

## To tolerate weather and to tolerate pain – two sides of the same coin? The Tromsø Study 7

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## Introduction

It is a common belief that weather or constituents of weather, like temperature, barometric pressure, and humidity causes or aggravates episodes of pain [35,37]. This effect has been suggested to apply to pain of diverse origins, ranging from musculoskeletal pain [3] to headache [24,40] and migraine [40]. In a study of weather patterns and pain, chronic-pain sufferers experienced the most pain on days characterized by below-normal barometric pressure, higher precipitation, above-normal relative humidity, and stronger winds [31]. However, other studies have shown conflicting results; many authors have concluded that the effect of weather on pain is either non-existent or very small [3,41]. These conflicting results could be due to differing methodologies, the complexity underlying pain and how we experience weather. Few existing studies have had sufficient power to address possible non-linear associations, nor did they use methodologies that could address the issue of non-linearity. Studies on the association between temperature and mortality suggest a non-linear relationship between weather and health [13]. Another problem is that the effect of weather likely depends on the preceding weather; indeed, one experiences a temperature of 10°C differently when the preceding temperature was -5°C than when it was 25°C. Therefore, the effect of weather on pain may vary depending on the current, the preceding, and the change in weather.

Humans adapt physiologically to the climate they live in; they can show a reduced response to cold temperatures after being exposed to them only a few times [25]. This adaptation could contribute to the differences observed in the association between temperature and mortality across cities, countries, and times of the year [13,23], as well as to different results regarding pain and weather. In addition, different meteorological variables might interact, e.g. humidity and wind speed may alter the experienced temperature. Furthermore, adaptation to one stressor could affect the response to a novel stressor [6]. This cross-adaptation and cross-sensitization could imply that preceding temperature alters the effect of barometric pressure on the organism. This possible non-linearity and state dependency is typical of biological systems and may occlude analyses and possible causal relationships, i.e. weather and pain could be positively correlated, negatively correlated, or not correlated, depending on when, where, and over what period the associations are studied [34]. Due to these characteristics, traditional regression analyses are not suited to capture the actual association between weather and pain.

One way to study the effect of weather on pain is to use self-reported pain, which can be influenced by participants' beliefs regarding the connection between weather and health. Quantitative sensory testing is another way to assess the effect of weather on the sensory system. Different tests attempt to measure the amount of painful stimuli a person can tolerate [5,15,19]. Although experimental

pain tolerance is not the same as the experience of chronic pain, chronic-pain sufferers have been reported to have a lower pain tolerance [5,15,19]. We hypothesize that meteorological variables have an effect on pain tolerance, and aim to investigate the seasonal variation and impact of weather on pain tolerance.

## **Methods**

We used data from seventh survey of the Tromsø Study (Tromsø 7). Tromsø is located at 69° north, with a mean temperature of -3.3°C in February as the coldest month, and a mean of 12.3°C in July. The westerlies give rise to frequent low pressure systems that affect the climate in the area. Tromsø 7 was conducted from March 2015 to November 2016. 32,591 individuals aged 40 years or older were invited, 21,083 participated, 19,540 performed at least one test of pain tolerance, 18,987 performed the cuff-algometry test, and 18,285 underwent the cold pressor test. Examination dates were randomly selected, and participants could choose another date if the given date was not suitable. During the examination, participants cycled through all research stations, normally starting with a physical examination station, followed by various questionnaire stations, and finally cuff-algometry and the cold pressor test station. However, wait times did occur at the stations, and these times differed depending on the number of people attending at that moment. Acclimatization time was calculated as the time between the physical examination station and the cold pressor test station; we were unable to include any wait time that occurred before the physical examination.

### **Pressure pain tolerance**

Pressure pain tolerance (PPT) was tested with computerized cuff-algometry (NociTech, Aalborg, Denmark). Both legs were fitted with a cuff. Starting with one leg, the cuff was inflated by 1 kPa/s to the maximum pressure the participant could tolerate or to 100kPa, whichever came first; then the procedure was repeated on the other leg. PPT was calculated by taking the mean of the two inflations, one on each leg, for each participant. For amputees and those with a cast, the test was performed on one leg (ramp), and the single test results were used.

Participants were asked whether there was a reason not to undergo the test. Only those who stated no reason, were willing, and had no open sores were tested. Examples of reasons for not completing the test included hyperalgesia, or problems with peripheral circulation. Individuals unable to understand instructions did not undergo cuff-algometry.

### **Cold pain tolerance**

Cold pain tolerance (CPT) was tested by the cold pressor test. Participants submerged their open and relaxed dominant hand and wrist into a 13-liter plexi-glass vat containing circulating cold water

(3.0°C). Temperature and continuous circulation of the water were controlled by an attached cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH, Seelbach, Germany, 22 l/min). Participants were asked to hold their hand and wrist in the water as long as possible, up to a maximum of 120 s. Time to withdrawal was used as the outcome of the test.

Participants were asked whether there was a reason not to perform the test. Only those who stated no reason and were willing underwent the cold pressor test. Examples of reasons for not performing the test included Raynaud's syndrome or cold allergy which the participant believed to be an obstacle, bilateral loss of sensitivity, or breached skin affecting both hands. Individuals unable to understand instructions did not undergo the cold pressor test.

### **Meteorological variables**

Data on daily mean temperature, barometric pressure, precipitation, relative humidity, and wind speed for the period 1990-2020 was obtained from the Meteorological Institute of Norway's web-services (eKlima.net). As there is little geographical variation in weather within the municipality of Tromsø, we used the daily mean of meteorological observations from one station (Tromsø 90450). The station is located approximately 2.5 km from the test center of The Tromsø Study 7. A large majority of the inhabitants in Tromsø municipality live within 10 km from this station. To eliminate seasonal variation in meteorological data, we calculated meteorological anomalies as the difference between expected and observed meteorological variables. The expected meteorological variables for each specific date were determined by creating a 7-day moving average for the period 1990-2020 and calculating the mean of these averages for each date. We then determined the meteorological anomalies for each date by subtracting the expected from the observed values.

### **Chronic pain**

Data on chronic pain were obtained with the question "Do you have persistent or recurrent pain lasting 3 months or more" (Yes/No).

### **Statistical analysis**

#### **Seasonal variation**

To investigate the variation in pain tolerance throughout the study period, we categorized participants according to the month in which they were examined, and calculated the range, median, and quartiles of PPT and CPT.

For CPT, we performed a Cox proportional hazard regression with month of examination as the exposure and time to withdrawal as the survival time. We used January 2016 as the reference month

and assessed the proportional hazard assumption with Schoenfeld residuals and log-log plots. The difference in hazard between sexes tended to decrease during the cold pressor test. However, stratified analysis or models allowing the effect of sex to vary over time- had little effect on the estimates for months. Sex is therefore included as a covariate. To test the possible interaction between age, sex, and month of examination, we included interaction terms for age and sex in the regression model. The pre-test hand temperature could bias the result, as the shock from the cold water might be less for a hand which was already cold. Therefore, we fitted an interaction term between month of examination and acclimatization time. We also repeated the analysis in the subgroup of participants with an acclimatization time >60 min.

### **Short-term variation**

To investigate the possible variation in shorter time periods, e.g. days and weeks, we used daily mean PPT. Due to right-censoring in the data from the cold pressor test, we calculated daily CPT as the daily proportion of participants with a time to withdrawal >100 s in the cold pressor test. To illustrate the variation throughout the study period, we created 7-day moving averages of the daily measures of PPT and CPT. Because of a seasonal variation in CPT, we fitted a sinusoidal curve to the daily CPT, and used the difference between the sinusoidal curve and the daily CPT to study the short-term variation in CPT. To identify any possible correlation from one day to the next, we calculated the autocorrelation for each time series. For time series with an autocorrelation, we assumed an exponential decay and used a generalized linear model with gamma distribution and a log-link function to estimate the average timescale of which the different measures of pain tolerance varied. We repeated the same procedure for meteorological anomalies. Assuming an exponential decay in the autocorrelation is an often used method for calculating the intrinsic timescales of different phenomena, for example in neuroscience [27].

To study if there was any difference in attendance by sex, age, or chronic pain, we calculated the proportion of females and participants reporting chronic pain at each date and used the daily mean of age. Due to a drop in both age and proportion of females from July 2016, we repeated the time series analysis in a reduced dataset, which included data from March 2015 to July 2016. We then used the reduced dataset to calculate the autocorrelation for daily proportion females and participants reporting chronic pain, as well as for the daily mean of age. To further investigate if differences in mean age, proportion of females, day of week, or study technician rotation could introduce the observed autocorrelation in pain tolerance, we first conducted univariate analysis for each variable. We then made 500 randomly shuffled copies of the PPT time series. Using these copies, with no association to weather, we simulated the effect of sex, age, day of the week, and

study technician rotation by adding twice the observed differences from the univariate analysis. For each randomly shuffled copy, we calculated the autocorrelation. Finally, we tested if the combination of sex, age, and study technician rotation could be the source of the observed autocorrelation.

### **Association between pain tolerance and meteorological variables**

We created 3-day moving averages for PPT and the daily measures of CPT with the seasonality removed and used cross-correlation to investigate the possible association between pain tolerance and meteorological variables. We primarily used meteorological anomalies as they do not have any seasonal variation, but as the calculation of anomalies introduces noise in the time series we repeated the analysis with the observed meteorological variables. As we expected to find different correlations in different periods, we first performed the cross-correlation for the whole period, then for each half-year. To assess the likelihood of spurious correlations, we repeated this process for 500 randomly shuffled copies of PPT and CPT. One single correlation coefficient outside these random simulations would correspond to a p-value of approximately 0.002.

To describe the weather in periods with high or low pain tolerance, we chose the local maxima and minima that were above the 90<sup>th</sup> or below 10<sup>th</sup> percentile in the 3-day moving average of PPT and CPT (Supplementary figures 1 and 2). If two maxima or minima were closer than 6 days together, we defined them as being from the same maximum or minimum. We then calculated the mean of the 3-day moving averages of PPT and CPT for those days, as well as for 14 days before and after, and the mean of the 3-day moving averages of the meteorological anomalies for the same days.

To test if meteorological variables could predict future pain tolerance, we fitted a vector autoregressive model to the daily means of PPT, temperature, and barometric pressure. We used both meteorological anomalies, and the observed temperature and barometric pressure. We chose the number of included lags (days) from the likelihood ratio (LR) test, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) resulting in six different models, and performed a Granger causality test for all models [14]. To further assess the fit of the different models we calculated the autocorrelation of the residuals from the different models.

The autocorrelations and generalized models of them were performed in R.3.6.3. All the other analyses were performed in STATA 16.

### **Missing**

Age and gender were collected from the official registry in the invitation process and are complete. Therefore, the Cox-regression including only sex and age as covariates included all cold pressor tests

performed. In the remaining analyses we used daily measures of central tendency. These were calculated from all tests performed.

17,749 out of the 19,540 performing at least one test of pain tolerance answered the question about chronic pain, and these answers were used to calculate the prevalence of chronic pain and its possible non-random variation over time. However, data from the chronic pain question was not included in any other analysis, and no participants were excluded from any other analysis due to a missing value on this question.

To further assess whether the missing values on the chronic pain question could be a potential source for a non-random variation over time, we calculated the autocorrelation of the daily proportion missing on the question. In addition, we performed multiple imputation with chained equations. To increase the probability of detecting any variation over time we used all participants in Tromsø 7 (21,083). We included sex, age, chronic pain, CPT, and PPT. To improve prediction we also added education, pain the last 4 weeks from a computer based questionnaire included in Tromsø 7 [33], and 6 questions about musculoskeletal complaints lasting 3 months or more. We imputed 20 datasets and then calculated the prevalence of chronic pain, as well as the daily proportion having chronic pain and the autocorrelation of these daily proportions.

