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Our climatic environment and pain

Exposure to cold environment at work and the weather in daily life

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Foreword

In this thesis, I have challenged my fields of competence. My intention was to write a comprehensive story about the effect of our climatic environments on our experience of pain, from a molecular level to the population level. In this attempt, I have read, interpreted, and referred to literature from fields in which I have limited background and ability to carry out thorough quality assessment. The abundance of literature also limited how systematic I could be when reading about subjects that are related to, but are not the focus of my thesis, such as neurology and endocrinology. Thus, I may not represent current discussions and contradictory explanations in a comprehensive manner. There is a huge difference between the molecular level and the population level, and there are likely many gaps in my hypotheses and explanations. Nevertheless, I have tried to understand by connecting the dots of observations. I hope I do not lose you on the way, and that you find my attempt at understanding interesting.

I would like to thank my supervisors Anje, Morten, and Tormod. Thank you for letting me do what I wanted. And thank you for your patience when reading unfinished manuscripts in which half of the argument was still in my head instead of in the text. To Martin Rypdal, thank you for showing me that the world can be complex, and for giving me a new set of tools to understand it. Thank you, Anja, for listening, and for creating a social environment that made it fun to be at work. That environment would also not be possible without all my other colleagues. Thanks to all of you.

My thanks goes to those who participated in the Tromsø Study, for answering the comprehensive questionnaires, and for enduring tests of pain tolerance for no other reason than science itself. Without your more than 20 000 minutes in pain, this thesis would not have been possible.

Finally, thank you, Mariia, for believing in me, for reminding me that I am more than my research, and that my research does not define who I am.

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Summary

Chronic pain is a major health challenge, and musculoskeletal pain is among the main contributors to years lived with disability worldwide. Earlier research found an association between cold exposure at work and musculoskeletal pain. However, the literature is scarce, especially regarding chronic pain. It is a common belief that weather affects pain experience, but the literature on this topic is conflicting, and many researchers have concluded that there is no association. Therefore, the aims of this thesis are to study whether cold exposure at work is associated with chronic pain, and if weather affects pain tolerance.

This thesis consists of three studies, all of which use data from the Tromsø Study. The first is a cross-sectional study of the association between working in a cold environment ≥25% of the time, the frequency of feeling cold, and chronic pain. The second study asks whether those working in a cold environment ≥25% of the time have an increased risk of future musculoskeletal complaints compared to those working in a cold environment <25% of the time. The third study is an analysis of the association between weather and pain tolerance.

The results from the two first studies indicate that cold exposure at work is a risk factor for chronic pain and musculoskeletal complaints. Those working in a cold environment ≥25% of the time had more chronic pain, and the association was strongest for those who felt cold often. Those working in cold environment ≥25% of the time also had an increased risk of future musculoskeletal complaints. The third study found that cold pain tolerance was highest in the winter and that there was a non-random variation in pressure pain tolerance. The timescale of this variation was 5.1 days (95% confidence interval: 4.0-7.2), which is similar to that of the meteorological variables studied. Further, both pressure pain tolerance and cold pain tolerance correlated with meteorological variables, these correlations changed over time, and temperature and barometric pressure predicted future values of pressure pain tolerance. Taken together, these findings suggest that weather affects pain tolerance in a dynamic non-linear way.

Sammendrag (Summary in Norwegian)

Kroniske smerter er en stor helseutfordring, og smerter fra muskelskjelettapparatet er blant de viktigste årsakene til år levd med tapt levekvalitet over hele verden. Tidligere forskning har funnet en sammenheng mellom eksponering for kulde på arbeidsplassen og muskelsmerter, men det er begrenset med litteratur, spesielt når det gjelder kronisk smerte. Det er vanlig å tro at vær påvirker smerteopplevelsen. Litteraturen er imidlertid motstridende, og mange forskere konkluderer med at det ikke er noen sammenheng. Målene med denne avhandlingen er derfor å studere om eksponering for kalde omgivelser på jobben er assosiert med kroniske smerter og om været påvirker smertetoleranse.

Denne avhandlingen består av tre studier, som alle bruker data fra Tromsø-studien. Den første studien er en tverrsnitts studie av sammenhengen mellom å jobbe ≥25% av tiden i kalde omgivelser, hyppighet av å fryse på jobb og kronisk smerte. Den andre studien handler om hvorvidt de som arbeider ≥25% av tiden i kalde omgivelser har økt risiko for fremtidige muskelskjelettplager sammenlignet med de som jobber <25% av tiden i kalde omgivelser. Den tredje studien er en analyse av sammenhengen mellom vær og smertetoleranse.

Resultatene fra de to første studiene indikerer at kuldeeksponering på jobb er en risikofaktor for kroniske smerter og muskelskjelett-plager. De som jobbet ≥25% av tiden i kalde omgivelser hadde mer kroniske smerter, og assosiasjonen var sterkest for de som ofte frøys på jobb. De som jobbet ≥25% av tiden i kalde omgivelser hadde også en økt risiko for fremtidige muskelskjelettplager. Den tredje studien fant at kuldesmertoleranse var høyest om vinteren, og at det var en ikke-tilfeldig variasjon over kort tid i trykksmertoleranse. Tidsskalaen for denne variasjonen var 5.1 dager (95% Konfidens intervall: 4.0-7.2), noe som er i samme størrelsesorden som for de studerte meteorologiske variablene. Videre korrelerer både trykksmertoleranse og kuldesmertoleranse med meteorologiske variabler. Denne korrelasjonen endres over tid, og temperatur og barometertrykk kan predikere fremtidige verdier for trykksmertoleranse. Samlet tyder disse funnene på at sammenhengen mellom vær og smertetoleranse er dynamisk og ikke-lineær.

List of papers

Paper 1

Farbu EH, Skandfer M, Nielsen CS, Brenn T, Stubhaug A, Höper AC. Working in a cold environment, feeling cold at work and chronic pain: a cross-sectional analysis of the Tromsø Study. *BMJ Open* 2019;9:e031248.

Paper 2

Farbu EH, Höper AC, Brenn T, Skandfer M. Is working in a cold environment associated with musculoskeletal complaints 7-8 years later? A longitudinal analysis from The Tromsø Study. *Int Arch Occup Environ Health* 2021;94:611-619.

Paper 3

Farbu EH, Rypdal M, Skandfer M, Steingrímsdóttir ÓA, T Brenn, Stubhaug A, Sivert Nielsen C, Höper, AC. To tolerate weather and to tolerate pain – two sides of the same coin? The Tromsø Study 7. *Accepted for publication in Pain 13.07.2021*.

Abbreviations

BMI	body mass index
CI	confidence interval
CPT	cold pain tolerance
IASP	International Association for the Study of Pain
IRR	incidence rate ratio
MSC	musculoskeletal complaints
NREE	Norwegian Register of Employers and Employees
OR	odds ratio
PPT	pressure pain tolerance
TRPM8	transient receptor potential melastatin 8

1 INTRODUCTION

Pain is a major public health challenge, regardless of whether it is a symptom of underlying disease or experienced in the absence of a well understood biomedical cause (1). Musculoskeletal pain is a major cause of years lived with disability (2, 3). The socioeconomic costs of chronic pain and its consequences are substantial. Quantifying these costs is difficult, but estimates range from 3% to 10% of the gross domestic product (4).

A common assumption is that the weather affects people's pain conditions (5, 6). Further, exposure to cold temperatures is associated with people's experience of pain, whether it is in daily life (7), at the workplace (8, 9), or in an experimental setting such as immersing one's hand in ice-cold water (10). Thus, elucidating the association between our physical environment and pain might better our understanding of pain and our ability to prevent it.

1.1 Pain

Until recently, the International Association for the Study of Pain defined pain as:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (11).

This definition has been criticized for trivializing severe chronic pain as something "unpleasant" (12). However, the definition is meant to capture all pain, not only severe chronic pain (13), which is why it does not specify important aspects of pain like intensity, duration, and how widespread the pain is. The International Association for the Study of Pain's updated definition is:

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (11).

Common to both definitions is that they do not include the cause of pain. Pain can be caused by non-neural or neural tissue damage. On the other hand, as the new definition points out "… *resembling that associated with, actual or potential tissue damage*", the experience of pain is not always accompanied by tissue damage that can explain it. Indeed, the correlation between observable tissue damage and pain experience is often poor (14), and only some individuals who suffer from disease actually develop chronic pain (15, 16). With this in mind, pain can be studied as a disease state in itself, instead of just a symptom caused by a specific disease or occurring at a given anatomical site (1).

1.1.1 Acute pain and persistent/chronic pain

Acute pain is an immediate response to something that can threaten the organism and is an important trait for survival. Indeed, humans who are unable to feel pain are at risk of dying at a younger age due to high fever or injuries, like burns or fractures and their complications (17). One can see acute pain as a mechanism to protect tissues, or adjust the stress put on them in order to protect from damage and enhance healing. In many cases, pain is a transient symptom. For example, patients with acute low back pain, a common musculoskeletal disorder (18), improve markedly in the 6 weeks after the onset of pain (19).

The definition of chronic pain by duration has been widely discussed, but it has been suggested that, for pain to be considered chronic, it should last or recur for more than 3 to 6 months (20). In the International Classifications of Diseases, revision 11, chronic pain is defined as a pain condition that persists or recurs for longer than 3 months (21). This definition is only slightly different from that used in this present thesis: "lasted for 3 months or longer", but inconsistencies in the definition are common throughout the research field (22). Still, the definition can have an impact when calculating prevalence. A systematic review found a lower prevalence in studies that defined chronic pain as lasting 6 months or longer compared to 3 months or longer, but this difference was not significant. Further, the estimated prevalence of chronic pain varied substantially (from 8.7% to 64.4%), and the pooled estimate was 31% (22). This large variation in prevalence reflects our poor understanding of chronic pain. Further, dichotomizing pain into acute or chronic could be simplifying and limiting, as research using trajectory analysis has indicated distinct variants of pain, and showed that a small proportion of people with chronic pain do get better (23, 24). Nevertheless, this common dichotomization is used throughout this thesis. For a discussion on measuring chronic pain, see section 5.1.4.

1.1.2 Risk factors for chronic pain

There seems to be substantial heritability in different phenotypes of chronic pain (25, 26), and pain among parents is reported to be a risk factor for pain in their offspring (27, 28). There is a higher prevalence among females (22), and several studies have found an increase in the prevalence of chronic pain with increasing age (22, 29). No substantial period-cohort effects have been found (30), and it is probably not all nature; nurture likely plays a role as well. For example, the increased risk of chronic pain associated with parental chronic pain seems to be modified by physical activity (27), and adverse events in childhood are associated with future chronic widespread pain (31, 32).

As for many other diseases, chronic pain is unevenly distributed across socioeconomic positions, with a higher prevalence and higher risk of future chronic low back pain among those with lower socioeconomic position (33) and more chronic musculoskeletal complaints (MSC) among those with lower education (34, 35). A systematic review of studies on children and adolescents found some evidence for a long-term effect of socioeconomic position on the risk of future chronic pain (36). The causal pathways between socioeconomic position and chronic pain are not well understood. Lower socioeconomic position is associated with poor health, and poor self-reported health and existing pain are important risk factors for chronic pain (23, 35, 37). Several diseases are also more frequent among those with lower socioeconomic position, and some of the effect on pain could be mediated through these diseases, for example increased risk of neuropathic pain due to diabetes mellitus type 2 (38-41).

Occupational exposures could also explain some of the socioeconomic differences in the prevalence of chronic pain. Heavy manual labor, poor ergonomic positions, and poor psychosocial work environment are all associated with different chronic pain conditions (42-44). Whole body vibration and vibration from handheld equipment may also cause different pain conditions. However, authors have not discussed the contribution of vibrations to any chronification of these conditions (45).

Individual risk factors such as smoking, obesity, and physical inactivity tend to be unevenly distributed along the socioeconomic gradient, with a higher prevalence among those with a lower socioeconomic position, and they have also been identified as possible risk factors for various chronic pain conditions. Smoking is associated with an increased risk of future chronic MSC (46), with persistent pain, and with developing pain over a 15-year period (23). However, this relationship is complex, as nicotine also has both a peripheral and central analgesic effect (47). High body mass index (BMI) was associated with an increased risk of both widespread and regional chronic pain in a Norwegian population (48, 49). A meta-analysis on physical activity as a risk factor for chronic low back pain found a small preventive effect of physical activity. However, the authors of the review advised careful interpretation due to limitations in the original studies (50). One prospective study of risk factors for fibromyalgia found a small, non-significant, protective dose-response relationship with physical activity (49). There are also indications that physical activity has an effect in the treatment of chronic pain (51).

Sleep has a bidirectional relationship with pain: poor sleep can increase the frequency of pain symptoms the next day and vice-versa (52). Poor sleep is also associated with the development of chronic pain and chronic widespread pain over the course of years (53, 54). A recent mendelian randomization reported that poor sleep can have a causal effect on pain, but that pain has a smaller effect on sleep (55).

Poor mental health is also associated with a higher risk of chronic pain (41), and is also likely a bidirectional relationship. In addition, chronic pain and depression may share a genetic predisposition (56). Poor mental health is not only a risk factor for chronic pain, it also modulate the outcome of chronic pain. For example, positive affect states, like gratitude and happiness, seem to decrease pain severity among patients with chronic pain (57), whereas more specific psychological constructs, like pain catastrophizing, increase pain (58).

1.2 How do we feel? The basics of perception and pain

The brain constructs our experience of pain, temperature, and the position of our limbs. However, a variety of sensory input is important for these constructions. This chapter will give a very simplified introduction to the physiology of our sensory system. The nervous system is full of redundancy and overlapping functions, and the interaction between the "pain system" and the immune system, the endocrine system, the autonomic nerve system, and other cognitive processes will not be the subject of comprehensive discussion here.

In general, a sensory signal starts with the nerve endings transducing a mechanical, chemical, thermal, or other stimuli into an action potential, an electrical signal (Figure 1A). These nerve endings can be free or coupled to specialized cells in skin, muscles, or other tissues (59). The action potential then continues along the nerve and into the dorsal horn of the spinal cord (Figure 1B). Here the signal is transmitted through a synapse to a new neuron that passes the signal on to thalamus, and further on to other parts of the brain involved in perception and pain (Figure 1C and 1D). However, along the way from the nerve ending to the brain, the signal might be modulated or affected by different processes or properties.

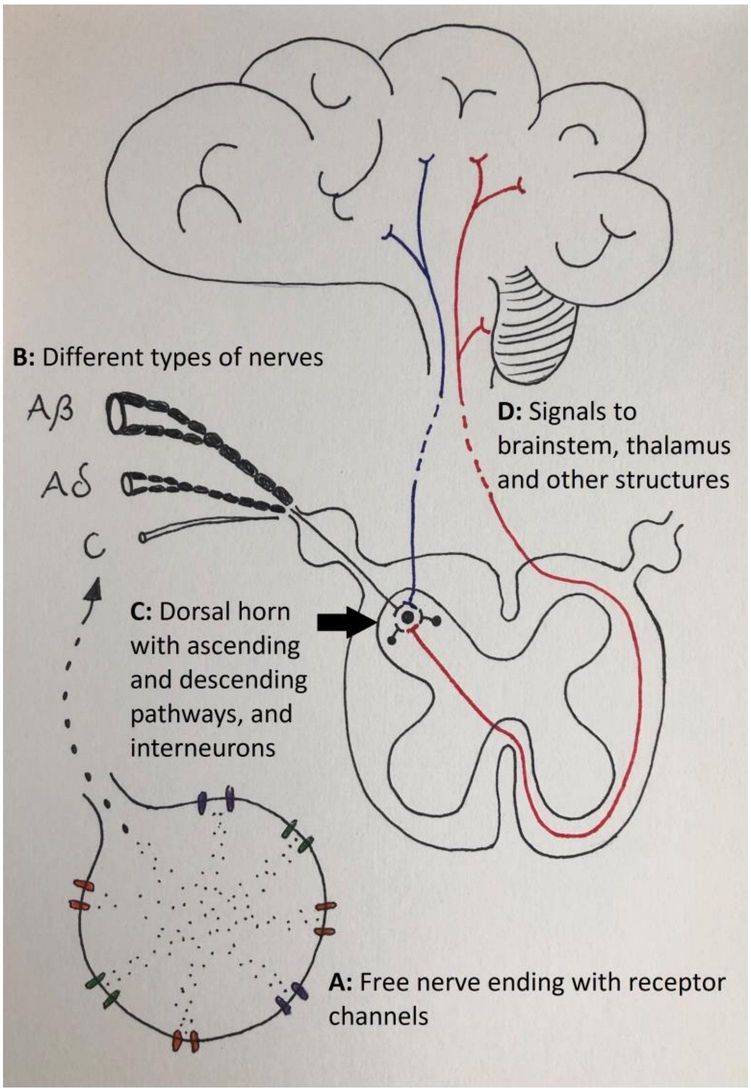

Figure 1. Simplified figure of the sensory system. Drawing by Mariia Pihlainen.

