding that most patients with severe FMS have temperature-pain sensitising immunoglobulin G auto-antibodies point to a potential root-cause31, but neuropathic33 or central mechanisms13, 14, 74 likely contribute. The here-reviewed studies only occasionally investigate FMS subgroups, but those which do find temperature sensitive sub-populations, 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. Given that FMS patients can be classified for presence, absence, and degree of small fibre pathology33 it is tempting to speculate that this feature might affect temperature sensitivity.

**[Figure 4]**

**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 cite84; 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 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 fibre pathology and genetic heterogeneity (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 *(Figure 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 decades38 and so information empowering clinicians to provide lifestyle advice and validate symptomatology is vitally important.

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**Legends**

**Figure 1 - Study protocol: 1a Observational studies, 1b 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 two reviewers (R.B. & S.S.), independently, based on the criteria set out in the study protocol.*

**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. ~~a~~ One study (Hagglund* *et al.* 35) has been included twice because it presented both self-reported relationships and meteorological correlations). 6/9 of the negative studies are at risk of bias compared to 1/5 studies in support of an association (*see Table 1*).

**Figure 3 - Scatter plot of QST study CPTs FMS v.s HC**

*Fibromyalgia syndrome (FMS) cold pain thresholds (CPTs) range between 10.9°C - 26.3°C vs. 5.9°C - 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 analysed the same populaton. Data can be seen in Supplemental Table S1.*

**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.*

**Table 1 - Observational studies into FMS pain and meteorological temperature**

*Meteorological studies identified in Part 1 of the search protocol.* *Bias scores from two independent reviewers included were (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)* **a** *See Supplemental Figure S1 for the diagnostic criteria.* **b** *The term ‘spoonie’ is 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.* **c** *‘Myalgic score’ is a summation of dolometric values 0-9 at 6 sites on the right body side. The score ranges from 0-54.* **d** *’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.* **e***Indicates authors deemed overall high risk of bias. Abbreviations: PR, Prevalence ratio; CWR, Chronic widespread pain, BPR, Brief pain inventory; FIQR, Fibromyalgia impact questionnaire revised.*

**Supplementary Figures**

**Table S1 - Cold pain thresholds from QST studies in FMS**

*The abbreviations are as follows: FMS, Fibromyalgia syndrome; HC, Healthy control; KNR, Ketamine non responder FMS patients; KR, Ketamine responder FMS patients; ACR, American College of Rheumatology; CPT, Cold pain threshold; CDT, Cold detection threshold; WDT, Warmth detection threshold; PHS, Paradoxical heat sensation; HPT, Heat pain threshold; NS, Not specified; n.s., not significant. ‘****f****’ Denotes a flooring effect from an experimental cut off, as the true CPT was not found in 15/20 because it was below the lower temperature limit (10°C). Here, the p value is calculated using 10°C as the CPT. The symbols represent the following:* ▼*, Diminished CPT (i.e. cold pain felt at a higher temperature);* ~*, No change in CPT. Z scores = (value of the subject – mean value of controls)/(standard deviation of controls). Negative z-scores indicate a loss of function, positive z-scores a gain of function. Studies were deemed high risk for bias (<7/9) using the Newcastle Ottawa Scale 88, scores for two reviewers displayed. a These studies appear to use the same study population and so CPT data has only been used for Hurtig et al. 37.*

**Table S2 - Evidence from QST studies in FMS**

*The abbreviations are as follows: FMS, Fibromyalgia syndrome; HC, Healthy control; KNR, Ketamine non-responder FMS patients; KR, Ketamine responder FMS patients; Hemisensory syndrome, HSS; ACR, American College of Rheumatology, CPT, Cold pain threshold; HPT, Heat pain threshold; WDT, Warmth detection threshold; CDT, Cold detection threshold; NS, Not specified; ’f’ Denotes a flooring effect as the true CPT was not found in 15/20 because it was below the lower temperature limit (10°C). Here, the p value is calculated using 10°C as the CPT. HPT and CPT data is displayed in bold. Studies were deemed high risk for bias (<7/9) using the Newcastle Ottawa Scale 88, scores for two reviewers displayed. a The study populations in these studies appears to be the same so only HPT & CPT data for Hurtig et al. 37.*

**Figure S1 - Diagnostic criteria in FMS**

*The abbreviations are as follows: ACR, American College of Rheumatology*