## **Results**

Among the 19,540 performing at least one test of pain tolerance the mean age was 56.9 years (Standard deviation: 11.1 years), 10,065 (51.5%) were female and 17,749 answered the question about chronic pain, yielding a prevalence of 36.9% among the responders of the question. The prevalence in the imputed data was 37.7%. PPT was measured in 18,987 participants. The distribution of PPT was right-censored to some degree, as a proportion of participants reached the maximum pressure (100 kPa) in every month (Figure 1a). 18,285 of the participants underwent the cold pressor test. Times to withdrawal were substantially right-censored (Figure 1b), as over 25% of participants reached the maximum time (120 s) in every month except July 2016, which was a month with few participants due to summer holidays.

### **Seasonal variation**

There was no clear seasonal variation in PPT (Figure 1a). However, the median time to withdrawal in the cold pressor test tended to be highest around January 2016, and lowest in August 2015, July 2016, and August 2016 (Figure 1b). A Cox proportional hazard model, in which month of examination was the exposure and the month of January 2016 was the reference, revealed a seasonal pattern in the hazard ratios, with a lower CPT in warmer parts of the year (Figure 1c). We found no significant

interaction between month of examination and sex, age, or acclimatization time, meaning the effect of month did not differ by sex, age or acclimatization time. The seasonal pattern was still evident in a model restricted to those with an acclimatization time of >60 min (Supplementary figure 3).

### **Short-term variation**

Daily mean PPT and daily CPT are depicted with 7-day moving averages in figure 2. There was a clear autocorrelation for daily mean PPT (Figure 3), meaning the PPT on one day was correlated with the observations from preceding days. The autocorrelation for PPT had a mean lifetime of 5.1 days (95% confidence interval (CI) 4.0-7.2). This is within the range of mean lifetime for the meteorological anomalies, which varied from 2.6 days (95% CI 1.9-4.0) for precipitation to 6.2 days (95% CI 5.5-7.2) for barometric pressure (Supplementary table 1). We found no autocorrelation for daily CPT after seasonality was removed (Figure 3). However, there was a weak autocorrelation for weekly mean CPT, indicating non-random short-term variation (Supplementary figure 4). Due to the lack of a clear systematic short-term variation in daily CPT we present results from the analyses made with PPT, and present results from analyses of daily CPT in the supplementary materials when appropriate.

Variation due to sex, age, day of the week, and study technician rotation are potential sources of systematic error and might theoretically contribute to the observed autocorrelation for PPT. Due to a lower proportion females and lower mean age of the sample towards the end of the study period, we repeated the time series analysis for PPT in a reduced dataset, which included data from March 2015 to July 2016, and found an autocorrelation similar to that observed in the complete dataset. Simulations of the effect of sex, age, day of the week, and study technician rotation on PPT in the reduced dataset did not introduce autocorrelation as observed in the reduced dataset (Supplementary figures 5-7). The reduced dataset revealed some autocorrelation for the daily mean age, but no autocorrelation for the daily proportion of females or of participants reporting chronic pain (Supplementary figure 8). Further, there was no autocorrelation in the daily proportion missing on the chronic pain question, and no autocorrelation in the daily proportion having chronic pain in the imputed data (Supplementary figure 8).

### **Association between pain tolerance and meteorological variables**

For the whole survey period, PPT correlated poorly with the investigated meteorological anomalies (Figure 4a). However, the correlations varied depending on the time period for which they were calculated (Figure 4: b-e). For example, there was a small negative correlation between barometric pressure and PPT in the period from July to December 2015 (Figure 4c), but a positive correlation from July to November 2016 (Figure 4e). Similar results were seen for CPT. All cross-correlations for



PPT and CPT and the assessment of the likelihood of the correlations to be random are presented in supplementary figures 9-18.

The local minima in PPT were preceded by a rise in temperature, barometric pressure, and wind speed, and by a fall in relative humidity (Figure 5). Precipitation went from below normal before the minima to above normal 3 days after the minima. However, the maxima in PPT coincided with falling temperature, precipitation, and relative humidity, and a rising barometric pressure (Figure 5). Similarly, the maxima in CPT coincided with a decrease in temperature and an increase in barometric pressure (Supplementary figure 19). The minima of CPT coincided with an increase in temperature and precipitation, a lower than normal barometric pressure, and a higher than normal relative humidity (Supplementary figure 19).

When fitting vector autoregressive models to PPT, temperature, and barometric pressure, the number of lags (days) identified as optimal differed depending on whether we used meteorological anomalies or observed weather, and whether the LR-test, the AIC or BIC were used (Supplementary table 2). However, four models that included temperature and barometric pressure predicted PPT significantly better than models without them. In some of the models, temperature was a significant predictor; in others barometric pressure was significant (Supplementary table 2). BIC opted for models using a one day lag, in these models temperature or barometric pressure did not predict PPT. However, the residuals from the models using one day lag had more autocorrelation compared to the ones using more lags, indicating a poorer fit (Supplementary figures 20-21). Due to the lack of autocorrelation in CPT, no vector autoregressive model was fitted.

## **Discussion**

We found a clear seasonal variation in CPT and a non-random short-term variation in PPT. Furthermore, PPT and meteorological anomalies varied on similar timescales, and PPT and CPT correlated with meteorological variables. These correlations changed depending on the time period for which they were calculated. This could be a phenomenon called mirage correlation, meaning the sign and magnitude of the correlation changes with time. We also found that temperature and barometric pressure predict future values of PPT.

The seasonal variation in CPT, the correlation between temperature and CPT, and the pattern of falling or rising temperature at the maxima/minima, make it likely that CPT is affected by temperature. Together with the lack of a distinct seasonal variation in PPT, these findings indicates

that the seasonal variation in CPT is due to changes in temperature, and not to other seasonal factors like variation in daylight.

Possible relevant effects of weather on the organism range from physiological responses, like adaptations [25], increased blood pressure, and increased blood viscosity [22], to psychological responses [9]. Molecular mechanisms reported in the literature include adaptations in cell lines [1], and in gene expression of Transient receptor potential melastatin 8 (TRPM8), a receptor for cold and pain [38]. Interestingly, one study of repeated cold-water immersion over 15 days found a decrease in pain experience in both hand and foot exposed to repeated immersions (trained) and in the hand and foot not exposed to these immersions [11], though the change was larger in the trained hand and foot. Thus, exposure to cold may induce local adaptations that affect how we experience temperature, and simultaneously train the central nervous system to inhibit noxious cold stimuli.

The similar weather patterns, a decrease in temperature, and an increase in barometric pressure at the maxima in PPT and CPT, also indicate central mechanisms that are not necessarily specific to the test stimuli. Indeed, innocuous stimuli activate nociceptive fibres [16,36], and nociception could be interpreted as “homeoception”. In such a case, it may be that we experience pain if and when the homeostasis of the organism is threatened [4,8], and that the feeling of pain is meant to induce a behavioral response to a homeostatic threat. Temperature, barometric pressure, precipitation, and humidity, alone or in combination, have a direct effect on homeostasis. A change in these meteorological variables will therefore alter the input to many structures used in the processing of pain [8]. Experimental studies have found that lowering barometric pressure increased pain behavior in rats [12,29] and induced neural activation in superior vestibular nucleus in mice [30]. Therefore, a possible explanation for the observed association between meteorological variables and pain tolerance could be that these stimuli change the state in the parts of the brain that are involved in processing pain.

Weather might also affect people’s mental status, which likely affects the capacity to endure pain [39]. There is some support for a seasonal variation in clinical depression [42]. However, the observed lack of seasonal variation in PPT, higher CPT in winter, and inconsistencies in the literature regarding seasonal affective disorder and mental distress [20,42], make it difficult to describe the possible role of mental status in explaining our results. In summary, it is unlikely that one singular mechanism can explain the variations in pain tolerance observed in the current study; it is more probable that this is the net result of many, possibly antagonistic, mechanisms.

Earlier research has found that chronic-pain sufferers experience more pain when meteorological variables fall outside of normal ranges, i.e. when barometric pressure is lower, and precipitation,

relative humidity, and wind speed are higher than normal [10,31]. Such observations are in line with our result of local minima in CPT coinciding with below-normal barometric pressure and above-normal relative humidity. Earlier research has suggested that chronic-pain sufferers have a lower pain tolerance [5,19]. The hypothesized effect of weather on parts of the brain that are involved in processing pain could explain why some chronic-pain sufferers experience more pain in certain weather conditions. Indeed, these individuals might have a sensory system that is already “off balance”, i.e. have disturbed bodily representation [26], sensitized nociceptors, and reduced descending inhibition [2]. These changes can reduce their ability to adequately adapt to a changing environment.

A large proportion of people with chronic pain report that changes in weather affects their pain [18]. Therefore participants’ own beliefs about this topic could have been of interest. However, we consider it a strength that participants were not informed of the purpose of this particular study, and thus expectation bias is reduced. Another strength of the current study is that Tromsø was carried out over 20 months, so the study period provided data from all seasons and from more than one complete seasonal cycle.

One limitation of our study is that PPT and CPT were measured only once. Thus, we studied the average pain tolerance of a population and were unable to include possible individual variation or adaptation over time. Previous studies on musculoskeletal pain, headache, and migraine have suggested that only a portion of patients is sensitive to changes in weather [32,40]. Thus, we might have underestimated the effect of weather on pain tolerance if only a proportion of the population is affected. A lower attendance rate among the youngest and oldest invitees could limit the generalizability. However, it is unlikely that this selection bias or selection into pain tolerance tests should differ over time and thus introduce any systematic variation over time. The data was collected 4-6 years ago, but changes in climate or characteristics of the population is unlikely to be of such a magnitude that they greatly limit the external validity of the results.

Other limitations were mitigated by carrying out additional analyses. We tried to minimize the influence of pre-test hand temperature by repeating the Cox regression analysis among participants with an acclimatization time >60 min; seasonal variation was still evident in that analysis. The limitation of non-random attendance of participants was examined through simulations on shuffled datasets. These simulations did not introduce an autocorrelation similar to that observed for PPT, and therefore the likelihood of non-random attendance giving rise to the results are considered small.

Cross-correlation is a crude analysis with no method for adjusting for possible confounders. Further, as the timescale of PPT was substantially shorter than months, there might be mirage correlation within these periods. Therefore, the correlation coefficients must be interpreted with caution.

Empirical analysis of dynamic non-linear systems is inherently difficult, and even though we found that barometric pressure and temperature can predict future PPT in the models that showed the best fit, the analysis might be flawed. An important assumption in the Granger causality test is that variables in the model should be separable [14]. But since temperature and barometric pressure are closely associated, and probably pain tolerance as well, past values of one of these will also contain information about the others. Further, the appropriateness of the Granger causality test for use in dynamic non-linear systems continues to be debated [34]. Several findings from our analysis and in the literature makes us believe that we are studying a dynamic, non-linear system: the possible mirage correlation between meteorological anomalies and PPT and CPT, the habituation and physiological acclimatization to temperature, an dynamic effect of TRPM8 in pain and on vascular tone [17,21,28], and the fact that neural networks behave in a dynamical non-linear way [7]. However, the individual differences in the study sample from day to day probably introduce a lot of noise in the time series. Also, the lack of tests on Sundays or holidays limits the power in the time-series analyses. Together, this decreases the likelihood of capturing the dynamics of the association between weather and pain tolerance, which in turn decreases the likelihood of arriving at a better description of the causal structures involved.

Even though the climate in Tromsø is cold compared to many areas, the winters are relatively mild. The mean difference in other meteorological variables like barometric pressure, wind speed and relative humidity are less pronounced. While it is possible that cold temperatures limit the generalizability of the results, patients' belief of weather affecting pain conditions is prevalent also in other climates [18,35,37]. In addition, there seems to be a day-to-day variation in PPT and CPT at temperatures above 10°C, and PPT often correlates strongest with meteorological variables from preceding or succeeding days, indicating that changes are as important as absolute values. The dynamic relationship over time in Tromsø indicates that there are spatial and temporal differences in these relationships.