The properties of a nerve vary according to what information the nerve transmits. Nerve fibers that transmit information about proprioception or touch (Aβ-fibers, Figure 1B) are thicker and more myelinated than Aδ- and C-fibers, which transmit pain and temperature. Thickness and myelination increases the speed of transmission. This explains why you feel the blow before the pain when you hit your toe (59).

Some nerves with free nerve endings are called nociceptors, which, when stimulated, can cause an experience of pain. Nociceptors respond to different stimuli depending on which receptor channels are embedded in their cell membrane (Figure 1A). For example, the channel named transient receptor potential melastatin 8 (TRPM8) is involved in the feeling of cold, and mice without this channel have heavily impaired cold sensitivity (60).

A complicating factor is the existence of polymodal nociceptors, which react to two or more stimuli (59). Even though nociceptors are often called “pain receptors”, there can be nociceptive signals without pain, pain without nociceptive signals, and nociceptive signals without any real threat to the tissue (61).

A key feature of many sensory neurons is their ability to adapt rapidly. In such neurons, the rate of action potentials is dependent on the rate of change in stimuli, rather than the intensity alone. The rate of signals decline over time when the stimuli remains at the same intensity (59). For example, thermoreceptors are very active during a change in temperature, but they can adapt to a stable temperature over time (62, p.14-15). In contrast to thermoreceptors, many nociceptors adapt slowly, meaning that they continue to send action potentials with sustained stimuli (63, p. 31).

The primary afferent sensory neuron connects to the dorsal horn of the spinal cord, where there are neurons that can forward the signal to the brain, but there are also several different types of interneurons. These interneurons are involved in the processing of sensory input and contribute to signal regulation, determining which signals from the primary afferent nerves are transmitted up the spinal cord (64). This regulation is also affected by descending nerve signals, which can be either excitatory or inhibitory (64).

Studies suggest that the feeling of pain, temperature, and itch are organized in labeled lines that travel from the nerve endings through the spinal cord and to the brain. These lines probably enable us to distinguish between these feelings (65). However, these hypothesized labeled lines are debated (66), and experimental data indicate cross-inhibition at the spinal level (67). In addition, a large part of C-fibers in mice are sensitive to both heat and cold, and the sensation of warmth is dependent on inhibition of cold active afferents (68). The central nervous system includes several structures involved in the processing of thermal or nociceptive signals (65). One is the brainstem, an important element in the regulation of homeostasis throughout the organism, but also an important part in the descending modulatory system (65). Another area that is involved in both thermal perception and pain is the insula (65, 69). Some experience a complete and selective loss of pain and thermal perception due to small infarctions in the insula (70).

As mentioned earlier, the experience of pain is not dependent on nociceptive signals. The occurrence of phantom limb pain is one example of the brain's ability to construct the feeling of pain without nociceptive signals (71). And the experience of pain seems to depend on both nociceptive and non-nociceptive sensory signals (72). Other processes in the brain may have an important impact on how intense or unpleasant pain is. The spontaneous baseline activity in the brain before an external stimuli has been shown to explain some of the variation in pain sensitivity (73). For example, negative emotional status can enhance pain experience, and the interpretation or anticipation of pain can modulate the experience (74). Pain intensity can be reduced if the pain is perceived as understandable, time-limited, and controllable. The intensity can also be modified by what is important for the organism, i.e., when survival is more important than pain, or when winning is more important than pain for athletes (61).

Properties that contribute to pain and that may contribute to the transition from acute to chronic pain

The following paragraph contains a brief description of some important properties that contribute to hyperalgesia, an increased response to a noxious stimuli, and allodynia, a painful experience from an innocuous stimuli, like a gentle touch (75). These same properties may also contribute to the transition from acute pain to persistent/chronic pain.

When an injury occurs in a tissue, a variety of chemical substances are released, often called the inflammatory soup. Nociceptors have receptors for these substances, and the net effect is that the nociceptors are more easily activated (76). Their increased excitability heightens one's sensitivity to, for example, touch or temperature, and is called peripheral sensitization. There are several mechanisms that can contribute to sensitization during the processing of the nociceptive signal in the dorsal horn, both locally in the dorsal horn, and by altered inhibition and excitation from descending pathways (76, 77). Patients with chronic pain also have different temporal summation than healthy controls, i.e., repeated stimuli and consequent neural firing become integrated over time, and thus pain experience increases (77). The response to nociceptive stimuli in the brain is also altered among patients with chronic pain

(78). For example, there seems to be a shift from nociceptive circuits to emotional circuits during the chronification of back pain (79).

1.3 Temperature, barometric pressure, relative humidity, and pain

1.3.1 Epidemiological studies on weather and pain

In this thesis, the term “climate” refers to the characteristic weather of a country or region; weather refers to the combination of all weather constituents: temperature, barometric pressure, wind etc.; weather constituents are sometimes also referred to individually.

A common belief is that weather affects people’s pain or health. This belief is reported to be held by over 40% of patients with osteoarthritis (5), fibromyalgia (80), chronic pain (81), or migraine (82, 83), and it is also highly prevalent in the general population (6). There might be differences depending on the climate and the population. For example, only 10% of migraine sufferers reported weather as a trigger in a small study from India (84). In a survey of the general population in Finland, almost 30% reported cold-related musculoskeletal pain; meaning they believed exposure to cold temperatures was the cause of an acute experience of pain (7, 85). A warmer climate, i.e., Turkey compared to Norway, may also improve rehabilitation outcomes (86).

On the other hand, studies that used meteorological variables to study the association between weather and musculoskeletal pain have shown conflicting results (87). For example, two different case-crossover studies concluded that meteorological variables had either no effect, or no effect of clinical importance, on the onset of low back pain (88, 89). Others have found that below-normal barometric pressure, above-normal relative humidity, higher precipitation rate, and stronger wind increased the risk of pain among chronic pain sufferers (90, 91). Nevertheless, many authors have concluded that this association is small or non-existent (87).

Some have suggested that pain among patients with rheumatoid arthritis is affected by cold temperatures, atmospheric pressure, and relative humidity. A systematic review of pain among these patients did not identify any consistent group effect, but concluded that some individuals might be affected more than others (92). In a study of fibromyalgia, lower barometric pressure was associated with higher pain intensity and pain unpleasantness, though a sub-group showed the opposite reaction (93).

Results regarding headaches and migraine are also inconsistent. Some studies found no correlation (94, 95), whereas others found an association between episodes of migraine and meteorological variables, including positive and negative changes in temperature (96), higher temperature (97), lower barometric pressure (97) , and decreases in barometric pressure (98). Some studies have reported an association on an individual level, showing that different weather constituents affect each individual differently (99). Other studies, which found no association in their whole study sample, argued that some individual participants were strongly affected by weather (95, 100).

There are several methodological difficulties in the field of pain conditions and weather that make comparisons between studies difficult. Firstly, the conditions, populations, places, and climates are diverse. Moreover, there is a high degree of heterogeneity in study designs; some are prospective, while others are diary-based surveys or cross-sectional studies. The outcome measures are also diverse; some studies use self-reported data, while others use emergency department visits or the purchase of medication. Moreover, many studies used multiple testing, but did not correct for it. Finally, researchers frequently make the assumption that the relationship between weather and health is linear and constant. This is discussed further in section 1.6.

1.3.2 Experimental studies on physical environmental factors and pain

Even though the experimental literature on how the physical environment can induce clinical pain in humans is scarce, many studies have used components from the environment to model pain. One study simulated airplane travel in a pressure chamber, which provoked headache among participants who were prone to them during airplane travel (101). A common experimental model of pain in humans is the immersion of a hand in cold water, called the cold pressor test (10). Another model is the thermal grill illusion, where simultaneous stimulation with non-noxious heat and cold can give rise to an experience of pain (66). An interesting finding is that pain caused by immersing a hand in water that is 8°C for 30 minutes tends to decrease with repeated exposures. However, the maximum decrease was reported to be reached at 5 days, with no additional decrease thereafter (102, 103).

Colder skin temperature due to colder ambient temperature might reduce cold pain, while the effect of cold skin temperature on heat and mechanical pain is uncertain (104). Further, studies have found that suppression of primary cold Aδ-fibers increases cold pain (105), and that cooling can induce an analgesic effect (106). A study of human participants immersed in a tank filled with 30°C water, which was subsequently cooled to 24°C and then warmed up to 39°C over 60 minutes, showed no change in participants' heat pain threshold or heat pain tolerance (107). A study of the thermal grill illusion found that body heating, by perfusion and circulating-water garment, increased participants' pain threshold, while cooling reduced it (108). They also found a correlation between whole body temperature and pain threshold, and the authors argued that nociception has an interoceptive dimension, meaning that sensory input about the internal state of the organism plays a role in the experience of pain. However, they found small differences when testing thermal pain threshold and intensities (108). These conflicting findings combined with the fact that the pain stimulus is a construct of thermal exposure makes it difficult to conclude or to generalize these findings to pain processing in general.

In the realm of animal studies, humidity, temperature, and barometric pressure have been reported to affect nociceptive sensitivity (109). These environmental factors are thought to result in stress-induced hypoalgesia or hyperalgesia, depending on the context (109). Other studies have reported that humidity interacts with season and affects thermal nociceptive sensitivity in mice, and that gene-environment interaction explains some of the observed variation (110). Some studies have found an increase in pain behavior when lowering barometric pressure and ambient temperature (111, 112). These results also indicated that the effect of barometric pressure was mediated by sympathetic activity. However, increased pain behavior due to lower temperature was not affected by a sympathectomy, indicating a different causal mechanism for lowered temperature (111).

1.4 Physiological and functional effects of cold exposure and changing barometric pressure

The increased mortality observed when temperatures are colder exemplifies the potential effect of temperature on health (113). Monitoring and implementing suitable reactions to the thermal environment are important for our survival. Indeed, our best protection against environmental stress is our behavior; we build warm houses and put on warm clothing. Nevertheless, when we are exposed to cold temperatures, many physiological responses are initiated to preserve or restore our thermal balance and increase the likelihood of survival. The main goal is to keep the body's core temperature within a suitable range. One tactic is constriction of the peripheral blood vessels, allowing the periphery to be cooled down (114). If the body's temperature drops further, it can increase the heat produced through increased muscle work, such as shivering.

When the temperature in different tissues drops, a variety of functions might be affected. In the musculoskeletal system, the short-term effects include decreased muscle power and contraction velocity (115), decreased nerve conductivity (115), and increased stiffness of tendons (116). In the vascular system, lower temperatures are associated with higher blood pressure (117-119), and even mild cooling (24°C and 10 m/s air velocity compared to 24°C) can increase blood pressure, platelet count, red cell count, and blood viscosity (120). Systolic blood pressure variability has also been found to increase at lower temperatures (121), and some have even suggested that temperature affects inflammatory markers (122) and metabolic pathways (123).

Exposure to cold temperatures does not only affect our physiology; it might also cause a variety of symptoms. Over 45% of participants in a Finnish study reported experiencing cold-related symptoms (7, 124), the most frequent of which were musculoskeletal symptoms, respiratory symptoms, and fingers turning white, blue, or blue-red (7). The prevalence of cold-related symptoms seems to increase in the presence of underlying diseases (124).

Several functions have been reported to decrease with decreasing temperature, for example reduced sensitivity and dexterity of the fingers, as well as the capacity to do heavy or prolonged physical work (7). It was also hypothesized that cold stress can steal attention away from other cognitive tasks and thus reduce performance. This effect seems to increase with increasing cold stress and difficulty of the cognitive task (125) . More subtle effects of temperature on health include the hypothesized evolutionary gradient in a gene encoding for a cold-receptor by latitude (126) and the possible cold-induced epigenetic programming of sperm (127).

The literature on the relationship between barometric pressure and health is scarce when compared to that on cold temperatures. However, one study indicated a negative correlation between barometric pressure and blood pressure (128).

1.4.1 Adaptation, cross-adaptation, and cross-sensitization

The term adaptation can have different meanings depending on the field. In biology, adaptation is something that happens over generations within a species, whereas acclimatization is the processes within one individual. In physiology, adaptation can occur within one individual or even one cell (129). Throughout this thesis, the term “adaptation” refers to physiological adaptation, and will be used interchangeably with acclimatization to respect the field from which the study originated. When the term “adaptation” is used to refer to the result of an evolutionary process, it will be specified.

Acute responses to cold exposure can be attenuated through adaptation, and reduced pain experience after repeated local cold exposures is a good example (102, 103). However, adaptation can also be a global response. Acclimatization can occur in three different ways or a combination of them: by lowered body temperature, by insulation (more fat), and by increased metabolic rate (130). For example, 10 days of cold exposure increased insulin sensitivity in patients with type 2 diabetes mellitus (131). However, many of the studies on acclimatization were carried out in an experimental setting with substantial cold exposure, in conjunction with expeditions, and among indigenous people or workers exposed to major cold stress. To what extent these adaptations occur after exposure to cold temperatures in daily life is uncertain (132). Nevertheless, repeated exposure to cold air (120 minutes, 10°C) decreased participants’ feeling of cold over a period of 11 days. In the same experiment, skin temperature increased during the first 5 days, but tended to decrease again towards day 10, and norepinephrine response to cold exposure was also attenuated at day 10 (133). Even though the magnitude of acclimatization in daily life is uncertain, it may explain the changing association between temperature and mortality over time (134).

A complicating factor is the suggested cross-adaptation and cross-sensitization (135) based on the observation that adaptation to one stressor affects the response to a novel stressor. For example, both cold water adaptation and heat adaptation lead to a smaller sympathetic response to exercise in a hypoxic environment (136, 137). However, the results are conflicting: some studies found no cross-adaptation, whereas some animal studies did report cross-sensitization (135).

1.5 Cold exposure at work and musculoskeletal pain

One way to study cold temperature as a risk factor for pain is in the occupational setting. Almost 13% of participants in the Norwegian workforce reported that they are exposed to a cold environment ≥25% of their working time. Workers in cold stores, fisheries, farming, and the construction industry most frequently reported that they were exposed to cold temperatures (138). Cold environment at work is defined as working in a temperature below 10°C (139). However, many other important factors influence a worker's thermal balance, such as the amount of insulated clothing, metabolic rate, air movement, and contact with cold liquids or surfaces (140).

The following gives a short overview of the literature on the association between cold exposure at work and musculoskeletal pain. The studies were identified during so farn unpublished systematic review on the topic. Only epidemiological studies with a certain quality of clearly defined exposure and outcome measures were included.

Most of the studies on the topic were cross-sectional, but one case-control study was also included (141). The study populations were mainly based on occupations or workplaces, including cold store workers (8), construction workers (142), fishing industry workers (9), slaughterhouse workers (143), factory workers (144), and mine workers (145). However, one study included randomly selected workers from an occupational physician's clinic (146), and one study recruited patients with carpal tunnel syndrome (141). The number of participants ranged from 122 (8) to 134 754 (142).

Exposure and outcome measures were diverse: One study compared working in a cold store (-20°C) with working in a store with normal temperature (20-25°C) (8). Another used different regions in Sweden, i.e., different climatic conditions, as the exposure (142). Many studies used questionnaires to measure the exposure, e.g., under 10°C for more than 20 hours (145), wet clothes for more than 5 hours (145), feeling cold (9), or cooling of different body parts (143). Some studies asked if the participants were working in a cold/damp environment (141, 144, 146), without giving a definition for cold/damp environment.