In this study of the general population, there was a clear seasonal variation in CPT and a non-random short-term variation in PPT. The PPT and meteorological factors varied on similar timescales, PPT and CPT correlated with meteorological anomalies, and temperature and barometric pressure predicted future values of PPT. These observations, especially those for CPT, should be considered when

planning future studies on pain tolerance. Although observational, these findings suggest that weather has a causal, non-linear, dynamic effect on pain tolerance.

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#### **Competing interests:**

The authors declare that they have no conflict of interest.

#### **Ethics approval:**

The Regional Committee of Research Ethics approved the seventh survey of The Tromsø Study and this particular analysis.

#### **Consent to participate:**

Informed consent was obtained from all individual participants included in the study.

#### **Authors' contributions:**

EHF conducted the data analysis. MR assisted in the analysis. EHF wrote the manuscript with the assistance of ACH, MS, and TB. All authors contributed to the interpretation and revised the manuscript. CSN, OAS, and AS contributed to the data acquisition in the seventh survey of The Tromsø Study. All authors read and approved the final manuscript.

**Availability of data and material:** All data are available by applying to The Tromsø Study

<http://tromsundersokelsen.uit.no/tromso>

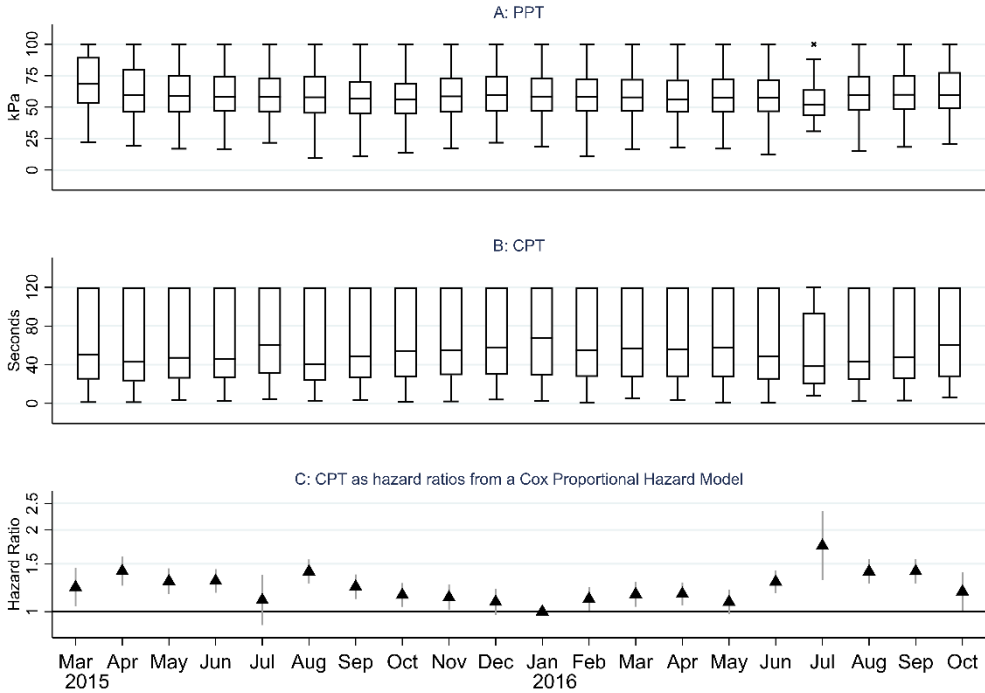
**Code availability:** The code is available at <https://github.com/erlendhfarbu/To-tolerate-weather-and-to-tolerate-pain>

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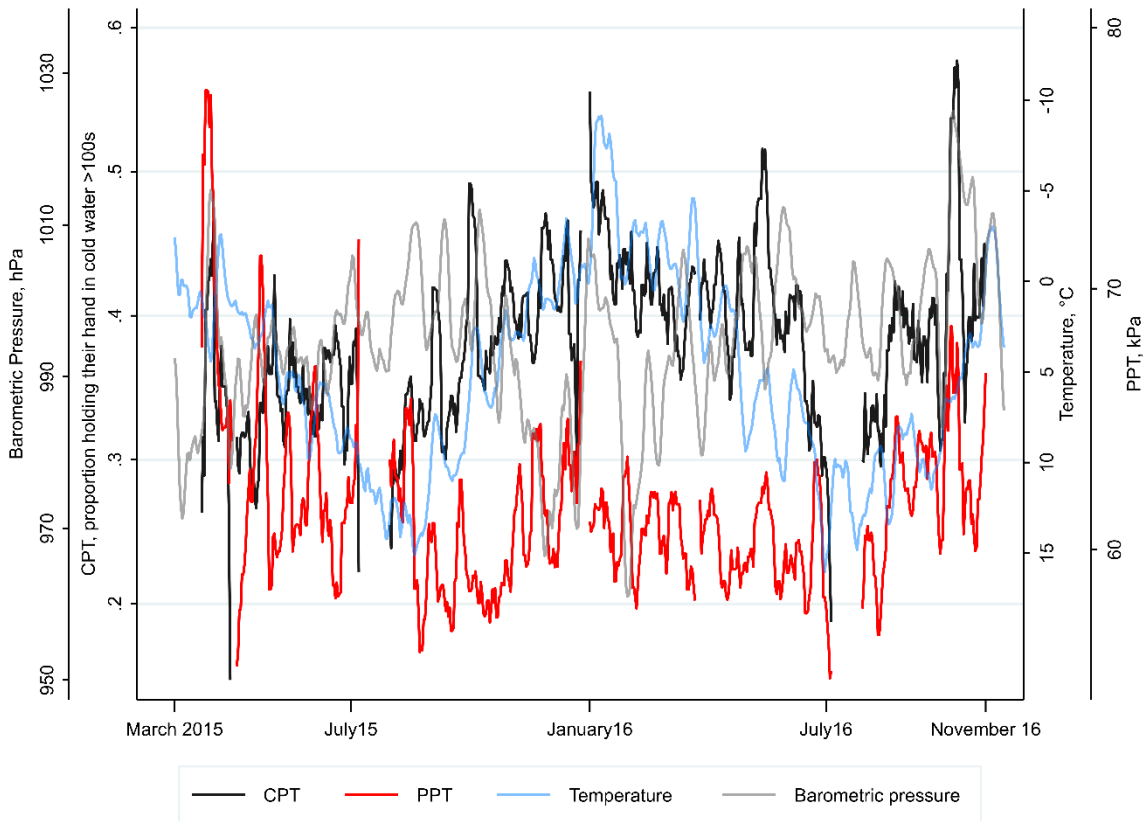
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**Figure legends**

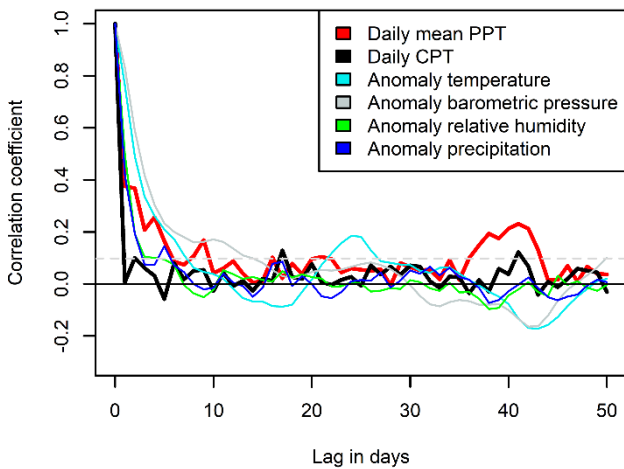


**Figure 1:** Monthly variation in pressure pain tolerance (PPT) and cold pain tolerance (CPT) **a:** Box-plot of monthly PPT, **b:** CPT as time to withdrawal in the cold pressor test and **c:** CPT as hazard ratios from a Cox proportional hazard model using time to withdrawal in the cold pressor test as survival time and month of examination as exposure and adjusted for age and sex

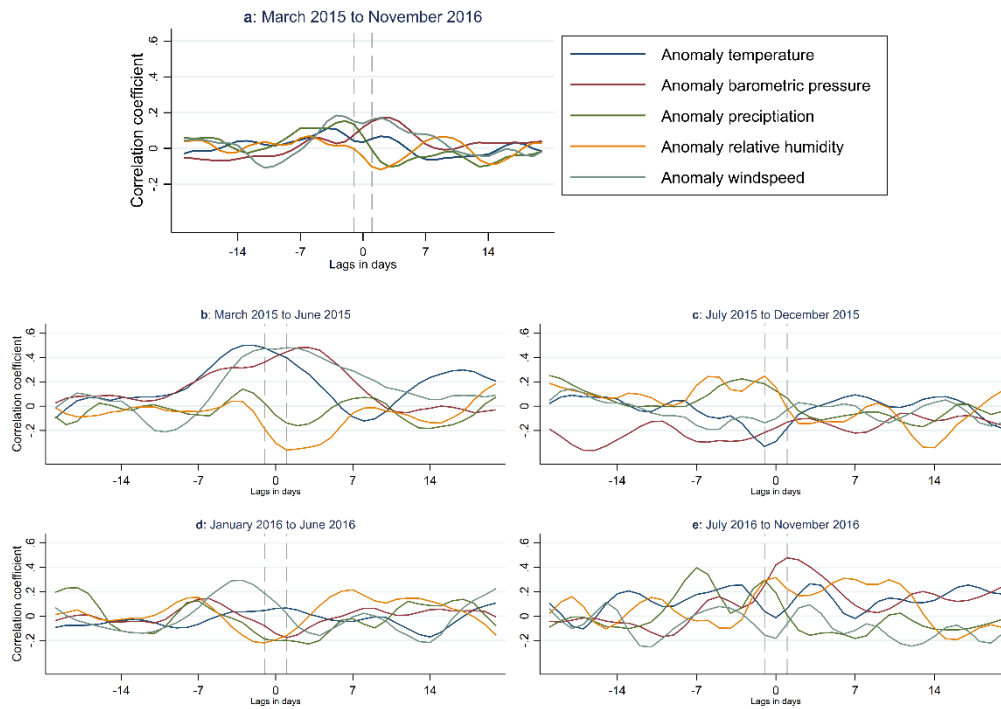




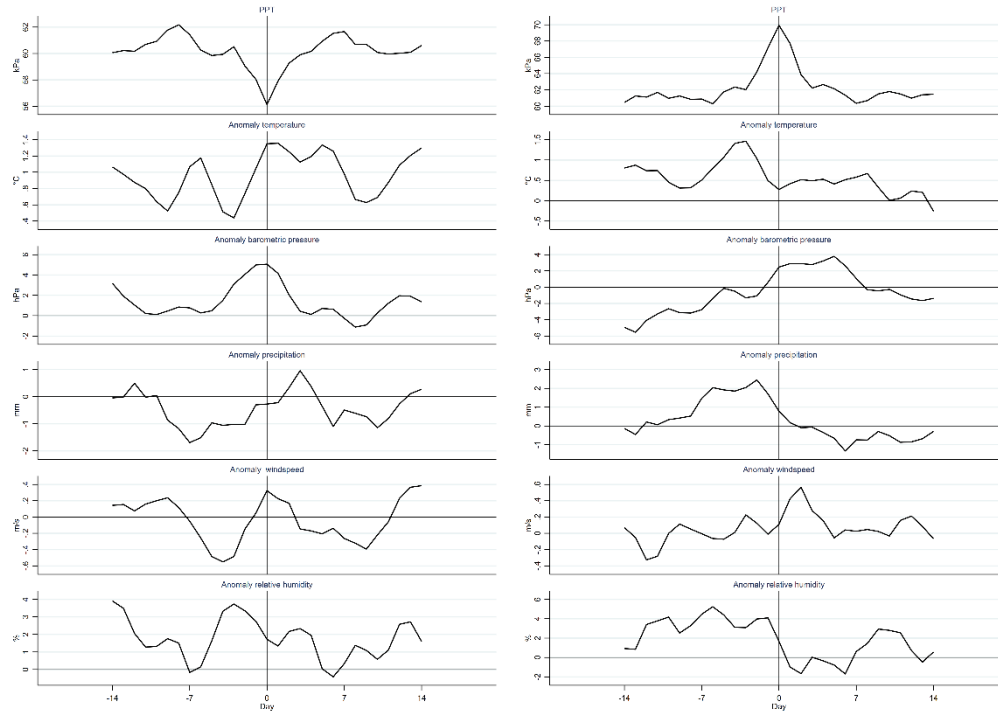
**Figure 2:** 7-day moving averages for daily mean of pressure pain tolerance (PPT), daily proportions of participants who held their hand in cold water >100s (CPT), barometric pressure, and temperature. The scale of temperature is inverted. The average from 31 March 2015 is not drawn, as the proportion of participants who held their hand in cold water >100s on that date was 0