The majority of the studies also used questionnaires to measure the outcome. Questionnaires collected information on pain in the last 12 months, with some additional specifications, such as pain at specific locations (8, 145), pain that reduced the ability to work (142), or pain that caused disability in activities of daily living (143). One study used carpal tunnel syndrome, which was diagnosed using a nerve conduction velocity examination conducted by a physician (141). No studies reported asking for the duration of pain or used chronic pain as an outcome.

The studies consistently observed an association between cold exposure or an experience of cold exposure and musculoskeletal pain (8, 9, 141-146). However, there was heterogeneity in the observed strength of the associations. The point estimates ranged from low (odds ratio, OR 1.19) (142) to high (OR 21.65) (143). There were also large uncertainties in the estimates of some studies. In one study it was probably due to the small sample size (N=122) (8), whereas in others it could have been because of the small numbers in the different strata of the exposure (9, 146).

One study found that workers in cold stores had more back pain than workers in stores with normal temperature (OR 2.9, 95% confidence interval, CI 1.3-6.7) (8). In a study of Russian mineworkers, exposure to a cold environment (<10°C) for more than 20 hours and having wet clothes for more than 5 hours per week were associated with low back pain (OR 1.3, 95% CI 1.1-1.53 and OR 1.81, 95% CI 1.54-2.14, respectively) (145). In a study of seafood processing workers, there was a strong association between often feeling cold at work and musculoskeletal pain, especially back pain (OR 11.0, 95% CI 4.5-26.8) (9). The experience of cooling of a particular body part was strongly associated with pain in that body part that led to disability in activities of daily living (143).

In summary, the literature indicates a possible association between cold exposure at work and musculoskeletal pain. However, the outcome is often defined as 12-month prevalence. We know that acute cold exposure can cause pain, and that people report cold-induced musculoskeletal pain (85). However, when asking participants if they experienced any musculoskeletal pain in the last 12 months, it is impossible to know if they experienced pain when exposed to a cold environment on one or more occasions, or if they experienced pain in other environments or for longer periods as well.

1.6 Challenges when studying temperature and health

The heterogeneity in the literature on cold exposure at work might be due to difficulties in defining cold exposure. Even though the ISO-standard definition of cold work is based on a given temperature (139), ambient temperature could be a poor measure of exposure. In a study of workers in the fishing industry, the authors could not establish a simple relationship between thermal environmental factors and the prevalence of workers feeling cold. They also found that participants had low finger temperatures and a major drop in foot temperature even when working in relatively high temperatures (147). Individual differences in heat loss, protection, and adaptation, such as behavioral responses, adjusting clothing, or increasing physical activity, are very difficult to measure and probably vary. Also, feeling cold or cooling of a body part is a subjective experience; it thus contains limited information about actual environmental factors that can contribute to heat loss, such as ambient temperature, humidity, and air velocity. However, thermal comfort and sensation seem to be closely connected to both average skin temperature and rectal temperature (148). Thus, although subjective, feeling cold or cooling might be a good indication of the environment's effect on the body. This could explain why studies that used feeling cold or cooling as the exposure (9, 143) have higher effect estimates than studies that used regions as a proxy for climate (142), hours exposed to an environment that was less than 10°C, or working more than 5 hours with wet clothes (145).

The hypothesis that the subjective experience of feeling cold is representative of the stress imposed by the thermal environment implies that the association between temperature and health is not a simple, linear relationship. For example, a preceding temperature of -15°C or 25°C will affect how one experiences a subsequent temperature of 10°C. On a longer timescale, adaptations to temperature and possible cross-adaptations and cross-sensitization over days and weeks create the possibility that the experience of temperature is dependent on past temperatures, and perhaps on other meteorological variables as well (see section 1.4.1). This suggests that the relationship between the environment and our experience of the environment is dependent on the state of the system, also called state-dependency (149). The different associations between temperature and mortality between cities and countries, as well as over time (113, 134), support the notion that the effect of weather/temperature is dependent on past weather/temperature, and thus represents a state-dependency. Further, the association between temperature and mortality is non-linear, indicating a non-linear association between temperature and other health outcomes. State-dependency and non-linearity is common in biological systems, and these systems can be described as dynamic non-linear systems (149). A known phenomenon in dynamic non-linear systems is mirage correlation, meaning that the sign and magnitude of the correlation between two variables vary over time, and that there might be no correlation if the two variables are sampled over a substantially long period. In Figure 2, the time series of a deterministic and dynamic system, given by the following difference equations, are illustrated (149).

$$X(t+1) = X(t)[3.8 - 3.8\,X(t) - 0.02Y(t)]$$

$$Y(t+1) = Y(t)[3.5 - 3.5\,Y(t) - 0.1X(t)]$$

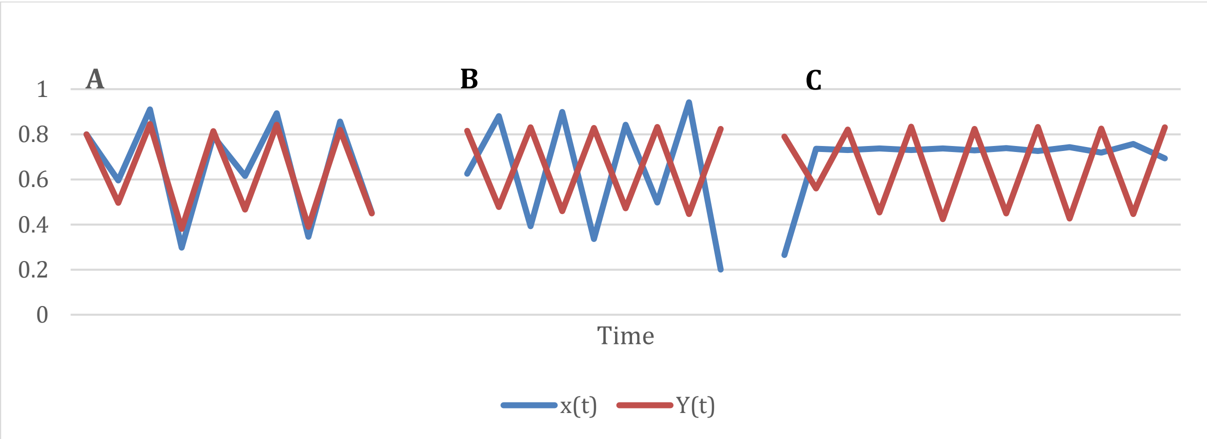

Figure 2. Illustration of mirage correlation. A: a period of positive correlation, B: a period of negative correlation and C: no correlation. If the simulation of the system is continued to n=1000, the correlation coefficient will be 0.0054 (p=0.864). Figure reproduced from equations given in Sugihara et al. (149).

The results from a study of temperature and mortality in the United States strongly indicated the existence of this kind of mirage correlation. When comparing mortality at 25°C to that at 18°C, increased, decreased, or no difference in mortality was found depending on where and in which season the comparison was made (134). In summary, the possible dynamic non-linear association between weather and pain could explain the discrepancy between patients' beliefs and the existing literature on weather and pain. It could also explain the conflicting results between studies, and the lack of association often reported in the literature on weather and pain.

2 RATIONALE AND AIMS OF THE THESIS

Physiologically and psychologically, our different modalities of perception, including pain, are not entirely separate, and different stimuli, including temperature and pressure, can cause pain. The existing literature on cold exposure at work supports the hypothesis that cold exposure is a risk factor for musculoskeletal pain. Whether this is due to acute cold exposure or if cold exposure increases the risk of musculoskeletal pain beyond acute cold exposure is uncertain. Prospective studies on this topic are lacking, as are studies on cold exposure as a risk factor for chronic pain.

It is a common belief that weather affects pain. However, studies that used meteorological data have reported inconclusive results, and many authors have concluded that there is no association. This is contrary to patients' beliefs and to experimental results, and could be due to methodological problems and the choice of analytical methods, which might not be applicable to the phenomenon.

The aims of the thesis were therefore:

1. To study cold exposure at work as a risk factor for pain lasting 3 months or more, both cross-sectionally and longitudinally.
2. To study if meteorological variables have an effect on pain tolerance.

3 MATERIALS AND METHODS

3.1 Study population

The Tromsø Study is a cohort study conducted in the municipality of Tromsø, which has approximately 77 000 inhabitants. The regional hospital and university are situated in the city, and thus a large proportion of the population is employed in the health and education sectors. Another industry that employs a large proportion of inhabitants in Tromsø is trade (150). Tromsø is situated at 69° north, well into the Arctic Circle. Due to the Gulf Stream, the climate is moderately cold. The temperature is below 10°C for a major part of the year, but it seldom drops below -15°C.

The Tromsø Study currently consists of seven surveys; Tromsø 1 was carried out in 1974 and Tromsø 7 in 2015-2016. Each survey consists of both clinical examinations and extensive questionnaires about health and health-related behavior. This thesis used data from Tromsø 6 and 7 (Table 1).

In Tromsø 6, 19 762 inhabitants of Tromsø were invited; 12 984 attended, yielding a participation rate of 65.7%. The age of the participants ranged from 30 to 87 years. The two questionnaires used in Tromsø 6 are presented in Appendices 1 and 2. In Tromsø 7, all inhabitants of Tromsø aged over 40 years (n=32 591) were invited; 21 083 (64.7%) attended. The first questionnaire in Tromsø 7 is presented in Appendix 3, and the second questionnaire is available on the Tromsø Study webpage (151).

Paper 1

In Paper 1, we used data from Tromsø 6. Participants who reported to be retired, those who were receiving fulltime disability benefits, and those with missing values were excluded from the analysis. The final study sample comprised 6533 participants.

Table 1. Tromsø Study participants included and excluded in the different papers by survey.

	PAPER 1		PAPER 2		PAPER 3	
Tromsø 6	Invited	19 762	Invited	19 762		
	Attended	12 984	Attended	12 984		
	Excluded	5326	Excluded	7812		
	Missing	1125	Missing	1819		
			Eligible for follow-up	3353		
Tromsø 7			Did not attend Tromsø 7	724	Invited	32 591
			Missing outcome	282	Attended	21 083
					Tests of PPT[1]	18 987
					Tests of CPT[2]	18 285
	Number of included participants	6533	Number of included participants	2347	All tests performed were used in the analysis	

[1]Number of participants who underwent cuff-algometry to assess pressure pain tolerance (PPT) [2]Number of participants who underwent cold pressor test to assess cold pain tolerance (CPT)

Paper 2

We included participants who attended both Tromsø 6 and Tromsø 7 in Paper 2. We assumed that the probability of developing MSC decreases after retirement (152); therefore we excluded participants who were older than 60 years at the time of Tromsø 6, as they had an increased likelihood of retiring during follow-up. We also excluded those who reported that they were retired or were receiving fulltime disability benefits at the time of Tromsø 6. The final study sample comprised 2347 participants.

Paper 3

In Paper 3, we used data from Tromsø 7. We did not exclude any participants due to any characteristics, and we used all results from cuff-algometry (18 987) and cold pressor tests (18 285).

3.2 Cold exposure and feeling cold

The measure of cold exposure was taken from the Tromsø 6 questionnaires. The first questionnaire included the question, "Do you work outdoors at least 25% of the time or in cold buildings (e.g., storage/industry buildings)?", with response options "yes" and "no". Participants who answered yes were asked to complete a second questionnaire that specifically covered working in a cold environment. One of the questions was, "Do you feel cold at work?", with the response alternatives "yes, often", "yes, sometimes", or "no, never". In Paper 1 we used both of the above-mentioned questions, while in Paper 2 we used only the index question on whether the participant worked in a cold environment ≥25% of the time.

3.3 Measurement of chronic pain and musculoskeletal complaints

The questionnaires are not identical across the Tromsø surveys, and the lack of repeated questions limits the possibilities for longitudinal analysis. As a consequence, we had to use answers to different questions as the outcome in Papers 1 and 2.

Paper 1

In Tromsø 6, participants were asked, "Do you have persistent or recurrent pain lasting 3 months or more?", with response options "yes" and "no". Those who answered yes were given an additional questionnaire concerning the anatomical site(s), cause, duration, and intensity of pain, and its impact on their daily life (Appendix 2). Anatomical sites included were: jaw, neck, back, shoulder, arm (including elbow), hand, hip, leg (including thigh, knee, and calves), foot (including ankle), head (including face), chest, stomach, genitals, skin, and other. The number of sites at which participants reported pain was categorized into 0, 1-2, and ≥3.

Paper 2

In Tromsø 7, the extra questionnaire about anatomical sites given in Tromsø 6 was substituted with the newly developed, computer-based Graphical Index of Pain (153). Thus, we could not use chronic pain in the longitudinal analyses.

In both Tromsø 6 and 7, participants were asked, "During the last year have you been bothered by pain and/or stiffness in muscles or joints lasting at least 3 months?", and six different regions were specified: neck, upper back, lumbar back, hip or leg, arm, and other. For each region, participants could choose from three response alternatives: "no", "moderate", or "severe". These questions and their derived outcome variables are termed MSC throughout the thesis. We combined the questions on MSC into three different dichotomous outcome variables: 1) any MSC, 2) severe MSC, 3) MSC in ≥3 regions.

3.4 Measurements of pain tolerance

Pressure pain tolerance

Computerized cuff-algometry (NociTech, Denmark) was used to test pressure pain tolerance (PPT). A cuff was fitted to each leg, and the tests were carried out by inflating one cuff at a time by 1 kPa/s to the maximum pressure the participant could tolerate, or to 100kPa, whichever came first. We used the arithmetic mean of two inflations, one on each leg, as the measure of PPT. For participants who only completed one inflation, we used the single inflation results.

Prior to the test, participants were asked whether there was any reason they could not undergo the test. Reasons not to be tested included hyperalgesia and problems with peripheral circulation. Individuals who consented to undergo testing were then checked for open sores; cuff-algometry was conducted only if there were no open sores where the cuff would be placed.

Cold pain tolerance

Cold pain tolerance (CPT) was measured with a cold pressor test. Participants were asked to submerge their open and relaxed dominant hand into a 13-liter plexi-glass vat of cold water

(3.0°C) and to hold the hand and wrist in the water as long as possible. Time to withdrawal was used as the outcome, and the test was stopped at a maximum time of 120 seconds. The temperature and circulation of the water were controlled by a cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH Germany, 22 liters/min). The cold pressor test was performed on participants who consented and stated no reason not to perform the test when asked. Reasons given for not undergoing the test were Raynaud's syndrome, cold allergy, and bilateral loss of sensitivity or breached skin.

3.5 Covariates used in Papers 1 and 2

Weight and height measured at the examination was used to calculate BMI, which was then categorized into underweight/normal weight (<25 kg/m^2), overweight (25 kg/m^2-29 kg/m^2) and obese (≥30 kg/m^2). BMI was included as a continuous variable in the multiple regression analyses in Paper 1.

We obtained information on the possible confounders sex, age, education, smoking, and degree of physical work from the Tromsø 6 questionnaire. We categorized smoking into present, former, and never smoker. The degree of physical work was determined by the question, "If you have paid or unpaid work, which statement describes your work best?", with response options "mostly sedentary", "requires a lot of walking", "requires a lot of walking and lifting", and "heavy manual labor".

Covariates used only in Paper 1

In Paper 1 we also included the covariates insomnia and leisure time physical activity. Information on insomnia was obtained with the question, "In the past 12 months, how often have you suffered from sleeplessness?". Participants reported their leisure time physical activity level as: 1) sedentary (reading, watching TV, or other sedentary activity); 2) low (walking, cycling, or other forms of exercise at least 4 hours per week); 3) moderate (recreational sports, heavy gardening for at least 4 hours per week); and 4) high (hard training or sports competition, regularly several times per week).

Covariates used only in Paper 2

In Paper 2, we included the variable self-reported health, which was measured with the question, "In general, how do you consider your own health to be?", with five response alternatives: “excellent”, “good”, “neither good nor bad”, “bad”, and “very bad”. In the analysis, bad, very bad, and neither good nor bad were merged into one category, as few respondents gave a measure of bad or very bad.

3.6 Norwegian Labour and Welfare Organization State Register of Employers and Employees

The Norwegian Register of Employers and Employees (NREE) is the responsibility of the Norwegian Labour and Welfare Organization. All employers are required to register employees whose employment lasts at least 7 days and likely will involve an average of no fewer than 4 hours of work per week. The employee is registered with his or her personal identification number, a unique 11-digit number assigned to all individuals living in Norway. In addition, each employee is registered with an industrial classification code, the county of work, and the first and last date of employment. The NREE was established in 1978, became operational in 1983, and contains employment records from 1981 onward. From 2003, the NREE began to include information on occupation, but this information was not systematically collected until 2015 (154).

Classification of occupation in the NREE

At the time of Tromsø 6 (2007-2008), the NREE used the STYRK classification, a Norwegian standard for classification of occupation, which is a modified version of the International Standard Classification of Occupations from 1988 (155). The International Standard Classification of Occupations and STYRK classifications are based on skill level and specialization. The different levels are based on years of education, the complexity of the work tasks, and the amount of knowledge demanded to solve them.

The classification is divided in 10 major groups, which are further divided into sub-major groups, minor groups, and unit groups. The result is a 4-digit occupational code, where each number represents one of these partitions. The STYRK classification is similar to the International Standard Classification of Occupations on a 3-digit level, but has some differences on the 4 digit-level (155).

3.7 Meteorological data

The geographical variation in weather in the municipality of Tromsø is small. We therefore used meteorological data from one station (Tromsø 90450). For the period 1990 to 2020, we obtained daily mean temperature, barometric pressure, precipitation, relative humidity, and wind speed at this station from the Meteorological Institute of Norway's web-services (eKlima.net). To get meteorological variables with no seasonal variation, we calculated anomalies, meaning the difference between expected weather and observed weather. We determined the meteorological anomalies for each specific date by first creating a 7-day moving average for the period 1990 to 2020, then calculating the mean of these moving averages for each date, and finally subtracting this mean from the observed weather.

3.8 Statistical analysis

3.8.1 Paper 1

To test the differences in prevalence, we used the Pearson chi-square test if all cells had n>5, and Fisher's exact if n≤5. We used logistic regression with pain at 1-2 or ≥3 anatomical sites as two different binary outcomes. In addition, we fitted the models to the anatomical sites. The models were not fitted to some of the anatomical sites due to a low number of participants who worked in a cold environment ≥25% of the time with pain at that anatomical site. The anatomical sites with low numbers were jaw (n=4), chest (n=10), skin (n=5), genitals (n=8), and other (n=3). Statistical analyses were performed in Stata MP 15.

3.8.2 Paper 2

To test if working in a cold environment was associated with future MSC, we used Poisson regression with robust variance to perform three different analyses with binary outcomes: any MSC, severe MSC, and MSC in ≥3 regions. The effect estimate in Poisson regression is incidence rate ratio (IRR), and it is argued that IRR can be interpreted as relative risk (156).

A large number of participants had missing values in Tromsø 6 and were therefore excluded. This reduced the statistical power and could have introduced bias; therefore we performed multiple imputation with chained equations as a sensitivity analysis. The dichotomous questions about chronic pain from Tromsø 6 and 7, and pain sites from Tromsø 7, were included in the imputation to increase the predictive power. We imputed 100 datasets by using the augment option. The IRRs in the main analysis were calculated after excluding participants who had severe MSC or MSC in ≥3 regions in Tromsø 6. To enhance the comparability between the results from the main analysis and the imputed analysis, we included an interaction term between having severe MSC or MSC in ≥3 regions in Tromsø 6 and working in a cold environment ≥25% of the time when analyzing the imputed datasets.

Occupational factors could confound the observed associations in the main analysis; therefore we conducted additional analyses using occupational codes obtained from the NREE. As this register was incomplete at the time of Tromsø 6, the additional analyses were restricted to those with an occupational code in 2007. Participants who had no code in 2007, but a valid code in 2008, were included with the code from 2008. The possible confounding effect of occupational code was then assessed by running three logistic regression analyses. One model was identical to the main analysis, one included the 10 major occupational groups in the STYRK classification as a categorical variable, and finally a mixed-effects logistic model with a random intercept for each 4-digit occupational code.

3.8.3 Paper 3

Seasonal variation

In order to investigate the possible seasonal variation in pain tolerance, we categorized the participants by month of examination. We then calculated the range, median, and quartiles for PPT and CPT. To further investigate the seasonal variation in CPT, we used month of the year as the exposure, and time to withdrawal in the cold pressor test as the survival time, and performed a Cox proportional hazard regression model. January 2016 was chosen as the reference month, and we tested the proportional hazard assumption with Schoenfeld residuals and log-log plots. Sex tended to break the assumption with less difference towards the end of the cold pressor test. However, conducting stratified analyses or including sex as a time-varying covariate minimally altered the estimates for the different months. Therefore, we used the simple model with sex as a covariate. Seasonal variation may differ by age and sex, so we fitted interaction terms for age and sex in the Cox regression model. A possible source of bias could be the temperature of the hand before the examination. Indeed, having a hand that is already cold might reduce the shock of the cold pressor test, and thus affect the time to withdrawal. To investigate this, we calculated the time available to warm the hand as the time participants spent waiting between their first examination and their cold pressor test. We then included an interaction term between this time in minutes and the month of examination, and finally repeated the analysis among those who had waited more than 60 minutes between their first examination and their cold pressor test.

Short-term variation

To identify any short-term variation, we calculated the daily means of PPT. The distribution of time to withdrawal in the cold pressor test was right-censored. We therefore calculated the daily proportion of participants who held their hand in cold water for more than 100 seconds. This duration was chosen as it provided a set of daily measures that were reasonably normally distributed and contained few extreme values of 0 or 1. We created 7-day moving averages of the daily measures of PPT and CPT, which were used to illustrate the variation throughout the study period. As CPT showed a seasonal variation, we fitted a sinusoidal curve to the daily proportions, calculated the difference between each daily proportion and the sinusoidal curve, and used these differences in further analyses. For each time-series, we calculated the correlation between one day and the following days, i.e., the autocorrelation. To estimate the average timescale on which pain tolerance varied, we assumed that the autocorrelation decayed exponentially and fitted a generalized linear model with a log link function and a gamma distribution. The autocorrelation and average timescale were also calculated for the meteorological anomalies.

Date of attendance to the Tromsø Study surveys might depend on sex, age, or chronic pain, and thus introduce spurious variation in the time series. We therefore calculated the daily proportion of females and participants reporting chronic pain and the daily mean age. Starting in July 2016, there was a drop in the proportion of females and in the daily mean age. Therefore, we repeated the time series analysis after excluding data from July 2016 to November 2016. To identify any non-random daily variation in the proportion of females, the proportion of participants reporting chronic pain, and the daily mean age, we calculated the autocorrelation for these time series. Missing values on the chronic pain question could be a potential source of a non-random variation. To study this we calculated the autocorrelation of the daily proportion missing on the question. We also performed multiple imputation with chained equations using all participants in Tromsø 7 (21,083). We included age, sex, PPT, CPT, and chronic pain. In addition, we included education, the 6 questions about musculoskeletal complaints lasting 3 months or more, and pain the last 4 weeks from the computer based questionnaire included in Tromsø 7 as these variables might improve the prediction. We imputed 20 datasets and then calculated the daily proportion having chronic pain, and the autocorrelation of these daily proportions. In addition, we tried to simulate the effect of sex, age, day of the week, and technician rotation on PPT. First, we conducted univariate analysis for each variable. Second, we made 500 shuffled copies of the PPT time series, which have no association with weather. By adding twice the observed differences from the univariate analysis to the shuffled copies, we simulated the effect of sex, age, day of the week, and technician rotation on PPT. We then calculated the autocorrelation for each of these shuffled copies. To test if the combination of sex, age, and technician rotation could cause the observed autocorrelation, we simulated their joint effect on PPT.

Association between pain tolerance and meteorological variables

To study the association between pain tolerance and weather, we created 3-day moving averages for PPT, CPT, observed meteorological variables, and meteorological anomalies. We then calculated the cross-correlations for the whole study period and for each half-year. To assess whether the observations were due to chance, we made 500 shuffled copies of PPT and CPT, and cross-correlated them with the meteorological variables and meteorological anomalies.

To describe the specific weather patterns that coincided with low or high pain tolerance, we identified local maxima and minima in the 3-day moving average of PPT and CPT. Maxima were defined as values above the 90th percentile, and minima as those below the 10th percentile. Maxima or minima that were less than 6 days apart were considered as one maxima or minima, and the highest value of the two was used. Finally, we calculated the mean of the 3-day moving average of PPT, CPT, and the meteorological anomalies at the maxima and minima, and for each of the 14 days before and after the maxima and minima.

If weather causally affects pain tolerance, it should be possible to predict future pain tolerance based on the weather. We tested this by fitting six different vector autoregressive models to the daily means of PPT, temperature, and barometric pressure. The models were fitted with both the observed meteorological variables and the meteorological anomalies. To choose the number of lags to include in the model, we used both the likelihood ratio, Akaike Information Criteria, and Bayesian Information Criteria. To test if temperature or barometric pressure contribute in the model, we performed a Granger causality test for all models (157).

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

3.9 Ethics

Tromsø 6 and 7, as well as the project that is the object of the current thesis, and all changes made throughout the project, were approved by the Regional Committee of Research Ethics, reference numbers 121/2006, 2014/940, and 2018/38, respectively. All participants gave their written consent to participate in The Tromsø Study, and for their data to be used in medical research.

4 RESULTS

4.1 Paper 1

Working in a cold environment, feeling cold at work and chronic pain: A cross-sectional analysis of The Tromsø Study

The aim of this study was to investigate if working in a cold environment and feeling cold at work are associated with chronic pain. Among the 6533 participants included in the analysis, 779 worked in a cold environment ≥25% of the time. They were mostly men, were younger, had lower levels of education compared to the rest of the working population, and had a higher BMI. These individuals were also more likely to be current or former smokers, to have physically demanding work, and have lower leisure time physical activity levels. Working in a cold environment ≥25% of the time was significantly associated with chronic pain at ≥3 anatomical sites (OR 1.57, 95% CI 1.23-2.01) and with neck, shoulder, and leg pain. When the exposure was divided into frequency of feeling cold, those who felt cold sometimes or often had an increased odds for pain at ≥3 sites (OR 1.58, 95% CI 1.22-2.07 and OR 3.90, 95% CI 2.04-7.45, respectively).

4.2 Paper 2

Is working in a cold environment associated with musculoskeletal complaints 7-8 years later? A longitudinal analysis from The Tromsø Study

The aim of this study was to investigate if working in cold environment ≥25% of the time is associated with MSC 7-8 years later. Participants working in a cold environment ≥25% of the time had a significantly increased risk of experiencing any MSC at follow-up (IRR 1.16, 95% CI 1.02-1.31), but no significantly increased risk for severe MSC or MSC in ≥3 regions. Adjustment for major occupational groups did not alter the association.

4.3 Paper 3

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

There was a clear seasonal variation in CPT, with participants holding their hand in cold water the longest in the winter. There was no such seasonal variation in PPT. PPT varied on a shorter timescale, with an estimated mean lifetime of the autocorrelation of 5.1 days (95% CI 4.0-7.2). This timescale was similar to that observed for meteorological variables. PPT and CPT correlated with meteorological variables, and this correlation changed over time. Often the strongest correlation was with the meteorological variables from days before or after. Temperature and barometric pressure predicted future values of PPT. The maxima for PPT coincided with falling temperatures, precipitation, and humidity, and rising barometric pressure. A similar pattern with falling temperatures and rising barometric pressure was also seen in the periods with the highest CPT.

5 DISCUSSION

5.1 Methodological considerations

This chapter discusses different methodological issues in the study design, different sources of bias, and limitations in the statistical analyses. Selection bias and possible confounding will be discussed in separate sections, while recall bias and misclassification bias will be discussed in the sections about measurement of exposure and outcome.

5.1.1 Study design

The cross-sectional design of Paper 1 has some major limitations. The simultaneous measurement of exposure and outcome makes it impossible to determine the direction of the association. This is especially problematic when the exposure is categorized as feeling cold never, sometimes, or often. The possibility of reverse causation is discussed in section 5.1.3. Paper 2 has a longitudinal design, as the exposure is measured before the outcome, and that study might be helpful in determining the direction of the association.

Paper 3 covered variation in pain tolerance over time, and meteorological variables were introduced as exposures. An important assumption was that for every date, the survey drew a random sample from the study population of Tromsø 7; thus all variations were random and as such, there should be no correlation between the daily measures of central tendency in the samples, i.e., no correlation between one day and the next. The sensitivity analyses carried out in Paper 3 showed that sex, age, and chronic pain were not likely to cause the observed day-to-day variation. Nevertheless, there might be unknown processes that determined when someone attended Tromsø 7 that are also related to how much pain a person can tolerate.

5.1.2 Selection bias

The Tromsø Study attempts to recruit an age-specific, representative sample from the municipality of Tromsø. Attendance rates were reasonably high for both Tromsø 6 and 7 (>65%). However, there are probably differences between those who participated and those who did not, both before entering Tromsø 6 and during the follow-up to Tromsø 7. Non-participants in studies such as the Tromsø Study often have lower education than participants, and this was the case in Tromsø 6 (158). In addition, a large proportion of those working in occupations that include exposure to cold environments are migrant workers, who would not have been invited to the study. As an example, in 2008, around 12% of workers in the Norwegian construction industry were migrant workers (159). Thus, we might have underestimated the prevalence of workers exposed to cold environments in Papers 1 and 2. In another Norwegian study, those with severe chronic conditions were less likely to participate, while the opposite was found for common conditions like musculoskeletal pain and headache (160). Thus, the sample in Tromsø 6 might be less exposed to a cold environment at work and have more chronic pain or MSC than the general population in the municipality of Tromsø.

The “healthy-worker effect” might have influenced the results of Papers 1 and 2. The classic example of the healthy-worker effect is that the mortality of workers is lower than that of the general population, which is likely a consequence of the fact that working requires a minimum of health (161). Such self-selection processes might affect the results of Papers 1 and 2. If there is a causal relationship, some participants might have developed chronic pain from working in a cold environment, but changed their occupation prior to participating in Tromsø 6. Quantifying the size of this selection process is difficult, and other risk factors may also contribute. For example, many occupations that include working in a cold environment are physically demanding, which could make adjusting to chronic pain conditions at the workplace difficult (162). Thus, those with poor health might be less likely to start working or continue working in an occupation with cold exposure. Consequently, we could have a healthier exposed group with less risk of future MSC and chronic pain (35, 37, 163). The occupations themselves might have led to a selected group of workers who are less likely to develop chronic pain/MSC compared to the general population. Even though the healthy-worker effect is discussed under selection bias, one could argue that this effect is confounding by health status (164). Section 5.1.3 includes a further discussion of health status as a confounder.

In addition, as feeling cold is uncomfortable, it is more likely that those who feel cold often change occupation. The results of Paper 1 indicate an association between frequency of feeling cold and chronic pain. As both the exposure, feeling cold, and the outcome (chronic pain/MSC) might affect one’s decision to continue working in cold environment, the results might be vulnerable to Berksonian bias. This can introduce a downward bias, and in extreme cases the magnitude of this bias results in a negative association, although the true association is positive (161). Thus, these selection effects might have caused an underestimation of the associations in both Papers 1 and 2.

During follow-up in Paper 2, the aforementioned reasons for non-participation from other studies probably affected the attendance to Tromsø 7. The loss to follow-up was 21% in our study, which is reasonably low, but even a loss to follow-up of 20% to 30% can lead to biased estimates when there is reason to believe that the loss is associated with both the exposure and the outcome (161). The selection processes described in this chapter probably affected the loss to follow-up and consequently the estimates in Paper 2. The net size and direction of the bias introduced by the selection processes discussed in this chapter are difficult to assess.