**Figure 3:** Autocorrelations for pressure pain tolerance (PPT), daily cold pain tolerance (CPT) after removal of seasonality, and meteorological anomalies



**Figure 4:** Cross-correlation of 3-day moving averages of pressure pain tolerance (PPT) and meteorological anomalies. The correlation at day 0 should be interpreted as the correlation between the 3-day moving averages, of PPT and the meteorological anomalies, centered at day 0. At day -7 (seven days before day 0) it is the correlation between the 3-day moving average of PPT centered at day 0, and the 3-day moving average of the meteorological anomaly centered at day -7. Calculated for the whole period, March 2015 to November 2016 (a), and in 4 different time periods (b-e). Dashed lines indicate the 3 days of PPT with which the anomalies are correlated



**Figure 5:** Mean of 3-day moving averages of pressure pain tolerance (PPT) and meteorological anomalies at local minima and maxima of PPT, which were below 10<sup>th</sup> or above the 90<sup>th</sup> percentile, and in the 14 days before and after

**Supplementary information “To tolerate weather and to tolerate pain – two sides of the same coin? The Tromsø Study 7”**

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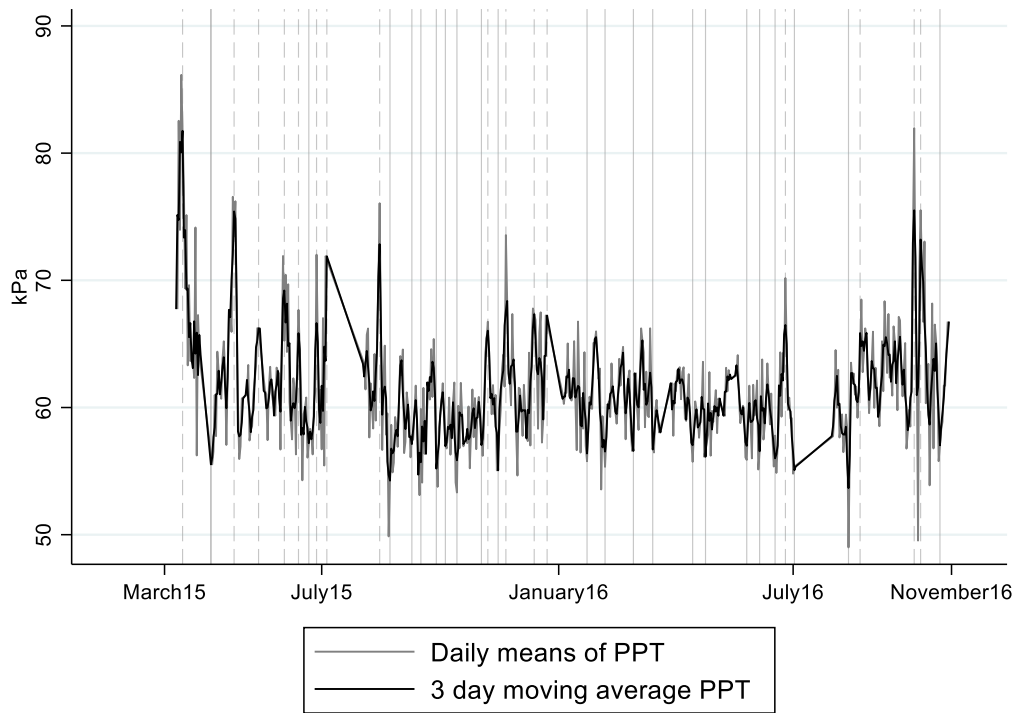
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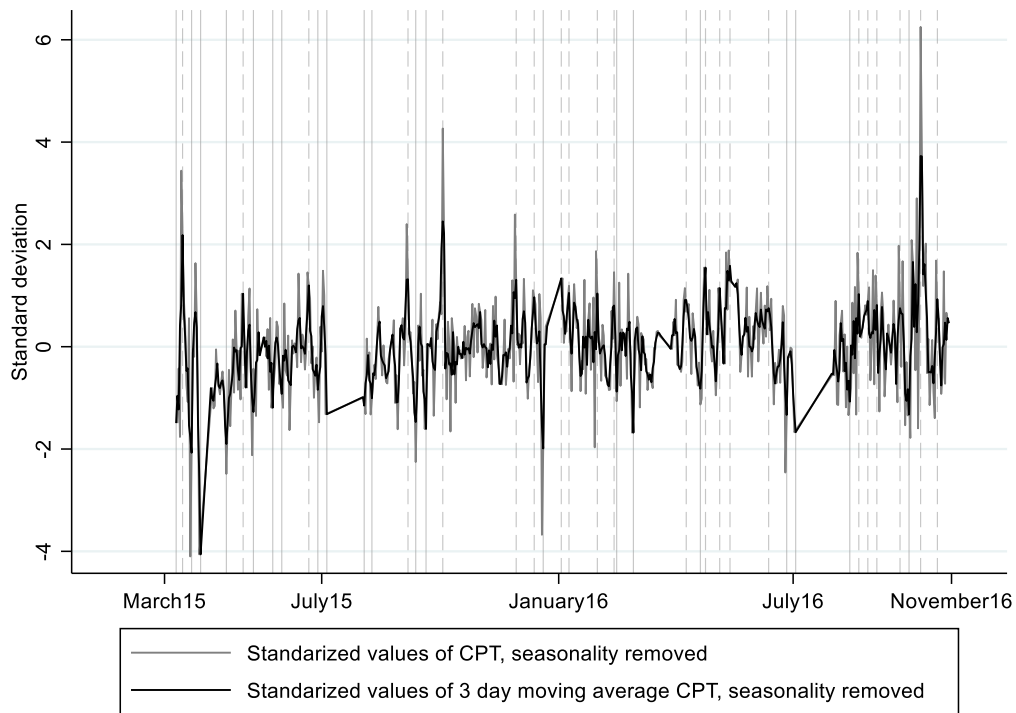
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Figures S1 to S21

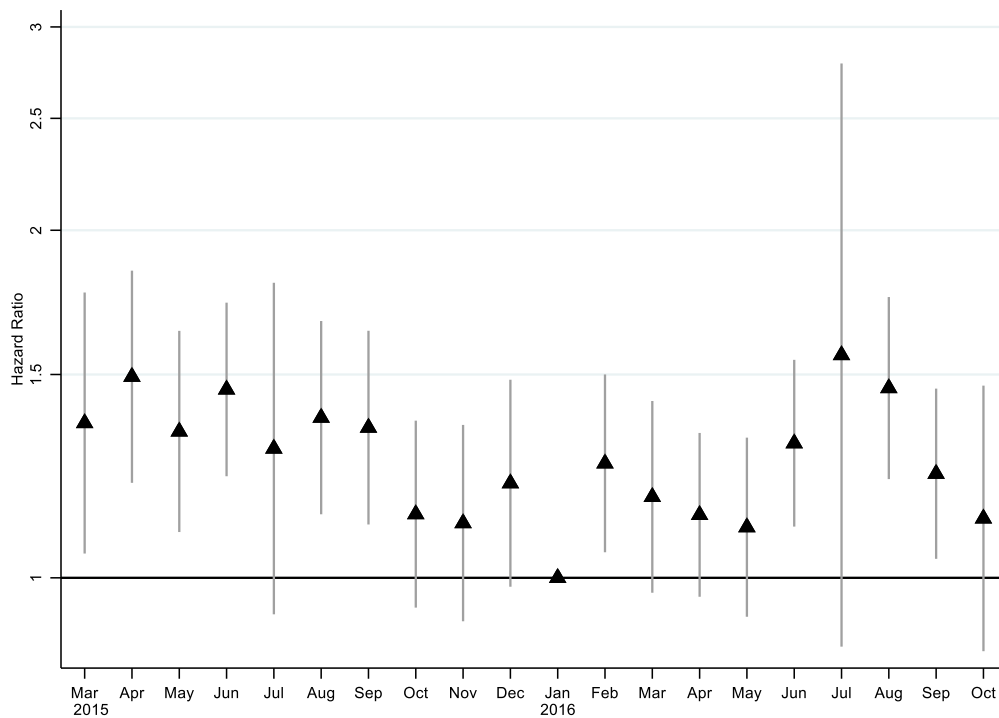
Tables S1 to S2



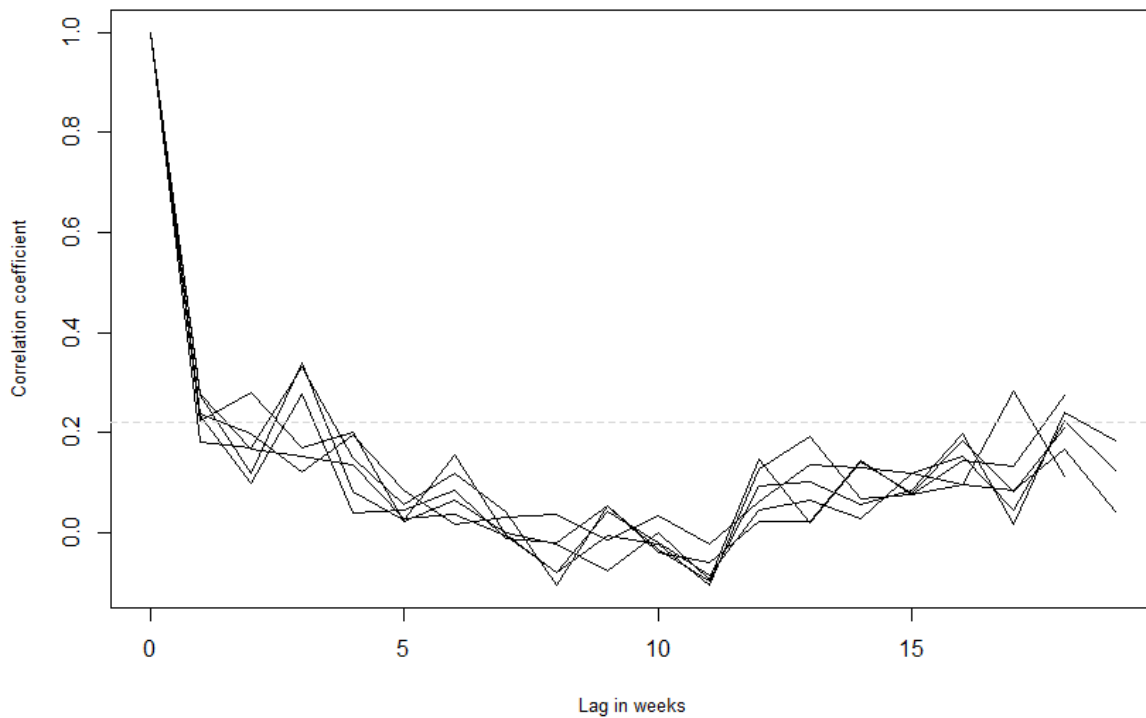
*Supplementary figure 1: Daily means of pressure pain tolerance (PPT) and the 3-day moving average of the daily means of PPT. The local minima and maxima in PPT were chosen from the moving average. Solid vertical lines indicate minima and dashed vertical lines indicate maxima*



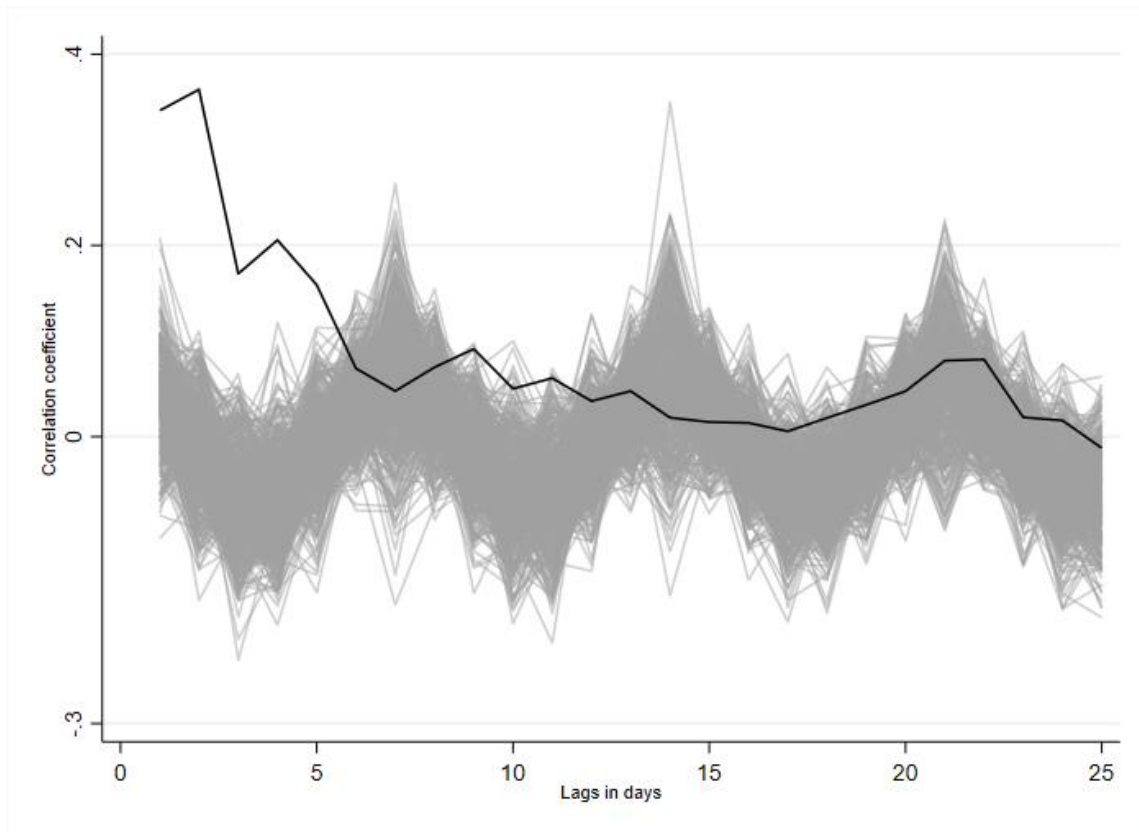
*Supplementary figure 2: Standardized values of cold pain tolerance (CPT) after removal of seasonal variation and the 3-day moving average of the standardized values of CPT. The local minima and maxima in CPT were chosen from the moving average. Solid vertical lines indicate minima and dashed vertical lines indicate maxima.*



Supplementary figure 3: Hazard ratio's from a Cox proportional model using time to withdrawal in the cold pressor test as survival time. Only participants with an acclimatization time (time between physical examination and the cold pressor test) >60 min are included. January 2016 was used as the reference.

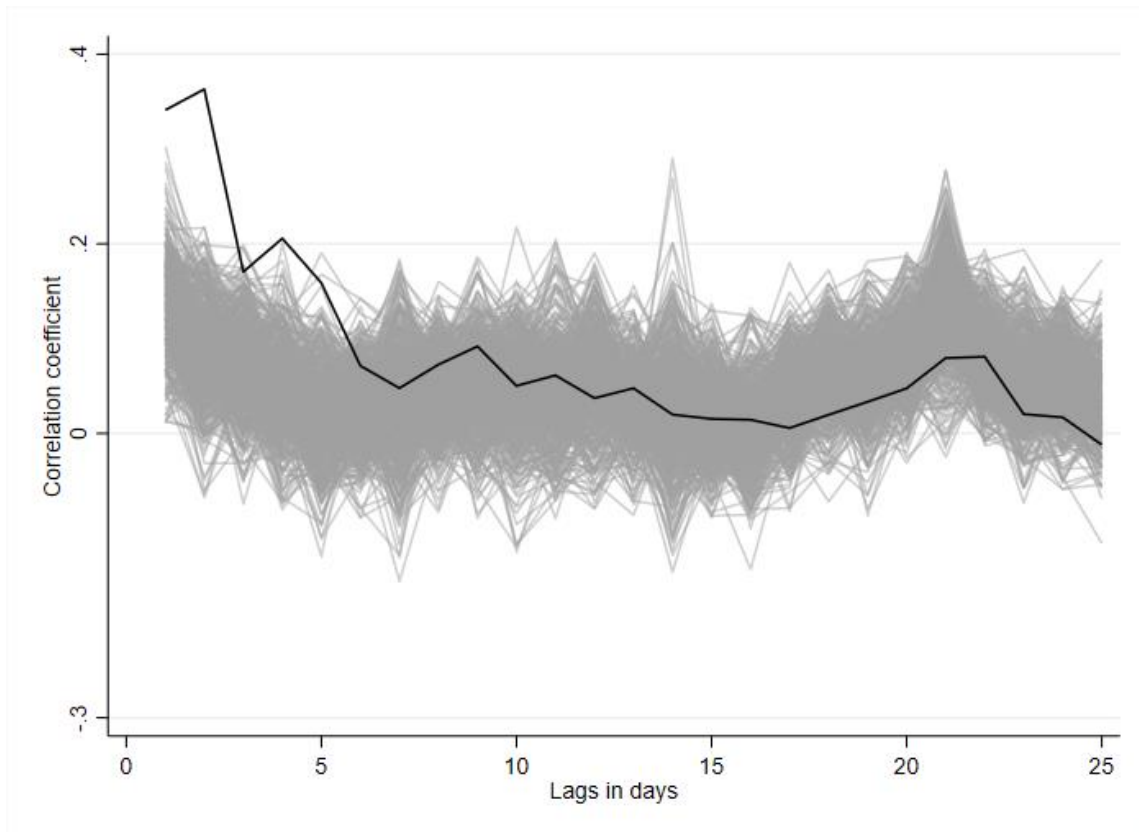


Supplementary figure 4: Autocorrelation for 7 different weekly averages of cold pain tolerance after removal of seasonality

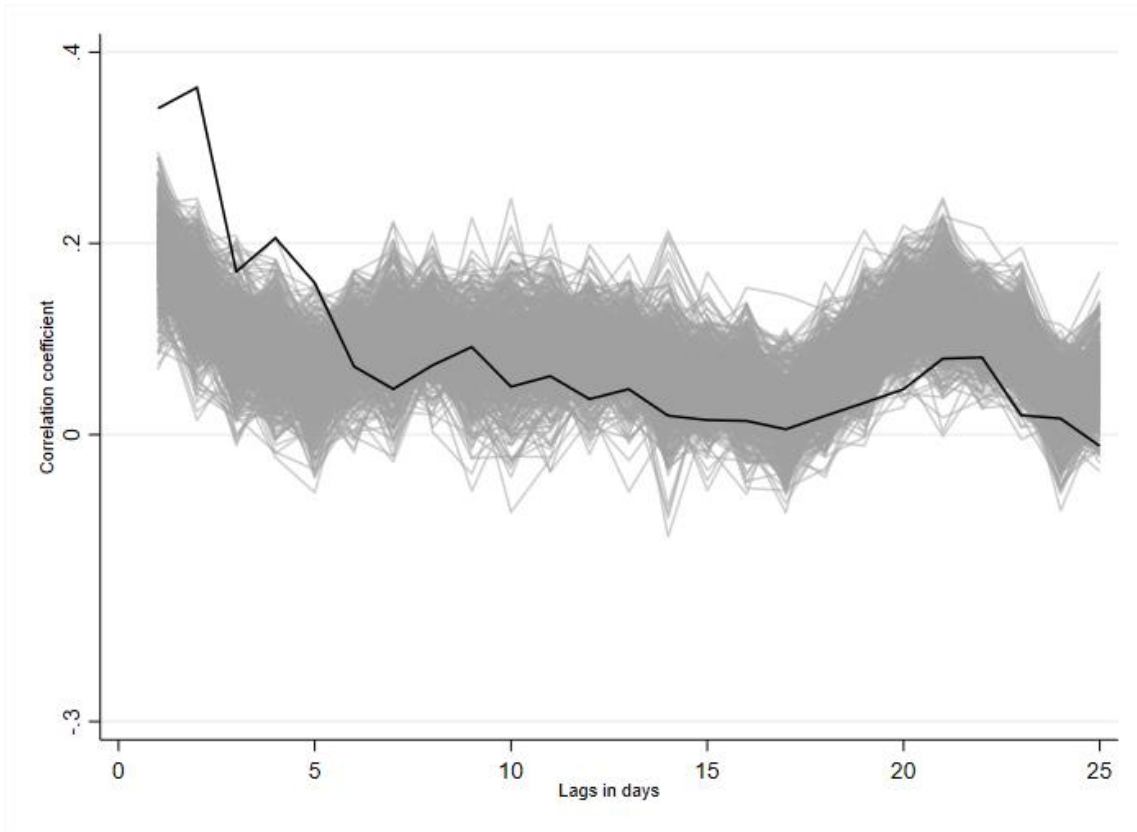


*Supplementary figure 5: Autocorrelation for pressure pain tolerance (PPT) and autocorrelation for 500 randomly shuffled copies of PPT with a simulated effect of day of the week on pain tolerance. The size of the effect is two times the observed differences between days of the week in the full dataset*

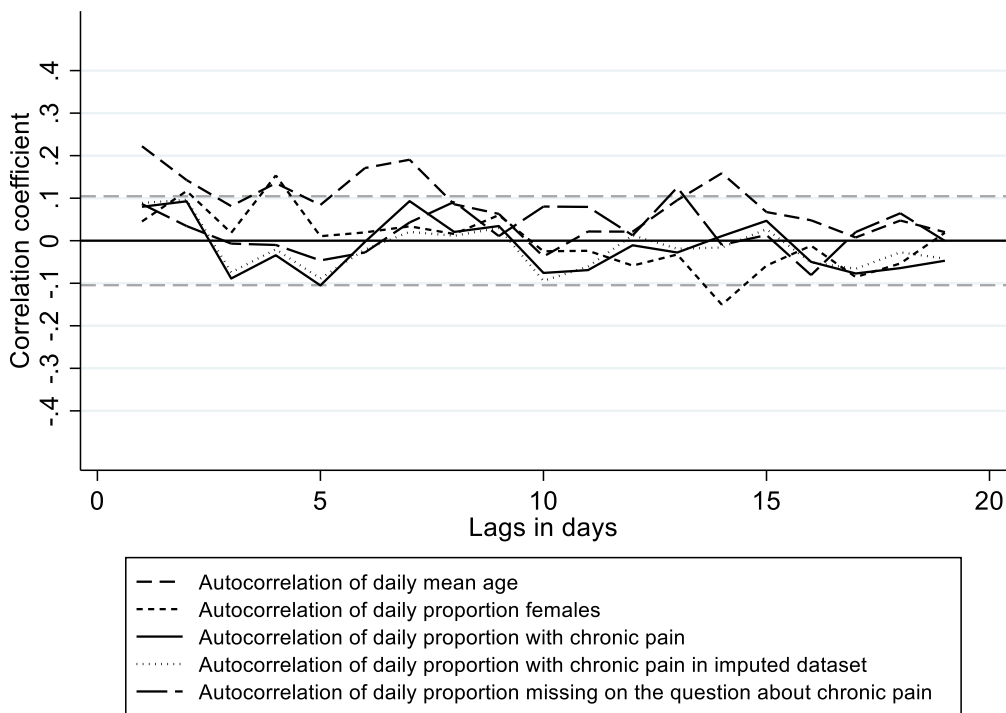




*Supplementary figure 6: Autocorrelation for pressure pain tolerance (PPT) and autocorrelation for 500 randomly shuffled copies of PPT with a simulated effect of study technician rotation on pain tolerance. The effect is two times the observed difference between study technicians in the full dataset*