5.1.3 Exposure measures in Papers 1 and 2

Working in a cold environment ≥25% of the time is a crude measure of cold exposure, as recollecting and estimating the percentage of time spent in a cold environment probably introduces some errors. Further, assuming that there is a causal relationship between cold exposure and chronic pain, the effect might depend on the duration of the exposure (165). Thus, we might expect a different effect for those working 25% of the time in a cold environment compared to those who work in this environment 90% of the time. There could also be a threshold of exposure for effect or adaptation that could modify the effect of cold exposure. We do not know, but by including those working in a cold environment≥25% of the time, we could be at risk of diluting the effect of cold exposure. Additionally, a large proportion of the time spent in cold temperatures at the population level is due to leisure time physical activity and commuting to and from work (166). Thus, it is possible that some participants who were categorized as exposed to a cold environment at work had a lower total exposure to a cold environment (occupational exposure + leisure time exposure) than a person in the non-exposed group (only leisure time exposure). Also, spending time in a cold environment voluntarily might differ from cold exposure in an occupational setting. Equivalent to what has been observed for the effect of physical activity at work and the effect of leisure time physical activity on cardiovascular health (167).

Another problem is that the proportion of time spent working in a cold environment does not give much information about the actual cold stress the participant experiences. Indeed, several other factors can affect the thermal balance of a worker. The behavioral measures to protect oneself from cold, like putting on more clothes or increasing one’s metabolic rate through physical activity, might differ between individuals.

In Paper 1, we divided individuals exposed to a cold environment at work by the frequency with which they reported feeling cold: those who never, sometimes, or often felt cold. Skin and core temperature seem to be closely related to how comfortable a person feels (148). Thus, feeling cold might be a good measure of the thermal stress a person experiences. One could then hypothesize a causal pathway like that depicted in Figure 3A.

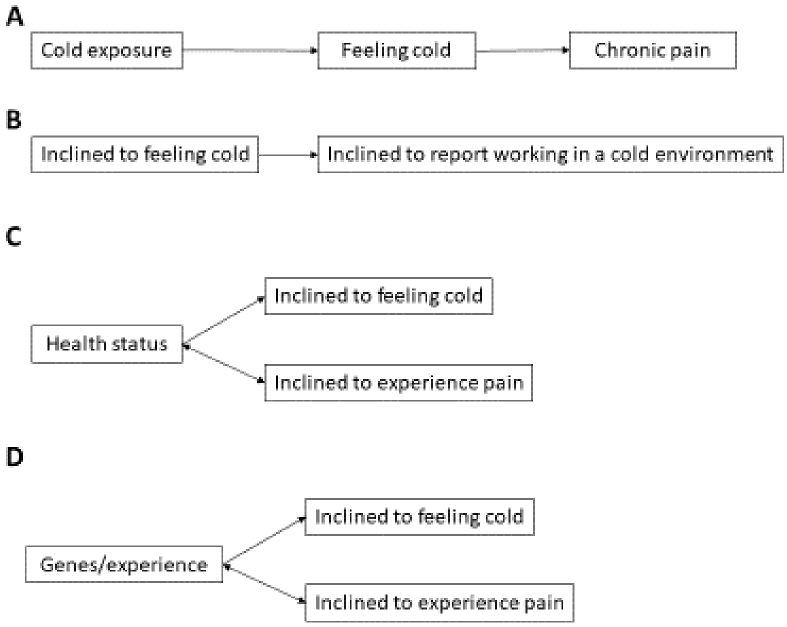

Figure 3. Four theoretical causal structures to illustrate the possible association between reporting to work in a cold environment, frequency of feeling cold, and the experience of pain.

Even though the question about cold exposure specified outdoors or cold buildings, like industry buildings and cold stores, some participants might have answered that they work in a cold building, referring to what they experience as a cold office. Among the participants who reported to work in a cold environment ≥25% of the time, there are likely some that worked in an office, for example, participants with the occupational code for executive officers or customer service officers (Paper 2, Supplementary table 3). Thus, reporting to work in a cold environment ≥25% of the time might, to some extent, represent perceived cold stress that is not associated with actual cold exposure, as depicted in Figure 3B.

Further, the frequency of feeling cold might be influenced by the health status of the individual (Figure 3C). One study found that participants with chronic pain had more complaints about the indoor climate, including cold temperature and draft (168). Another study found that participants with existing musculoskeletal pain had a higher risk of experiencing cold-related musculoskeletal pain and a higher temperature threshold for experiencing such pain compared to healthy participants (85). Thus, feeling cold and chronic pain might be associated through health status, and feeling cold may have no effect on pain.

Whether an individual feels cold or not is probably also determined by factors other than current health status, like genes or previous experience. The propensity of the individual to feel cold, whether it is inherent or acquired through adaptations, might be associated with experiencing more pain. For example, the experience and response to cold temperatures seem to differ by different alleles of TRPM8, a receptor channel for feelings of cold and pain (169, 170). There are also genetic differences in the ability to produce heat in the muscles, and consequently, cold resilience (171). Other examples of a possible common underlying phenotype is that slaughterhouse workers who complained the most about the indoor climate reported more chronic pain, but also a lower pain tolerance (168). One study from hospitals in the region around Rome found an association between being annoyed by environmental factors, like too low/high temperature or draft, noise, and light, and musculoskeletal pain (172). This underlines the possibility that feeling cold or cooling can be associated with pain through central sensitization, independent of the actual physical environment (Figure 3D).

These different causal pathways are problematic when interpreting the results of Papers 1 and 2, especially since the results of Paper 1 showed that the frequency of feeling cold was strongly associated with chronic pain. It might be that participants who reported working in a cold environment and feeling cold often are at a higher risk of chronic pain or MSC due to poor health or a propensity to feeling cold, and not because of exposure to a cold environment at work. Consequently, the effect sizes in Papers 1 and 2 might be overestimated, and the true association between chronic pain/MSC and working in a cold environment ≥25% of the time might be lower or non-existent.

In the prospective study reported in Paper 2, we do not know which participants changed their exposure between Tromsø 6 and 7. Those who reported to work in a cold environment ≥25% of the time could have changed that proportion to <25% of the time, and vice-versa. This misclassification could be differential, i.e., more participants stopped working in a cold environment than there were participants who started working in a cold environment. The younger age among those working in cold environment ≥25% of the time in Paper 1 would fit with this explanation. Thus, this misclassification could introduce bias towards the null in Paper 2.

5.1.4 Outcome measures in Papers 1 and 2

One of the aims of the thesis was to study cold exposure as a risk factor for pain lasting 3 months or more. However, Papers 1 and 2 used dissimilar outcomes: chronic pain and MSC. This chapter will first illustrate some differences in the two outcomes, and then discuss the difficulties in measuring chronic pain and the discrepancy between the two outcomes.

Table 2. Agreement between chronic pain, measured with a single item, and dichotomous variables on musculoskeletal complaints (MSC) as in Paper 2. Data from Tromsø 6. All participants with missing values were excluded.

Tromsø 6		Do you have persistent or recurring pain that has lasted for 3 months or more?					
		No		Yes		Total	
		n	%	n	%	n	%
Any MSC	No	3133	49	129	6	3262	38
	Yes	3248	51	2165	94	5413	62
Severe MSC	No	6032	95	1193	52	7225	83
	Yes	349	5	1101	48	1450	17
MSC in ≥3 regions	No	5293	83	795	35	6088	70
	Yes	1088	17	1499	65	2587	30

One would expect that those with MSC mostly had chronic pain. However, 51% of those who reported no chronic pain on the single-item question, reported having any MSC in Tromsø 6.

Also, 17% of those reporting no chronic pain report having MSC at 3 or more regions (Table 2).

Measuring pain is difficult because it is an experience. Common ways to measure pain include the Visual Analog Scale or the Numerical Rating Scale. They attempt to measure pain intensity on a scale going from no pain to the worst imaginable pain (173). However, the definition of chronic pain used in Paper 1 did not include any measure of pain intensity or impact on daily life; instead participants had to make their own distinctions between pain that should be reported and a nuisance that was not worth reporting. At the same time, including a scale and using a cut-off to define pain can also lead to misclassification, as the intensity can vary from mild to moderate over time (24).

The discrepancy between the two outcome measures could be due to differences in the wording of the questions. Chronic pain is dichotomous, while the questions on MSC had three response alternatives: no, moderate, and severe. Thus, the participants had to decide on two thresholds, one for having moderate and one for having severe MSC. It is likely that the threshold for moderate MSC was lower than for a single dichotomous question about chronic pain.

Another difference is that the question on chronic pain could well have been interpreted as having pain at the time of questionnaire completion, and that it should have lasted or been recurrent for 3 months or more, while the questions on MSC asked for a period lasting 3 months or more during the last year. This could explain some of the higher prevalence of MSC compared to chronic pain. Additionally, the definition of MSC included “pain and/or stiffness”, and we do not know how many of those with MSC were only bothered by stiffness. Another difference is that the questions used to compute MSC variables asked about pain/stiffness in more or less specific regions, while the chronic pain question asked about pain in general. One explanation for the discrepancy could be that participants were more inclined to report pain when asked about specific regions.

The questions about chronic pain and MSC might introduce recall bias. In Paper 1, participants had to remember if they had experienced pain in the previous 3 months or earlier, and whether the intensity was strong enough to actually be reported as pain. In Paper 2, participants had to remember if they had an episode of MSC during the past year, and if that episode lasted 3 months or more. One study reported that, over a 3-month period, individuals can recall their pain quite accurately (174). A study of days with low back pain found substantial recall bias at the individual level. However, at the group level they found that the average estimate of days was reliable (intraclass correlation coefficient 0.88, 95% CI 0.84-0.91) (175). A Norwegian cohort study asked about pain during the last week every 3 months, and subsequently asked about pain lasting longer than 6 months at 12 months. They found an intraclass correlation coefficient of 0.66 (95% CI 0.65-0.67) and concluded that pain reporting was stable (176). However, answering repeatedly about pain could affect one's ability to recollect pain when asked at a later time point. The recollection of musculoskeletal pain from years past is reported to be poor, and strongly influenced by current symptoms (177). The degree of recall bias could be influenced by other factors, such as the social support of colleagues (175). Altogether, the impact of recall bias on the results of Papers 1 and 2 is difficult to assess.

The different measures used in this thesis yielded different prevalences, but we do not know if any one measure is more correct than the others. Nevertheless, misclassification of chronic pain or MSC might contribute to bias in the estimated effects of working in a cold environment. A study using manikin and questions found that a larger proportion of participants with lower education reported pain on the manikin and not in the questions (178). Given the difference in education between those working in a cold environment ≥25% and <25% of the time, the questionnaires used in Papers 1 and 2 could introduce differential misclassification bias and consequently an underestimation of the effect.

5.1.5 Possible confounding in Papers 1 and 2

Those working in a cold environment ≥25% of the time tend to have less education, and previous findings have shown that that several risk factors (e.g., smoking and BMI) and health outcomes, including chronic pain, are unevenly distributed along the socioeconomic gradient (179). In Papers 1 and 2, we adjusted for education, BMI, leisure time physical activity, and smoking. In addition, we adjusted for degree of physical activity at work, as it is a possible risk factor for chronic pain (42, 44) . However, there might be differences in other known and unknown occupational risk factors between those working in a cold environment ≥25% of the time and those who are not (43). There is a socioeconomic gradient in occupational risk factors, and reports have demonstrated that these factors explain some of the difference in sick leave (180). Further, psychosocial factors, like demand-control-social support, or work organization are probable risk factors for chronic pain (181); as we had no data on these variables, our results might be vulnerable to confounding by these occupational factors. In Paper 2, we attempted to reduce possible confounding by occupational risk factors by utilizing occupational codes. Neither adjusting for the ten major occupational groups nor assigning a random intercept for occupational groups altered the estimates substantially, nor did it improve the model (judged by Akaike Information Criteria). However, there is still a risk of residual confounding by occupational risk factors. For example, there could be differences within the same occupational codes that determine who works in a cold environment and what other risk factors participants were exposed to.

5.1.6 Deficiencies and bias in the statistical analyses of Papers 1 and 2

Effect modification

No analysis for possible effect modifications was conducted in Papers 1 and 2, that is, if the effect of cold exposure differed by the presence or level of other variables (161). However, it is difficult to suggest effect modifications based on the existing literature. For example, smoking is a vasoconstrictor, thus it could preempt physiological response mechanisms. This could lead to a smaller initial response in blood pressure due to cold exposure, or a more rapid decline in skin temperature, and consequently, different afferent cold signals during cold exposure. How this might affect the adaptation to cold or the possible association between cold exposure/feeling cold and chronic pain is difficult to assess. Blindly testing for all possible interactions might yield a significant interaction term by pure chance. The possibility for further insights or less biased estimates from additional analysis was considered small given the lack of an obvious causal pathway and consequent hypotheses about effect modifications, the uncertainty in the measure of exposure, the risk of confounding, the cross-sectional design in Paper 1, and the limited sample size when stratifying for different confounders.

Introducing collider bias

Sleep, as included in Paper 1, may be bidirectionally associated with pain (23, 46, 47, 52, 55). Thus, poor sleep can be seen as an effect of chronic pain. In the example of sleep, cold exposure at work is often combined with working outdoors and more exposure to daylight, which could improve sleep patterns for some individuals. Given this causal pathway, we introduced collider bias by adjusting for sleep in the analysis. However, sleep seems to have a stronger effect on pain than pain does on sleep (52, 55). There could be other causal structures that imply the introduction of collider bias due to adjustment for bidirectional risk factors, such as leisure time physical activity (46).

Choice of statistical methods

In Paper 1, we used logistic regression, which yields estimates that are higher than prevalence ratios from Poisson, negative binomial, or Cox regression (182, 183), and this discrepancy increases with increasing prevalence (184). The prevalence of chronic pain in Paper 1 was around 15%, and the calculated OR should consequently be interpreted as an OR, and not as an approximation of relative risk or prevalence ratio.

5.1.7 Measurements of pain tolerance

Cuff-algometry and the cold pressor test measure the response to an external stimulus and cannot be interpreted as an equivalent of clinical pain, and probably even less as chronic pain. Clinical pain is often interpreted as pain in muscles, bones, ligaments, and internal organs. The cold pressor test is temperature applied to the skin, and the cuff cannot induce pain without also activating mechanoreceptors in the skin (185).

Both cuff-algometry on the leg and the cold pressor test have performed reasonably well as measures of pain tolerance in studies of test-retest reliability (186, 187). However, some studies that used the cold pressor test as a cardiovascular test have reported poorer reliability, seasonal differences, and differences between cold-adapted and -unadapted populations (188, 189). They have also shown the presence of within-subject variation, but the within-subject variation in pain tolerance and sensitivity seems to be substantially smaller than between subjects (186, 190). On the other hand, the mean of cuff-algometry performed on the arm, as well as some other measures of pain sensitivity, was significantly lower in the retest in a Danish study (186). None of the reliability studies have stated whether all subjects were tested and retested on the same dates. As the association between meteorological factors and pain tolerance seems to change over time, the variation due to meteorological variables could be cancelled out by the fact that different subjects were tested at different time points.

5.1.8 Empirical analysis of dynamic non-linear systems

The difficulties in understanding and predicting the behavior of dynamic non-linear systems is well known to all – just think of how often the weather forecast is wrong. There is little consensus on how causal strength should be estimated, or on how to establish a causal relationship between two time-series from dynamic non-linear systems (191). One possible approach is the Granger-causality test used in Paper 3 (192). However, this analysis might be flawed, since an important assumption for the test is that the variables are separable (149). Temperature and barometric pressure are closely associated, meaning this assumption was probably not met in our study. The large variation in pain tolerance between subjects, and the random sampling from day to day, introduced a lot of noise in the time-series. Another problem is that there were no tests on Sundays or holidays. The noise and the missing dates in the time-series probably thwarted our attempts to use other methods to better describe the causal structures in the relationship between meteorological variables and pain tolerance (149).

In Paper 3, we used cross-correlation to examine the possible association between pain tolerance and meteorological variables. Even though the study timespan was divided into periods of 4 to 6 months, the timescale on which PPT varied was substantially shorter. Thus, mirage correlation may still exist within those periods.

5.1.9 Analyzing measures of central tendency of samples in Paper 3

In Paper 3, we used the mean pressure and proportion of participants with cold pressor times less than 100 seconds as measures of the central tendency for each date. Thus, we studied how pain tolerance in the population changed over time; not individual variation. This measure is of course dependent on which test subjects attended the health examination on any given date. Random appointment dates and times were provided to Tromsø 7 participants with their invitations; however, participants did not have to respect this, and were allowed to attend testing on any date that suited them. Some factors, such as pain intensity or age, may have affected when and which participants attended. If these factors were also associated with differences in pain tolerance, our results in Paper 3 could be spurious. Examples of such factors are age and sex, as the mean age and proportion of females declined towards the end of the study. However, our simulations of the effect of age and sex did not introduce the autocorrelation observed in Paper 3.

When studying the differences between groups, attention must be paid to the ecological fallacy that conclusions drawn from the group level might not be correct on the individual level (161). Some authors have suggested that some individuals are more prone to be affected by weather (92, 193). For example, in an earlier study, lower barometric pressure was associated with higher pain intensity in the majority of the study population, but with a lower pain intensity in a sub-group of patients with fibromyalgia (93). However, as these patients reported pain intensities in different time periods, the results of the aforementioned study could be due to mirage correlation and different time of sampling (as illustrated in Figure 2 of this thesis), not to individual differences. In Paper 3, repeated measurements from the same individuals might have improved the internal validity of the study and identified different responses to the weather.

In the following discussion of the results, it is assumed that the observed variation in pain tolerance on the population level represents important variation on an individual level.

5.1.10 Generalizability

Generalizability or external validity in the epidemiological setting is the degree to which the results can be generalized beyond the source population or study sample. The climate in Tromsø is colder and harsher than that in most of the rest of the world. However, the seasonal variation in mortality attributed to cold temperatures is higher in the United Kingdom and Spain compared to the Nordic countries, and much of this difference is attributed to poor housing (194). This implies that it is not only the temperature outdoors that can cause an increase in mortality, but probably also the cold stress experienced by individuals after any protective behavioral measures are taken. Thus, working outdoors in a climate that is warmer than that in Tromsø might still yield cold stress. Additionally, cold work environments are relevant for most parts of the world, for example, in cold stores and food production. The results of Paper 3 indicate that the association between one meteorological variable and pain tolerance varies over time, likely depending on past weather and other meteorological variables. Thus, it is likely that a study in other climates would yield different observations. However, as a high proportion of the population in many countries believes there is an association between weather and their experience of pain (5, 6, 80-82), there is likely an association between meteorological variables and pain tolerance in other climates as well. Thus, the results from this thesis could be relevant for other populations, as well as for the sub-arctic study population.

5.2 Discussion of results

5.2.1 The environment and acute or experimental pain

Maintaining homeostasis is important for our survival, for example do many physiological mechanisms fail if the body temperature is too high or too low. Therefore, the existence of a sensory system that can convey information about homeostasis is important. The terms interoception and interoceptive system have been suggested to describe this information and the structures involved (195). Interoception includes C-fibers that transmit nociception, thermal sensation, and sensations from the viscera, all of which are anatomically arranged together in the spinothalamocortical pathway. Further, this sensory input terminates in the insula, which has been suggested to be essential in the construction of human feelings (195). An important purpose of interoceptive information and associated feelings like thirst, hunger, or cold, is to ensure homeostasis by provoking feelings that lead to behaviors that alleviate the homeostatic threat. As mentioned, nociception is a part of interoception, and pain can thus be understood as a homeostatic feeling (196). The finding of different thresholds in the thermal grill illusion with changing body temperature can support the hypothesis of an interoceptive dimension in pain (108). Others have also used experimental data to argue that perception, including pain, is cross-modal. This means that other external factors, such as visual stimuli, can alter pain experience (197). Thus, it is plausible that meteorological variables have an impact on our experience of pain and pain tolerance.

It is important to note that studies of interoception or cross-modal shaping tend to use tests that last only seconds or minutes; they study only the immediate impact of a stimulus, and have not tried to identify changes over time or dynamic behavior. In contrast, the timescale of the observed variation in pain tolerance in Paper 3 was 5.1 days (95% CI 4.0-7.2). This is not only within the range of observed intrinsic timescales of the meteorological variables in Paper 3, but also within the timescales observed in experimental research. In a study of repeated immersions of a hand in cold water, there was a decline in pain intensity within the first 4 to 5, days and no further decline after that (103).

A suggested important function of the insular cortex is to make predictions about the internal state of the organism and compare them with the sensory input, as these predictions and their errors are important in pain processing (198). Further, the resting-state activity in the brain, including the insular cortex, has been found to predict both pain sensitivity and pain intensity (73, 199). Thus, it is possible that the exposure and adaptation to meteorological variables alter resting-state brain activity, and consequently the predictions of the internal state of the organism. This hypothesis would concur with our findings from Paper 3, which showed that changes in meteorological variables might be as important as absolute values in affecting pain tolerance. A change could increase the risk of an incorrect prediction of the state of the organism. To my knowledge, there are few studies on the effect of weather on resting-state brain activity. One study in preprint found no effect, save an effect on the MRI machine itself, but they used a machine learning algorithm that assumed a constant linear relationship (200). Another study found some correlation between brain activity in the insula and a weather index (201). However, given the limited literature, the connection between weather and pain sensitivity through resting-state brain activity is somewhat speculative.

The analysis in Paper 3 was restricted to weather variables and pain tolerance tests. Studies indicate that there are a multitude of physiological effects that may be associated with pain. In the following, some examples regarding hormones, blood pressure, sympathetic and psychological involvement are given to exemplify the complexity of the topic. Many hormones have been suggested to be associated with pain (63), and there seems to be a seasonal variation in hormones (202), some of which could be due to a changing temperature. For example, cold exposure significantly reduced levels of arginine vasopressin (203). To further complicate matters, the reported analgesic effect of arginine vasopressin was only observed if the subjects (mice or humans) were male and not stressed (204). This is a good example of a non-linear effect on how we experience pain.

The reduced levels of arginine vasopressin during and after cold exposure could be caused by an increase in blood pressure due to cold-induced vasoconstriction. In addition to temperature, barometric pressure could affect blood pressure (128). Blood pressure could also be associated with how we experience pain independently of arginine vasopressin (205), as there seems to be less pain sensitivity when the blood pressure rises (205). More specific studies on the effect of barometric pressure on pain have found a sympathetically mediated increase in pain behavior in mice when lowering barometric pressure (111, 112, 206).

Cognitive processes have a seasonal aspect (207), thus meteorological variables might affect our mood and behaviors as well, which again might affect our ability to endure pain or the experience of pain. For example, depressed mood and less physical activity are reported to be associated with less pain tolerance (208, 209). A British population study found that a part of the association between increased pain experience and weather was mediated by lifestyle factors like less exercise (210).

In summary, meteorological variables probably have many different, simultaneous effects, but the net result of these mechanisms on pain tolerance is difficult to assess.

5.2.2 Cold environment at work and pain

The associations found in the cross-sectional Paper 1 and the single small effect estimate in Paper 2 indicate an increased risk of chronic pain when exposed to a cold environment at work. This is in line with previous studies on cold exposure and pain. However, the existing literature on cold environment at work as a risk factor for pain has several limitations, as, to some extent, do Papers 1 and 2. The exposure measure in the literature is often poorly defined, and most studies have a cross-sectional design. The study populations are often male workers in occupations where physical work and other possible risk factors for poor health are common (211). Thus, the results of most such studies could be confounded by other risk factors, and their generalizability is questionable. Studies on the topic have mostly investigated occupational risk factors for musculoskeletal pain in general and lack a clear aim to investigate the association between cold exposure and musculoskeletal conditions or pain. It is possible that other, similar studies that asked about time spent in cold environments did not find an association, and consequently did not include cold environment in their analysis and reporting. Thus, the existing evidence could be vulnerable to publication bias. The heterogeneity in exposure and outcome measures also makes it difficult to draw any conclusions.

The observed effect of meteorological variables on one's experience of pain can be a part of a causal pathway between cold exposure at work and pain. Exposure to a cold environment could increase the frequency or intensity of pain episodes, and thus increase the risk of chronic pain, as studies have found that reporting pain is a risk factor for future chronic pain (37, 163). The receptor channel TRPM8 has been reported to be involved in both cold and pain perception, and TRPM8 expression in the epidermis is associated with levels of cooling sensation (212). An interesting finding is that TRPM8 expression seems to be higher in the pathological periarticular connective tissue of the lumbar spine than in non-pathological tissue among patients with chronic low back pain (213). As inflammation increases pain experience and is believed to play a role in different pain conditions (214), higher TRPM8 expression could be related to an anti-inflammatory effect of TRPM8 activation (215). Studies of mice have reported an increase in TRPM8 expression in the hypothalamus after cold exposure (215, 216). One could speculate that this increase in expression might be present in the peripheral nervous system as well. If so, an increase in TRPM8 expression caused by cold exposure or chronic pain could explain the association between cold exposure and chronic pain, and the reported higher prevalence of cold-induced pain among those with existing musculoskeletal pain. However, a recent study in mice found that TRPM8 expression in the dorsal root ganglia decreased after 4 weeks of cold exposure (217), which again would fit with the seasonal variation in CPT in Paper 3. In summary, using single experiments on regulation of gene expression to explain observations at the population level is difficult. For example, the mice in the aforementioned study were continuously exposed to cold temperatures (217), while humans often experience intermittent exposure. This difference in exposure could lead to variances in adaptation and gene expression. Additionally, experiencing chronic pain is different from CPT, and the transferability of animal research is always questionable.

The integration of temperature and pain in the nervous system and the effect of temperature on the sensory system may not be the only causal pathways. Local effects of cold exposure, like cooled tissue, reduced biomechanical properties, and neuromotoric function (115) might also be part of some hypothetical causal mechanisms. These tissue-specific effects could play a role in localized conditions. Cold temperature was the most prominent variable that could explain the difference in incidence of tenosynovitis/peritendinitis between two groups of workers in a slaughterhouse (218), and a higher incidence of Achilles tendinosis/paratendinitis among military recruits in winter (219). Other studies have found a high risk of carpal tunnel syndrome among those with the combination of repetitive work and cold exposure (220, 221). These conditions are quite clearly defined in the clinical setting and include symptoms or clinical findings, such as crepitation and reduced nerve conduction, which are not easily explained by the alterations in the sensory system discussed earlier. A reported increased risk of rheumatoid arthritis among workers exposed to a cold environment indicates the possible involvement of inflammatory processes as well (222). As with the effect of weather on pain tolerance, there could be many possible mechanisms contributing to the development of chronic pain, and our current understanding is inadequate. Thus, more research is needed to understand the interplay between different factors.

5.3 Importance for public health and future research

Our finding of a possible effect of meteorological variables on pain tolerance might be difficult to directly translate into public health policies. Also, the validity of the results in a clinical setting is limited, since pain tolerance to an experimental stimulus is not the same as clinical pain. Nevertheless, these results merit the adoption of a different approach to understand individuals who complain that weather affects their pain. The effect of different meteorological variables changes with time, and trying to calculate an effect for, for example, 1°C or 1 hPa cannot capture or explain the relationship. Recognizing the complexity and the behavior that dynamic non-linear systems can exhibit might yield a new understanding of how we experience pain and how we choose to study risk factors and evaluate interventions for pain and chronic pain. There might be new insights to be gained if the transition from pain to chronic pain is studied as a transition in a dynamic non-linear system (223). For example, several studies have tried to use quantitative sensory testing to predict chronic post-operative pain, but the results are conflicting (224). One explanation could be that it is not only the pain threshold or tolerance compared to others that are of importance, but also the state of the system. The adaptability of the system or the system's resilience to external perturbations could yield information about the risk of a transition from pain to chronic pain (223).

The evidence for cold exposure at work, or in other settings, as a risk factor for pain or chronic pain is by no means complete. There are possible causal pathways, but the overall evidence is poor and not sufficient to make any strong recommendations. On the other hand, known protective measures like better clothing and increased activity are not costly and have few side-effects. Employers and employees should aim to organize and plan work in a way that allows for behavioral adjustments. Facilities should be constructed in a way that minimizes cold exposure through, for example, the building of windshields when appropriate. Independently of whether cold exposure causes chronic pain or not, workers are less likely to feel cold when protected, and such protection would increase the well-being of the worker.

6 CONCLUSION

There is ample evidence that the feeling of temperature and the feeling of pain are anatomically and physiologically related, and that both have an impact on how we humans experience our existence. Thus, the common belief and the current findings that weather affects pain experience is not surprising. Even though the results in this thesis indicate that exposure to a cold environment at work can be a risk factor for chronic pain, there is still a lack of good-quality studies.

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Paper 1

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Working in a cold environment, feeling cold at work and chronic pain: a cross-sectional analysis of the Tromsø Study.

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Working in a cold environment, feeling cold at work and chronic pain: a cross-sectional analysis of the Tromsø Study

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ABSTRACT

Aim The aim of this study was to investigate if working in a cold environment and feeling cold at work are associated with chronic pain (ie, lasting ≥3 months).

Methods We used data from the sixth survey (2007–2008) of the Tromsø Study. Analyses included 6533 men and women aged 30–67 years who were not retired, not receiving full-time disability benefits and had no missing values. Associations between working in a cold environment, feeling cold at work and self-reported chronic pain were examined with logistic regression adjusted for age, sex, education, body mass index, insomnia, physical activity at work, leisure time physical activity and smoking.

Results 779 participants reported working in a cold environment ≥25% of the time. This exposure was positively associated with pain at ≥3 sites (OR 1.57; 95% CI 1.23 to 2.01) and with neck, shoulder and leg pain, but not with pain at 1–2 sites. Feeling cold sometimes or often at work was associated with pain at ≥3 sites (OR 1.58; 95% CI 1.22 to 2.07 and OR 3.90; 95% CI 2.04 to 7.45, respectively). Feeling cold often at work was significantly and positively associated with pain at all sites except the hand, foot, stomach and head.

Conclusion Working in a cold environment was significantly associated with chronic pain. The observed association was strongest for pain at musculoskeletal sites and for those who often felt cold at work.

Strengths and limitations of this study

- ► The study has a high response rate (65.7%) which increases the likelihood that it is a representative sample of the working population.
- ► The observed associations in the present study are consistent for pain at multiple sites and at specific sites.
- ► The healthy worker effect may cause an underestimation of the associations.
- ► The results are to some extent vulnerable to residual confounding by other occupational risk factors.

INTRODUCTION

By evolution, humans are not physiologically fit to live in cold environments. To survive in such environments, we must use different strategies, such as insulating clothing, houses and heating, which protect us from low temperatures. However, these protective measures may not be sufficient, as there is an excess of deaths recorded during the winter season. This excess is only partly explained by seasonal diseases and thus indicates that even moderately cold temperatures induce a strain on the body and negatively affect health.[1]

Cold exposure can cause pain. Indeed, immersing one's hand in cold water is commonly used as a test of pain tolerance.[2] Exposure to a cold environment, at work or during leisure time, can cause one to experience acute pain. In Finland, the reported prevalence of musculoskeletal pain believed by respondents to be caused by cold exposure is as high as 30% for men and 27% for women.[3 4] Cold exposure is also known to reduce both physical and cognitive performance.[5 6] Cold temperatures may also have subacute effects. Working in a cold environment has been found to be associated with an increased prevalence of back, neck and shoulder pain.[7–10] In addition, it has been suggested that working in a cold environment is related to respiratory, cardiovascular and dermatological complaints and diseases.[11]

Factors that affect workers' thermal balance are contact with water or cold surfaces, humidity, air velocity, radiation, type of clothing and the heat produced by executing the work.[12] A cold working environment is defined as an environment with an ambient temperature below 10°C.[13] However, the ambient air temperature might not be a good measure of a worker's heat loss. In a study of seafood-processing workers, no relationship was found between workers' reports of feeling cold and measured air velocity, air temperature at the feet or air temperature 1.1 m above the floor.[14] This indicates that actual cold exposure is difficult to measure. Some studies have circumvented this problem by using self-reported cold experience as a measure of cold exposure.[15 16] Among workers in the food processing industry, self-reported experiences of cooling of the neck, shoulder, wrist and lower back were associated with a self-reported disadvantage in daily routines due to pain at those sites.[15] In a study of seafood industry workers, feeling cold often at work was associated with musculoskeletal pain.[16] Feeling cold often at work has also been associated with an increased prevalence of symptoms from skin and airways.[14]

These previous studies mostly used 12 months prevalence, that is, musculoskeletal pain over the last 12 months, as the outcome. This includes acute periods of pain within the past 12 months, but contributes no information about the duration of pain. Chronic pain, defined as pain lasting 3 months or longer, may be a better measure of the impact on quality of life and future work ability.[17 18] However, there is a lack of studies on the association between cold exposure and chronic musculoskeletal pain or pain in other tissues. Therefore, the main aim of this study was to investigate if working in a cold environment and feeling cold at work are associated with chronic pain. We hypothesise that exposure to a cold work environment increases the prevalence of chronic pain.