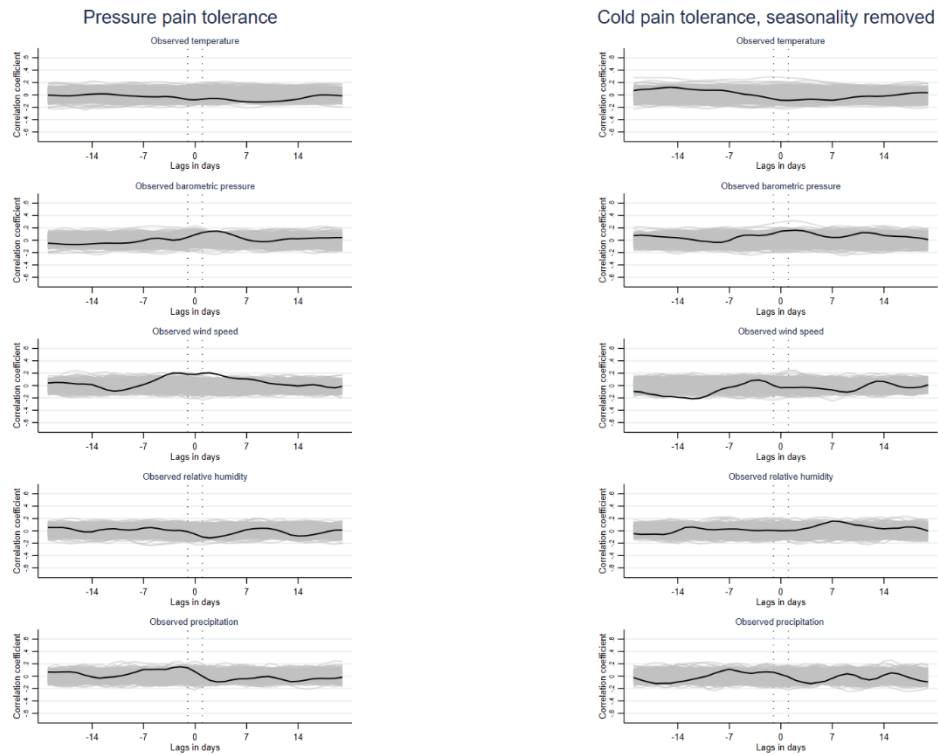


Supplementary figure 7: Autocorrelation for pressure pain tolerance (PPT) and autocorrelation for 500 randomly shuffled copies of PPT with a simulated combined effect of mean age, proportion of females, and study technician rotation on pain tolerance. The effect is two times the observed differences in the full dataset



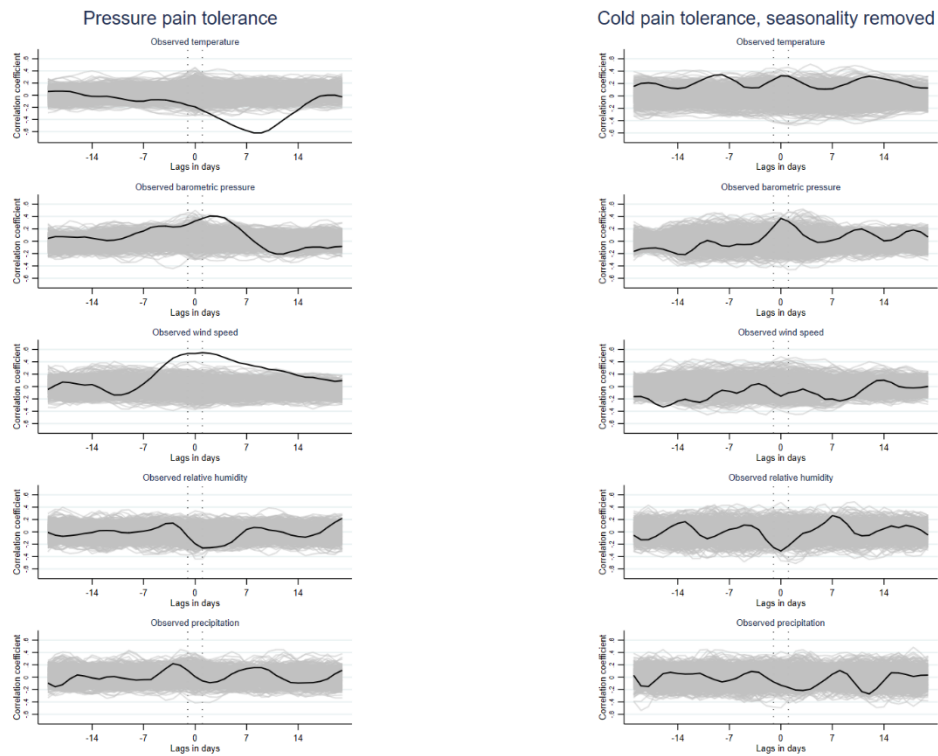
Supplementary figure 8: Autocorrelation for the daily mean age, daily proportion of females, daily proportion of participants reporting chronic pain, daily proportion with chronic pain in an imputed dataset, and the daily proportion missing on the question about chronic pain. Dashed grey lines indicate a significance level of 0.05 for the number of observations in the time series

Cross-correlation between pain tolerance and observed weather  
A: March 2015 to November 2016



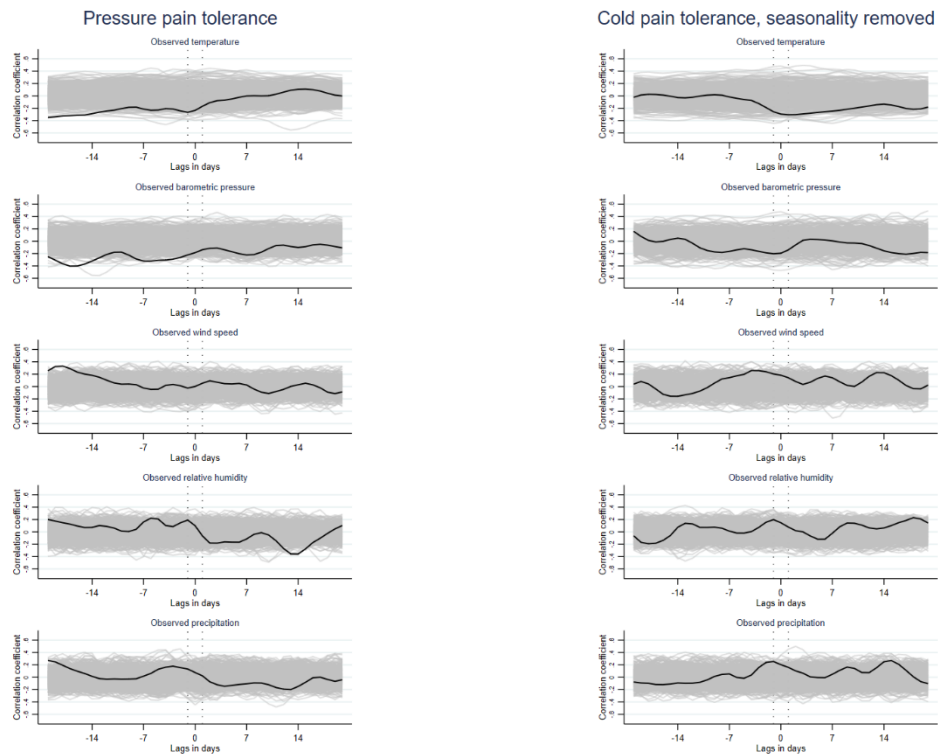
Supplementary figure 9: 3-day moving average of daily mean pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the whole study period, March 2015 to November 2016

Cross-correlation between pain tolerance and observed weather  
 B: March 2015 to June 2015



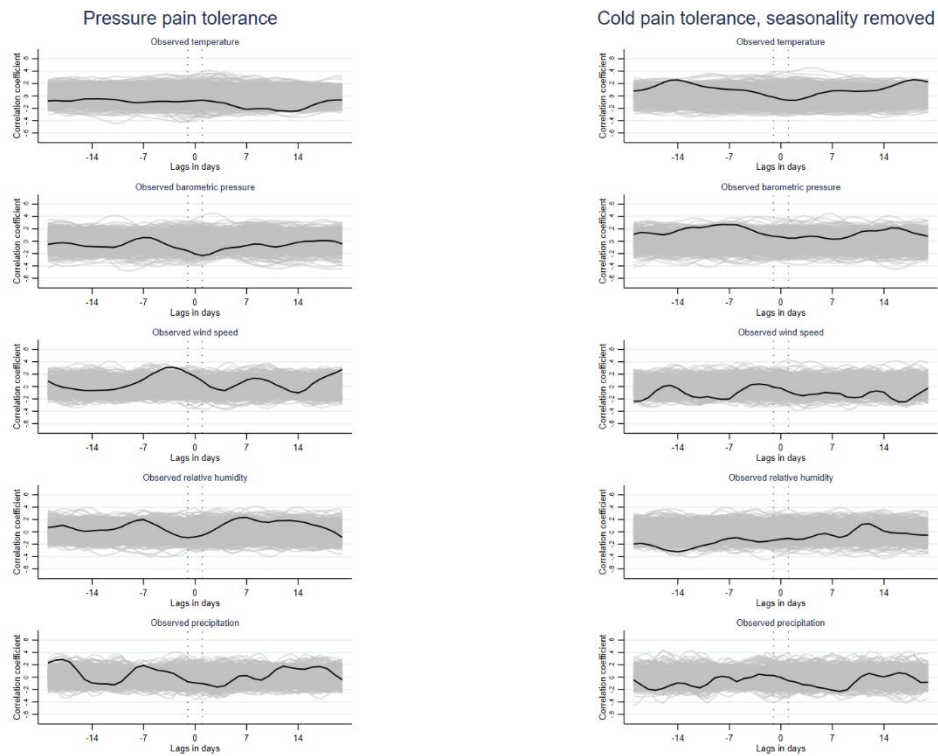
Supplementary figure 10: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period March 2015 to June 2015

Cross-correlation between pain tolerance and observed weather  
C: July 2015 to December 2015