METHODS

Participants

The Tromsø Study is a prospective cohort study performed in the municipality of Tromsø in Northern Norway. The study currently consists of seven surveys, with the first conducted in 1974 and the seventh in 2015–2016. Tromsø has a coastal climate; the outdoor temperature is below 10°C for a major part of the year and seldom falls below −10°C.[19] This study includes participants from the sixth survey of the Tromsø Study (Tromsø 6), which was carried out in 2007–2008 and encompassed physical examinations and extensive health questionnaires.[20] Of the 19 762 individuals invited to Tromsø 6, 12 984 (65.7%) participated. The age of the participants ranged from 30 to 87 years. We excluded participants who were retired, were above retirement age (ie, 67 years), on full-time disability benefits and those with missing values. Thus, the final study population comprised 6533 men and women (figure 1). The Regional Committee of Research Ethics approved Tromsø 6 and this particular analysis.

Pain

Participants were asked 'Do you have persistent or recurrent pain lasting 3 months or more' (Yes/No), and if so, at which anatomical site the pain was situated. The alternatives were jaw, neck, back, shoulder, arm (including elbow), hand, hip, leg (including thigh, knee and calves), foot (including ankle), head (including face), chest, stomach, genitals, skin and other. Sites where participants reported pain were then counted, and participants were categorised as having: no pain, pain at 1–2 sites and pain at ≥3 sites.

Cold exposure

The Tromsø 6 questionnaire included the question 'Do you work outdoors at least 25% of the time or in cold

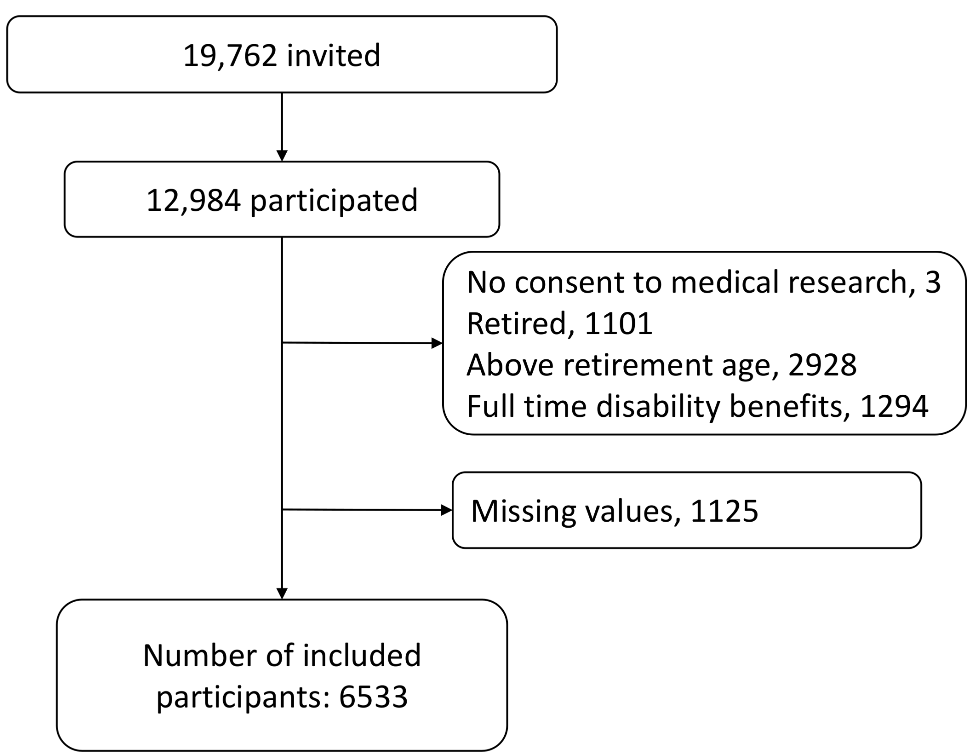

Figure 1 Flowchart presenting number of subjects invited to Tromsø 6, those who participated in Tromsø 6 and those excluded and included in the present analysis.

buildings (eg, storage/industry buildings)?'. Only those who answered 'Yes' were given an extra set of questions about working in a cold environment in the second questionnaire. Among those questions were 'Do you feel cold at work?' (yes, often/yes, sometimes/no, never).

Confounders

Possible confounders obtained from the questionnaires were age, sex, education, insomnia, physical activity at work, leisure time physical activity and smoking. Body mass index (BMI) was calculated from weight and height measured at the examination. BMI was categorised into underweight/normal weight (<25 kg/m^2), overweight (≥25 kg/m^2 and <30 kg/m^2) and obese (≥30 kg/m^2) in the descriptive statistics, but it was included as a continuous variable in the regression analysis. Insomnia was assessed by the question 'In the past 12 months, how often have you suffered from sleeplessness?' (never or just a few times a year/1–3 times a month/approximately once a week/more than once a week). Physical activity at work was measured with the question 'If you have paid or unpaid work, which statement describes your work best?' (mostly sedentary/requires a lot of walking/requires a lot of walking and lifting/heavy manual labour). Leisure time physical activity had four categories: sedentary, low, moderate and hard. Sedentary was described as 'reading, watching TV or other sedentary activity', low as 'walking, cycling or other forms of exercise at least 4 hours per week', moderate as 'recreational sports, heavy gardening for at least 4 hours per week' and hard as 'hard training or sports competition, regularly several times per week'. Smoking was categorised into current, former and never smoker.

Statistics

Pearson χ^2 test was used to test differences in prevalence if all cells had n>5; Fisher's exact test was used if n≤5. T-test was used for age. Multivariable logistic regression was used to assess the association between working in a cold environment ≥25% of the time and self-reported pain. All statistical analyses were performed in Stata MP 15.

Patient and public involvement

There was no patient or public involvement in this particular substudy.

RESULTS

Participants

Among the 6533 participants included in the study, 779 reported to work in a cold environment ≥25% of the time. These individuals were younger, were mostly men, had lower levels of education compared with the rest of the working population and had a higher BMI. They were also more likely to have physically demanding work, have lower levels of leisure time physical activity and to be current or former smokers (table 1).

Out of the 779 workers who reported working in a cold environment ≥25% of the time, 92 never felt cold at work, 635 felt cold sometimes and 52 felt cold often. The prevalence of chronic pain at different anatomical sites was higher in those who often or sometimes felt cold at work compared with those who never felt cold (table 2).

Multiple pain sites

Working in a cold environment ≥25% of the time was significantly associated with pain at ≥3 sites after adjustment (OR 1.57; 95% CI 1.23 to 2.01) (table 3).

n the fully-adjusted model, those who worked in a cold environment ≥25% of the time did not have higher odds for pain at 1–2 sites compared with those who worked in a cold environment <25% of the time. When those who worked in a cold environment ≥25% were divided by frequency of feeling cold, feeling cold sometimes and often was associated with pain at ≥3 sites (OR 1.58; 95% CI 1.22 to 2.07 and OR 3.90; 95% CI 2.04 to 7.45, respectively) (figure 2).

Pain at specific sites

In the analysis with pain at specific sites as outcomes, the low number of participants who worked in a cold environment ≥25% with pain in the jaw (n=4), chest (n=10), skin (n=5), genitals (n=8) and other location (n=3) prevented separate analyses for these outcomes. When using pain at the remaining 10 sites as separate outcomes, working in cold environments ≥25% of the time was significantly associated with pain at all sites except the foot, head and stomach in the model adjusted for age and sex (table 3). Although those working in cold environments ≥25% of the time had higher odds for pain at all sites except the foot in the fully-adjusted model, only the associations for pain at the neck, shoulder and leg were statistically significant (table 3).

When those working in cold environments ≥25% of the time were divided by frequency of feeling cold, those who felt cold sometimes or often at work had significantly higher odds for pain at most musculoskeletal sites compared with those working in a cold environment <25% of the time. In the model adjusted for age and sex, feeling cold often was significantly associated with head and stomach pain (figure 2).

After adjusting for possible confounders, only pain from musculoskeletal pain sites remained significant; workers who felt cold often had higher odds for neck, shoulder, arm, leg, back and hip pain compared with the group that worked in a cold environment <25% of the time (figure 2). The strongest association was for neck pain (OR 3.05; 95% CI 1.64 to 5.66). Among those working in cold environments ≥25% of the time, the group that reported feeling cold sometimes at work had higher odds for neck, shoulder and leg pain, with ORs between those who never felt cold and those who felt cold often at work (figure 2). In the group working in cold environments ≥25% of the time, never feeling cold at work was not

Table 1 Characteristics of the study population

	Working in a cold environment ≥25% of the time				
	No, n=5754		Yes, n=779		t/χ^2
	n	%	n	%	P value
Age (years)*	49.9	8.8	48.8	8.7	<0.001
Sex					
Female	3178	55.2	143	18.4	
Male	2576	44.8	636	81.6	<0.001
Education					
Primary/secondary	727	12.6	262	33.6	
Technical school	1261	21.9	308	39.5	
High school	513	8.9	75	9.6	
College/university<4 years	1350	23.5	94	12.1	
College/university≥4 years	1903	33.1	40	5.1	<0.001
Body mass index					
Under and normal weight (<25 kg/m^2)	2233	38.8	205	26.3	
Overweight (≥25 and <30 kg/m^2)	2494	43.3	406	52.1	
Obese (≥30 kg/m^2)	1027	17.8	168	21.6	<0.001
Insomnia					
Never or just a few times a year	3927	68.2	576	73.9	
1–3 times a month	1042	18.1	118	15.1	
Approximately once a week	365	6.3	42	5.4	
More than once a week	420	7.3	43	5.5	0.014
Physical activity at work					
Mostly sedentary work	3497	60.8	87	11.2	
Work that requires a lot of walking	1454	25.3	176	22.6	
Work that requires a lot of walking and lifting (n, %)	760	13.2	379	48.7	
Heavy manual labour	43	0.7	137	17.6	<0.001
Leisure time physical activity					
Sedentary	1081	18.8	186	23.9	
Low	3350	58.2	410	52.6	
Moderate	1176	20.4	174	22.3	
Hard	147	2.6	9	1.2	<0.001
Smoking					
Current	1111	19.3	211	27.1	
Former	2227	38.7	319	40.9	
Never	2416	42	249	32	<0.001

*Numbers are mean and SD for age, otherwise n and %.

significantly associated with chronic pain at any specific site in either of the models.

DISCUSSION

Key results

In this study, working in a cold environment ≥25% of the time was associated with chronic pain (ie, pain lasting ≥3 months) at the neck, shoulder and leg, as well as pain at ≥3 sites, even after adjusting for age, sex, education, BMI, insomnia, physical activity at work and leisure time physical activity. Those who felt cold often at work had significantly higher odds for pain at ≥3 sites and for pain at all specified sites except the hand, foot, head and stomach. Feeling cold sometimes at work was significantly associated with neck, shoulder and leg pain. We found no significant differences in chronic pain between those

Table 2 Prevalence of chronic pain in participants working in a cold environment <25% of the time and in those working in a cold environment ≥25% of the time by frequency of feeling cold

	Working in a cold environment <25% of the time n=5754		Frequency of feeling cold at work among those working in a cold environment ≥25% of the time n=779					
			Never, n=92		Sometimes, n=635		Often, n=52	
Anatomical sites	n	%	n	%	n	%	n	%
1–2 sites	783	14	14	15	91	14	8	15
≥3 sites	904	16	7	8	128	20	21	40
Neck	765	13	8	9	106	17	18	35
Back	811	14	6	7	106	17	14	27
Shoulder	753	13	8	9	113	18	18	35
Arm	465	8	6	7	69	11	11	21
Hand	341	6	3	3	39	6	6	12
Hip	514	9	7	8	49	8	9	17
Leg	557	10	7	8	76	12	13	25
Foot	385	7	3	3	36	6	4	8
Head	318	6	0	0	32	5	7	14
Stomach	210	4	1	1	27	4	5	10

who never felt cold when working in a cold environment ≥25% of the time and those who worked in cold environment <25% of the time.

There are many different aetiologies of pain and we do not have sufficient information to appropriately identify the origin of the pain.[21] Additionally, we have no information on whether the reported pain was present at all times or only when exposed to cold environment. Nevertheless, the ORs for chronic pain at musculoskeletal locations in the present study were lower than estimates for musculoskeletal pain during the last 12 months from studies of slaughterhouse and seafood industry workers.[15 16] Interestingly, in the fully-adjusted model, we found no association between working in a cold environment ≥25% of the time

Table 3 Logistic regression analysis with pain at 1–2 or ≥3 sites and specific pain sites as outcomes

	Working in a cold environment <25% of the time n=5754	Working in a cold environment ≥25% of the time n=779				
	Reference		Adjusted for age and sex		Fully adjusted model*	
Anatomical sites	n	n	OR	95% CI	OR	95% CI
1–2 sites†	783	113	1.15	0.92 to 1.44	0.95	0.73 to 1.24
≥3 sites‡	904	156	**2.02**	**1.64 to 2.48**	**1.57**	**1.23 to 2.01**
Neck	765	132	**1.78**	**1.44 to 2.20**	**1.46**	**1.13 to 1.89**
Back	811	126	**1.38**	**1.12 to 1.71**	1.18	0.91 to 1.52
Shoulder	753	139	**1.96**	**1.58 to 2.42**	**1.39**	**1.08 to 1.78**
Arm	465	86	**1.93**	**1.49 to 2.50**	1.34	0.98 to 1.83
Hand	341	48	**1.66**	**1.19 to 2.32**	1.16	0.79 to 1.71
Hip	514	65	**1.59**	**1.19 to 2.12**	1.26	0.90 to 1.75
Leg	557	96	**1.87**	**1.47 to 2.40**	**1.47**	**1.10 to 1.96**
Foot	385	43	1.16	0.83 to 1.63	0.80	0.54 to 1.19
Head	318	39	1.28	0.89 to 39	1.13	0.75 to 1.70
Stomach	210	33	1.42	0.96 to 33	1.30	0.82 to 2.04

Statistically significant results are highlighted in bold ($p < .05$)
*Adjusted for age, sex, education, body mass index, insomnia, physical activity at work, leisure time physical activity and smoking.
†Model does not include those with pain at ≥3 sites.
‡Model does not include those with pain at 1–2 sites.