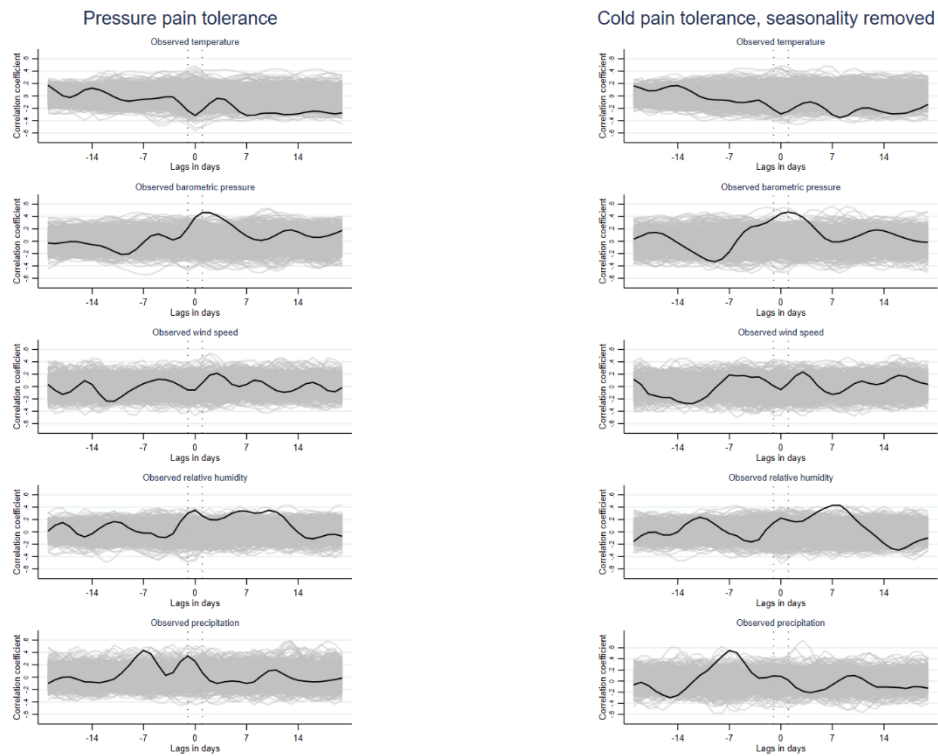
Supplementary figure 11: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period July 2015 to December 2015

Cross-correlation between pain tolerance and observed weather  
D: January 2016 to June 2016



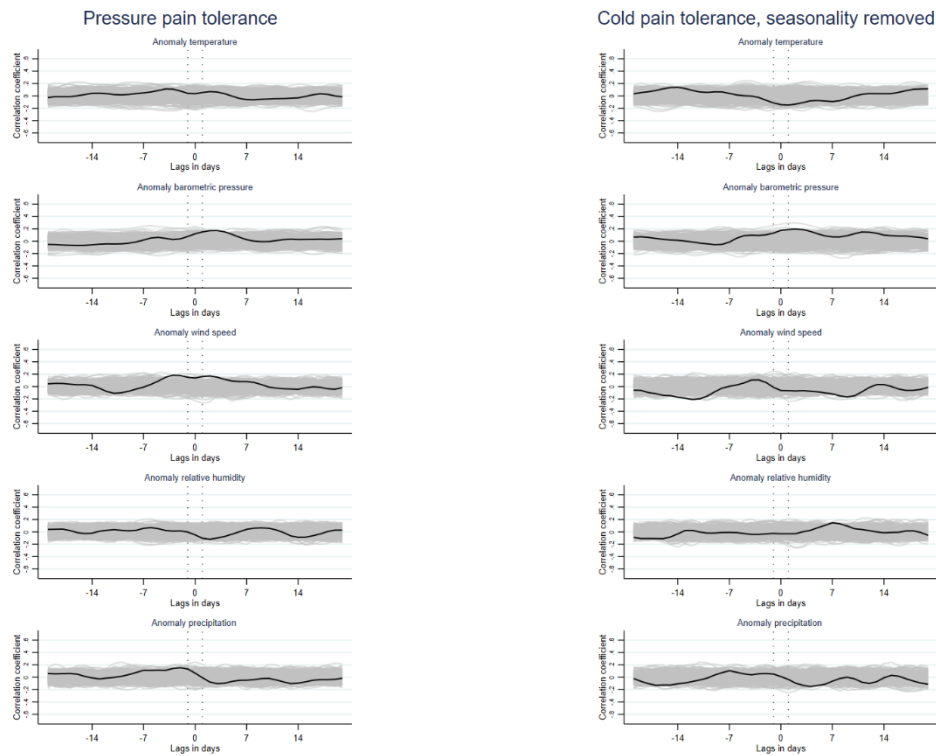
Supplementary figure 12: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period January 2016 to June 2016

Cross-correlation between pain tolerance and observed weather  
E: July 2016 to November 2016



Supplementary figure 13: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period July 2016 to November 2016

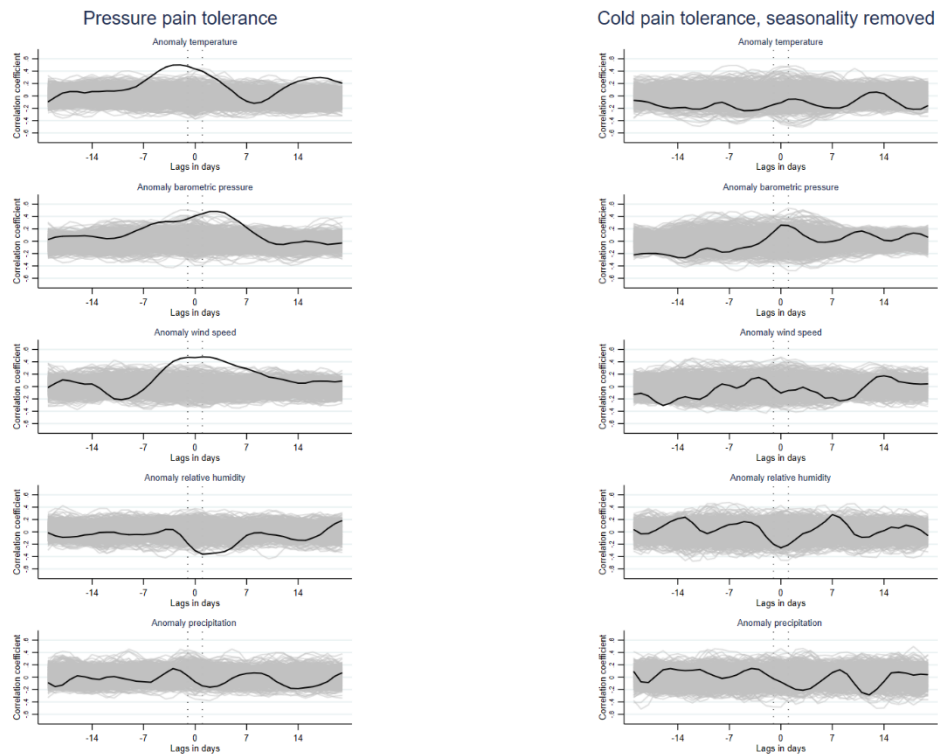
Cross-correlation between pain tolerance and meteorological anomalies  
A: March 2015 to November 2016



Supplementary figure 14: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the whole study period, March 2015 to November 2016

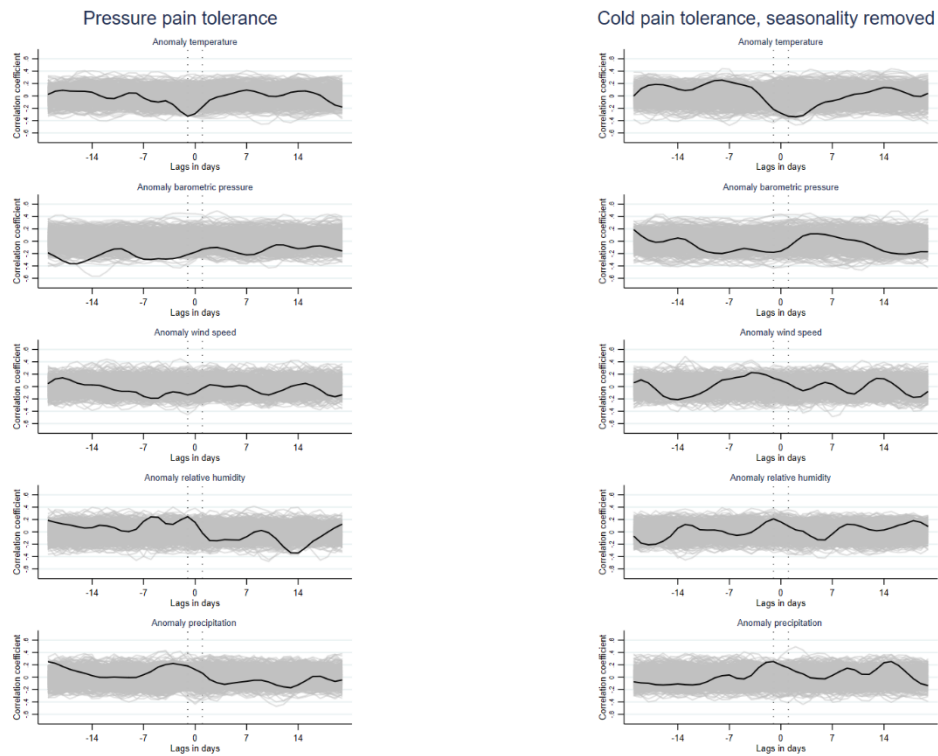


Cross-correlation between pain tolerance and meteorological anomalies  
 B: March 2015 to June 2015



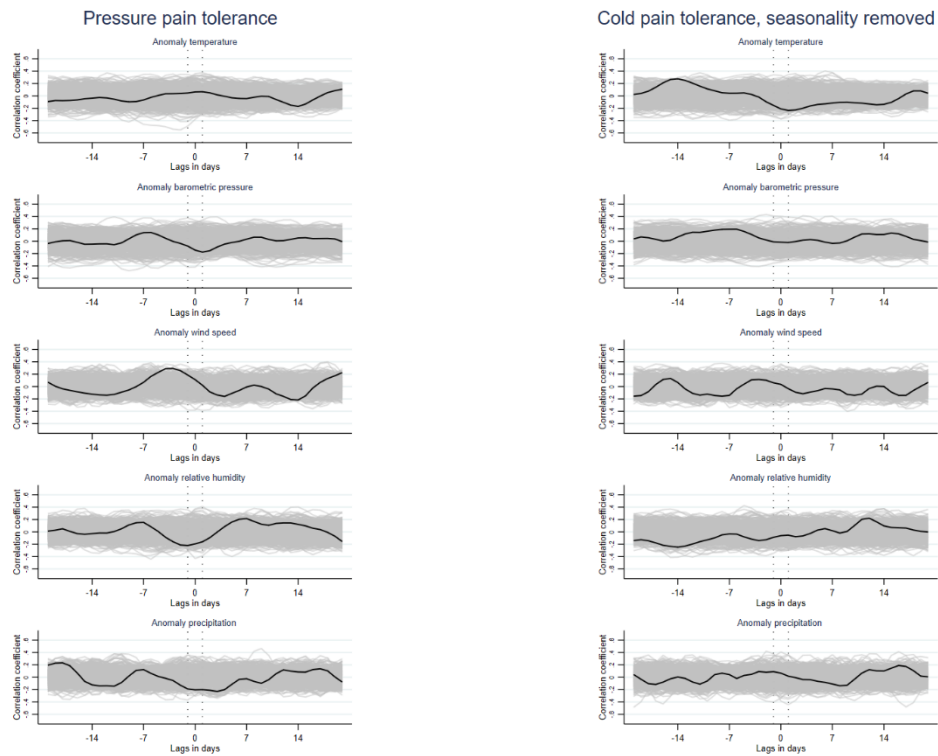
Supplementary figure 15: : 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period March 2015 to June 2015

Cross-correlation between pain tolerance and meteorological anomalies  
C: July 2015 to December 2015



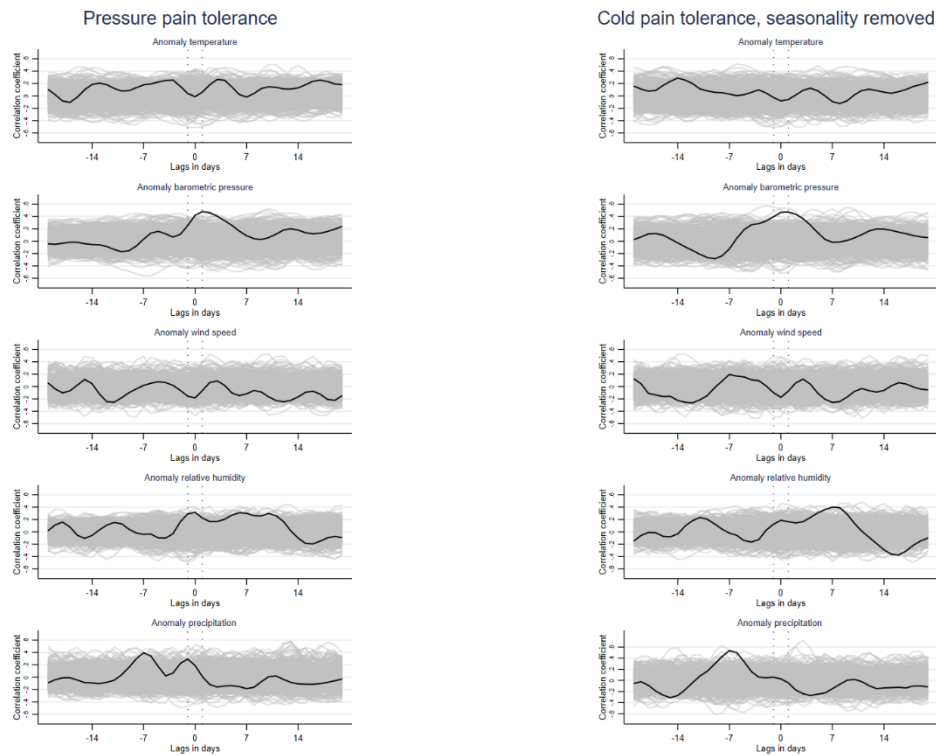
Supplementary figure 16: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period July 2015 to December 2015

Cross-correlation between pain tolerance and meteorological anomalies  
D: January 2016 to June 2016

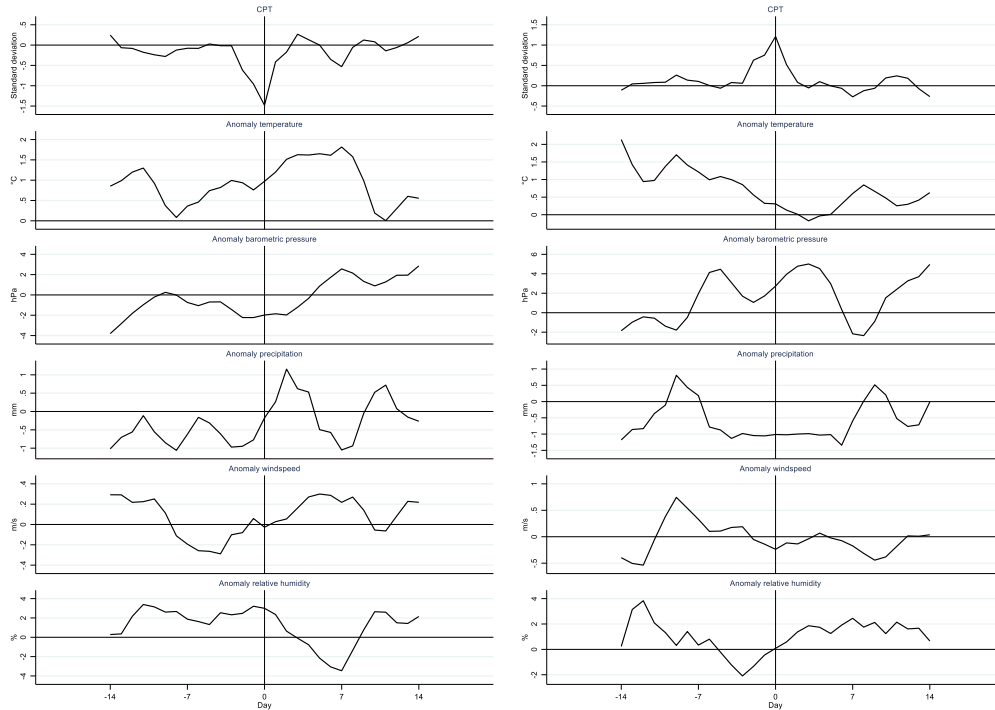


Supplementary figure 17: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period January 2016 to June 2016

Cross-correlation between pain tolerance and meteorological anomalies  
E: July 2016 to November 2016



Supplementary figure 18: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. Dashed lines indicate the 3 days of pain tolerance with which the observed meteorological factors are correlated. Calculated for the period July 2016 to November 2016



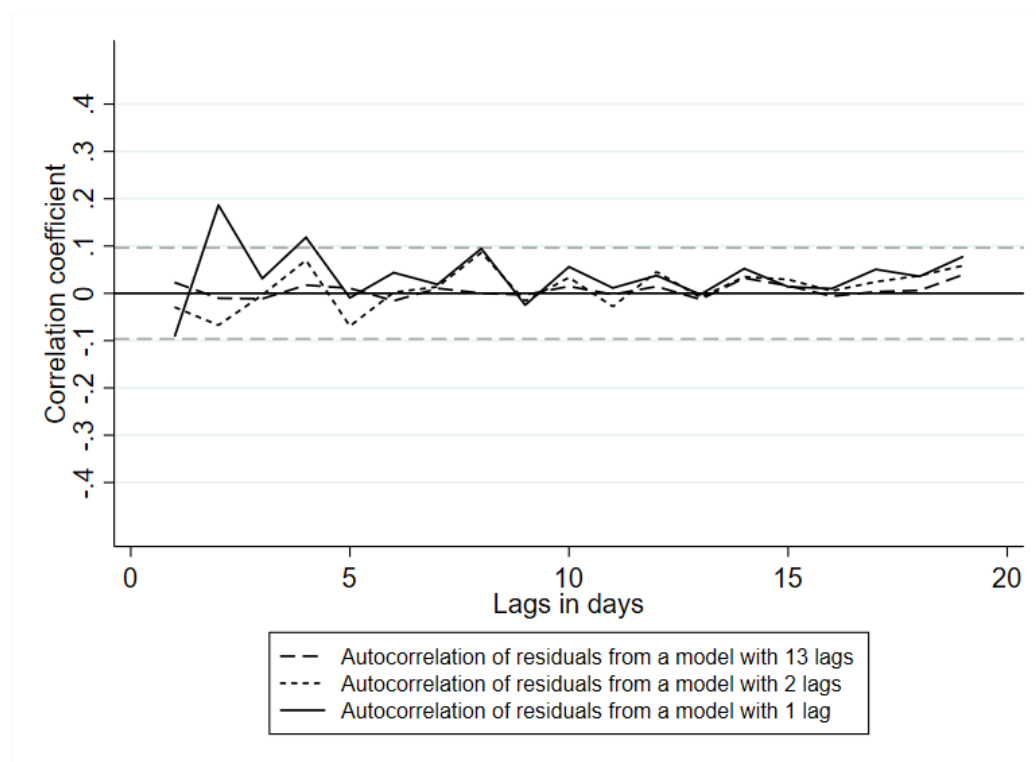
Supplementary figure 19: Mean of 3-day moving averages of cold pain tolerance (CPT) after removal of seasonal variation and meteorological anomalies at local minima and maxima of CPT, which were below 10<sup>th</sup> or above the 90<sup>th</sup> percentile, and in the 14 days before and after

Supplementary table 1 Estimated mean lifetime in days and 95% confidence interval (CI) for the autocorrelation of pressure pain tolerance (PPT) and weather anomalies using a generalized linear model with gamma distribution and log-link function

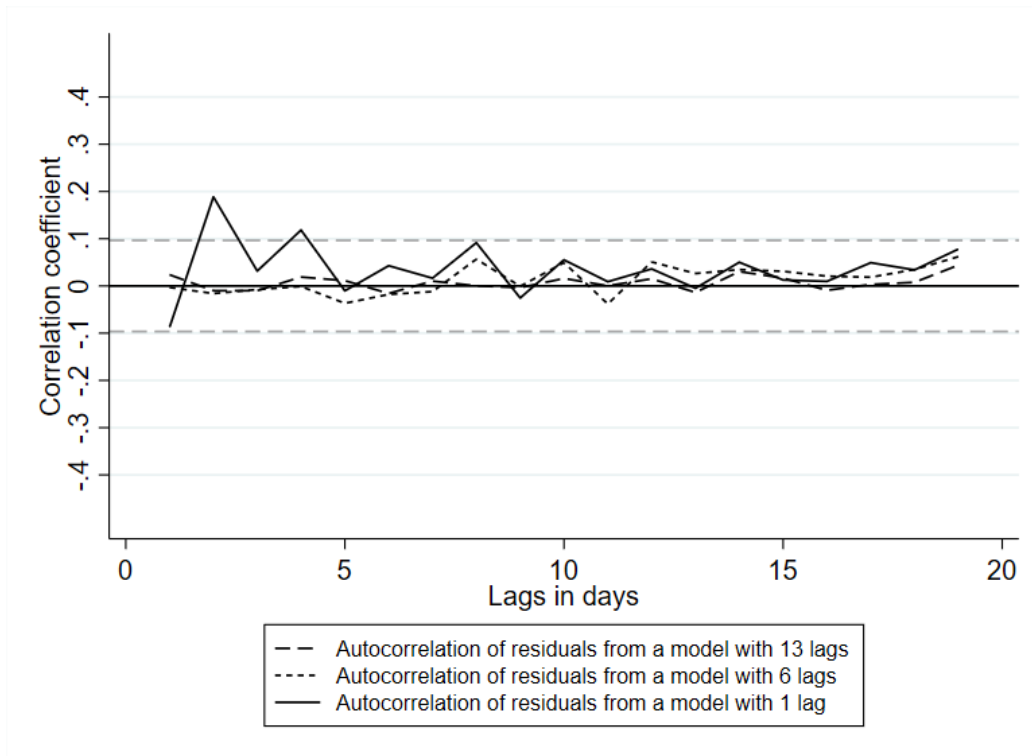
	Mean lifetime in days	95% CI	
		Lower	Upper
PPT	5.1	4.0	7.2
Anomaly temperature	2.9	2.8	3.2
Anomaly barometric pressure	6.2	5.5	7.2
Anomaly relative humidity	3.8	3.5	4.3
Anomaly precipitation	2.6	1.9	4.0

Supplementary Table 2: Granger causality test of meteorological anomalies and observed temperature and barometric pressure on pressure pain tolerance. The different number of lags in the vector autoregressive models are chosen based on either the likelihood ratio test (LR), Akaike Information Criteria (AIC), or Bayesian Information Criterion (BIC), resulting in 6 different models. The p-value indicates if adding the variable(s) to the model increases the predictive skill of the model.

	Models chosen with LR		Models chosen with AIC		Models chosen with BIC	
	Number of lags	p	Number of lags	p	Number of lags	p
<b>Anomalies</b>						
Temperature		0.260		0.009		0.820
Barometric pressure	13	0.009	2	0.736	1	0.891
All variables		0.007		0.020		0.963
<b>Observed</b>						
Temperature		0.175		0.062	1	0.233
Barometric pressure	13	0.010	6	0.017		0.826
All variables		0.006		0.003		0.489



Supplementary figure 20 Autocorrelation of the residuals of pressure pain tolerance from three different vector autoregressive models fitted to pressure pain tolerance, anomaly temperature and anomaly barometric pressure..



Supplementary figure 21 Autocorrelation of the residuals of pressure pain tolerance from three different vector autoregressive models fitted to pressure pain tolerance, observed temperature and observed barometric pressure.