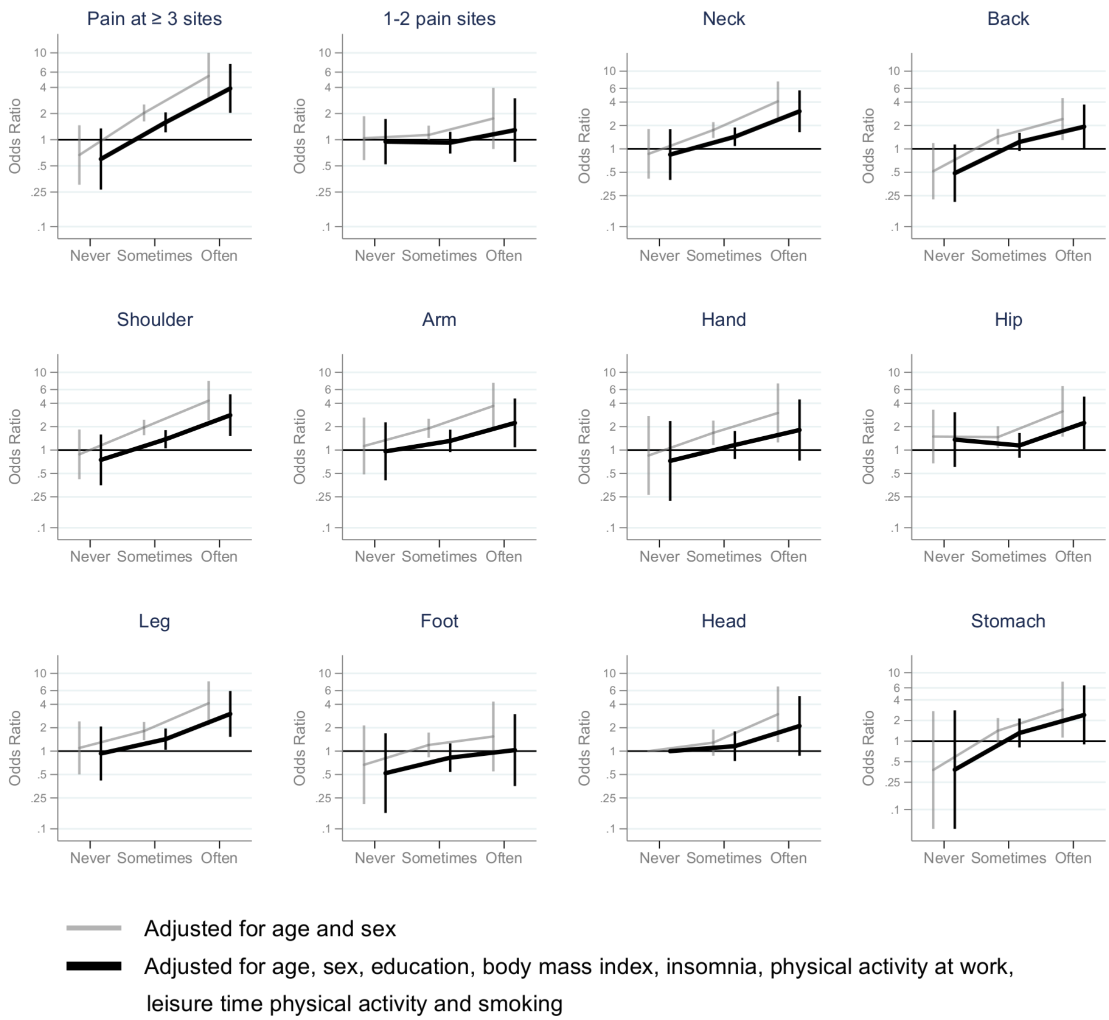

Figure 2 ORs with 95% CIs for chronic pain. Working in a cold environment ≥25% of the time and feeling cold never, sometimes or often compared with those working in a cold environment <25% of the time.

and hand and foot pain. These are the body parts that are most susceptible to cooling. If cooling of local tissue is the mechanism for a higher prevalence of chronic pain, one could assume that body parts most exposed to cold would be at a higher risk for pain. The results for hand and foot in the present study do not support such an assumption. However, this observation is in contrast to other studies that found associations between a cold environment or an experience of cooling of the wrist and pain in the wrist, hand and forearm.[7 15 22] The difference between earlier findings and the present study might be due to a different aetiology and pathology for chronic musculoskeletal pain and 12month pain prevalence. Different study populations and cold exposures could also contribute to the contradictory results.

Feeling cold is a subjective experience and contains little or no information about the actual environment, such as ambient temperature, humidity and air velocity. However, ambient temperature could also be a poor measure of cold exposure. A study of seafood industry workers could not establish a simple relationship between thermal environmental factors and the prevalence of workers feeling cold. The same study also found that working in relatively high temperatures (>12°C) led to low finger temperatures and a major drop in foot temperature.[14] Thermal comfort and sensation seem to be closely connected to both average skin temperature and rectal temperature.[23] Although subjective, feeling cold might be a better indication of the environment's effect on the body than ambient air temperature.

The general health status of a person might also influence to what degree they feel cold. Individuals with already existing diseases are more prone to report cold-related musculoskeletal pain,[24] and male slaughterhouse workers with chronic pain had more complaints about indoor climate, including complaints about temperatures that were too low and draughts, when compared with those without pain.[25] Chronic pain could also influence the perception of feeling cold. The design of the present study is not adequate to address the direction of the observed association.

Few plausible causal mechanisms between cold exposure and musculoskeletal pain, chronic or not, have been suggested. Studies have found that cooling induces acute physiological alterations in the musculoskeletal and neural system. There seems to be a dose-response relationship between the temperature in the muscle and muscle power, and the contraction velocity decreases with decreasing temperature. Further, there is an increased activation of the antagonist muscles indicating a reduced motor control.[26–28] Another study reports an enhanced fatigue in the muscles when performing repetitive work in a cold environment.[29] These alterations point in the direction that cold exposure increases the strain on the musculoskeletal apparatus . Repeated exposure to a cold environment can also have a long-term effect in the form of habituation or acclimatisation. Habituation is described as a reduction in shivering, vasoconstriction stress response and cold sensation. Additionally, different acclimatisation processes like lowering core temperature, increasing the metabolic rate and increasing vasoconstriction or subcutaneous fat have been reported.[30] However, a relationship between these altered acute and long-term physiological responses, and subsequent chronic pain has not been satisfactorily established. A cross-sectional study of slaughterhouse workers found that a lower pressure pain threshold was associated with more complaints about the indoor climate.[25] A possible explanation for the observed association between chronic pain and frequency of feeling cold in the present study could be that persons who felt cold have a lower pain threshold than those who did not. Future research should explore whether this is genetic or if thermal stimuli could contribute to a sensitisation process.

Strengths and limitations

In our study, participants who worked in a cold environment ≥25 of the time had generally low education and executed a lot of heavy physical work, both of which have been identified as risk factors for musculoskeletal pain[31–33]; adjusting for these confounders attenuated the associations in the present study. Workers exposed to cold are also exposed to several other occupational risk factors that can be associated with poor health, and physical activity at work is not a satisfactory measure of these risk factors.[34] Consequently, the results are to some extent vulnerable to residual confounding.

There are a number of clinical conditions that could be a cause of pain or increase the risk of chronic pain.[21] As these conditions could be unevenly distributed, they could confound the observed association. Our results could also be influenced by the healthy-worker effect.[35] Feeling cold is uncomfortable, and individuals negatively affected by a cold environment might change their occupation or workplace to avoid getting cold. The remaining employees exposed to cold may therefore be the ones that are the least negatively affected by the cold. Additionally, chronic pain can contribute to selection bias by having a different impact in different occupations. There is a social gradient in disability benefits, and physical work has been found to increase the risk for disability pension, even after adjustment for health status.[36] Thus, the effect estimates may be underestimated.

The high response rate (65.7 %) of Tromsø 6 is a major strength and increases the likelihood that the findings are representative of the general population. Nevertheless, non-participants in Tromsø 6 tend to have lower education than participants;[20] therefore, we cannot rule out that the prevalence of cold-exposed workers was higher among non-participants. Additionally, some of the occupations in which workers are typically exposed to cold environments have a high number of migrant workers, a group not invited to participate in The Tromsø Study. As an example, in 2008 in Norway, approximately 12% of workers in the construction industry were migrant workers.[37] These aspects may have led to selection bias and thus an underestimation of the proportion of workers exposed to a cold environment. How this selection bias affects the association between feeling cold and musculoskeletal pain or cold-related health complaints is not known.

A clear limitation of the study is the low number of participants who reported feeling cold often or never, resulting in large CIs. Also, there were few female participants working in a cold environment ≥25% of the time (n=123), which prevented any useful analysis stratified by sex. There are sex differences in types of work, prevalence of cold discomfort or cooling[15] and in the prevalence of musculoskeletal pain.[33] The association between working in cold environment and musculoskeletal pain is likely different by sex.

The observed associations in the present study are consistent for pain at multiple sites and at specific sites. Although not all the effect estimates were significant, the direction of the associations was consistent, with increased reporting of pain with increasing experience of cold at work, at all sites except the hip. This consistency and the high effect estimates indicate that the observed associations are robust and that additional adjustment for occupational risk factors would not explain all associations.

Even though Tromsø is situated at 69°N, the climate is relatively mild due to the Gulf Stream. There are also several factors other than ambient air temperature that can affect a worker's thermal balance, for example, amount of protective clothing. At work, individual differences in heat loss, protection and adaptations, such as behavioural responses, adjusting clothing or increasing physical activity, are very difficult to measure and would vary throughout a workday. The heat loss of one worker in a cold environment may be the same as that of another in a moderately cold environment if not properly protected. Thus, we believe the results of the present study are not specific to our study population, but relevant to others working in cold environments, whether they are indoor or outdoor.

CONCLUSION

Working in a cold environment ≥25% of the time was associated with chronic pain at ≥3 sites and with neck, shoulder and leg pain. Those who worked in a cold environment and felt cold often at work had higher odds for neck, shoulder, arm, back, hip and leg pain compared with those who worked in a cold environment <25% of the time. Working in a cold environment ≥25% of the time and never feeling cold was not associated with pain at any site. Organising work and workplaces in a way that ensures thermal balance for workers might reduce the risk of chronic pain.

Collaborators Lisbeth Aasmoe contributed to the data acquisition of questions regarding work in the cold from the 6th survey of the Tromsø Study.

Contributors EHF, ACH and MS designed the study. EHF conducted the data analysis and wrote the manuscript with the assistance of ACH and MS. TB assisted in the analysis. All authors contributed to the interpretation and revised the manuscript. CN and AS contributed to the data acquisition of questions regarding pain from the 6th survey of the Tromsø Study. All authors read and approved the final manuscript.

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Paper 2

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ORIGINAL ARTICLE

Is working in a cold environment associated with musculoskeletal complaints 7–8 years later? A longitudinal analysis from the Tromsø Study

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Abstract

Objective Exposure to a cold environment at work is associated with a higher prevalence of musculoskeletal pain and chronic pain in cross-sectional studies. This study aims to determine the association between working in a cold environment ≥ 25% of the time and musculoskeletal complaints (MSC) 7–8 years later.

Methods We followed participants from the sixth survey (Tromsø 6, 2007–2008) to the seventh survey (Tromsø 7, 2015–2016) of the Tromsø Study. Analyses included 2347 men and women aged 32–60 years who were not retired and not receiving full-time disability benefits in Tromsø 6. Three different binary outcomes were investigated in Tromsø 7: any MSC, severe MSC, and MSC in ≥ 3 anatomical regions. We excluded participants with severe MSC, MSC in ≥ 3 regions, or missing values in Tromsø 6. The association between working in a cold environment and future MSC were examined using Poisson regression and adjusted for age, sex, number of moderate MSC, education, physical activity at work, smoking status, body mass index, and self-reported health in Tromsø 6.

Results 258 participants reported to work in a cold environment ≥ 25% of the time in Tromsø 6. They had an increased risk of having any MSC in Tromsø 7 (incidence rate ratio 1.15; 95% confidence interval 1.03–1.29). There was no significantly increased risk of severe MSC or MSC in ≥ 3 regions.

Conclusion Working in a cold environment was associated with future MSC, but not with future severe MSC or future MSC in ≥ 3 regions.

Keywords Musculoskeletal pain · Musculoskeletal complaints · Cold environment · Epidemiology · Cold temperature

Introduction

Even moderately cold temperatures can cause stress to the human body and increase mortality (Gasparrini et al. 2015). Exposure to a cold environment at work has been suggested as a risk factor or aggravator of different health complaints, such as musculoskeletal pain and symptoms from skin, the respiratory system, and the cardiovascular system (Makinen and Hassi 2009).

A cold working environment is defined as a temperature below 10 °C (ISO 15743:2008 Ergonomics of the thermal environment—cold workplaces—risk assessment and managment 2008), but cold stress might be present even at higher temperatures in the workplace (Bang et al. 2005). In addition, ambient temperature is only one of many factors that determine a worker's heat loss. Clothing, air movement, contact with cold surfaces and liquids, and the amount of heat produced by the work can also have an impact on a worker's thermal balance and thereby possibly lead to health complaints.

Low back and neck pain are a major cause of disability-adjusted life years (Murray et al. 2012). Furthermore, chronic pain is strongly associated with future disability pension, due to both musculoskeletal and other disorders (Haukka et al. 2015; Saastamoinen et al. 2012). Several

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cross-sectional studies have found that working in a cold environment or feeling cold is associated with a higher prevalence of pain among slaughterhouse, construction, seafood industry, and storehouse workers, as well as in the general population. The association has also been found for musculoskeletal locations such as the wrist, back, neck, and shoulder (Aasmoe et al. 2008; Dovrat and Katz-Leurer 2007; Farbu et al. 2019; Pienimaki 2002; Skandfer et al. 2014). In a cohort of 134,754 male Swedish construction workers, there was a higher prevalence of musculoskeletal pain in geographical regions with lower mean temperatures (Burstrom et al. 2013). Some studies have reported a higher incidence of tendinopathies and associated disorders in colder environments (Kurppa et al. 1991; Milgrom et al. 2003). However, there is a need for more prospective studies investigating exposure to a cold environment at work as a risk factor for musculoskeletal pain.

Our previous cross-sectional study from the sixth survey of the Tromsø Study (Tromsø 6) found that working in a cold environment ≥ 25% of the time was associated with chronic pain lasting 3 months or longer (Farbu et al. 2019). In the consecutive, seventh survey of the Tromsø Study (Tromsø 7) the questions concerning chronic pain and anatomical sites were replaced with a computerised system, in which participants pointed and clicked on a digital mannequin to show affected sites, combined with questions. Thus, answers in Tromsø 6 and Tromsø 7 are not directly comparable. Therefore, the outcomes in this prospective analysis are based on another set of questions that were phrased identically in both surveys. However, as these questions assessed both pain and/or stiffness in the same question, we termed it "musculoskeletal complaints" (MSC).

This study aims to determine the association between working in a cold environment ≥ 25% of the time and MSC 7–8 years later.

Methods

Population: the Tromsø Study

The Tromsø Study is a prospective cohort study consisting of seven surveys carried out from 1974 to 2016. We used the data from Tromsø 6 (2007–2008) as the baseline and that from Tromsø 7 (2015–2016) as follow-up (Jacobsen et al. 2012). The surveys consist of a physical examination and questionnaires. As the risk of MSC is likely to decrease after retirement, we excluded all participants who were retired, older than 60, or receiving a fulltime disability pension at the time of Tromsø 6 (Neupane et al. 2018). Finally, we excluded all participants with missing values in Tromsø 6 (Fig. 1). The Regional Committee of Research Ethics approved Tromsø 6 and 7 and this particular analysis.

Exposure and confounders

The question "Do you work outdoors or in cold buildings (e.g. storage/industry buildings) at least 25% of the time?" (Yes/No) from Tromsø 6 was the exposure of interest. Tromsø has a coastal climate; the outdoor temperature is below 10 °C for most of the year and seldom falls below − 10 °C [Weather statistics for Tromsø observation site, Tromsø (Troms) 2018]. In Tromsø 7 there was no measure for cold exposure.

Information on age and education was taken from Tromsø 6. The degree of physical activity at work was assessed with the question "If you have paid or unpaid work, which statement describes your work best?", with four response alternatives: mostly sedentary, requires a lot of walking, requires a lot of walking and lifting, and heavy manual labour. Smoking status was categorised as current, former, and never smoker. Body mass index (BMI) was calculated from height and weight measures at the Tromsø 6 physical examination. Self-reported health was assessed with the question "How do you in general consider your own health to be?", with five response alternatives: excellent, good, neither good nor bad, bad, and very bad. Due to few respondents reporting bad and very bad, the categories were merged with "neither good nor bad".

Outcomes

In both Tromsø 6 and Tromsø 7, information on MSC was collected with the question "During the last year have you been affected by pain and/or stiffness in muscles or joints lasting at least 3 months?" with a list of six different anatomical regions: neck or shoulder, upper back, lumbar back, hip or leg, arm or hand, and other. For each site there were three alternatives: no, moderately, or severely. We investigated three different binary outcomes: any MSC, severe MSC, and MSC in ≥ 3 regions. Those reporting moderate or severe MSC at one or more regions were categorised as having "any MSC". Participants who reported severe MSC at any of the six regions were categorised as "severe MSC". For the third binary outcome, we counted the number of regions with MSC, regardless of severity, and categorised them into 0–2 regions and ≥ 3 regions. We excluded all those who reported severe MSC or MSC in ≥ 3 regions in Tromsø 6.

Statistical analyses

Pearson chi-square was used to test differences in prevalence, and *t* test was used for age. We used Poisson regression with robust variance to perform three different analyses for the three binary outcomes; any MSC, severe MSC, and

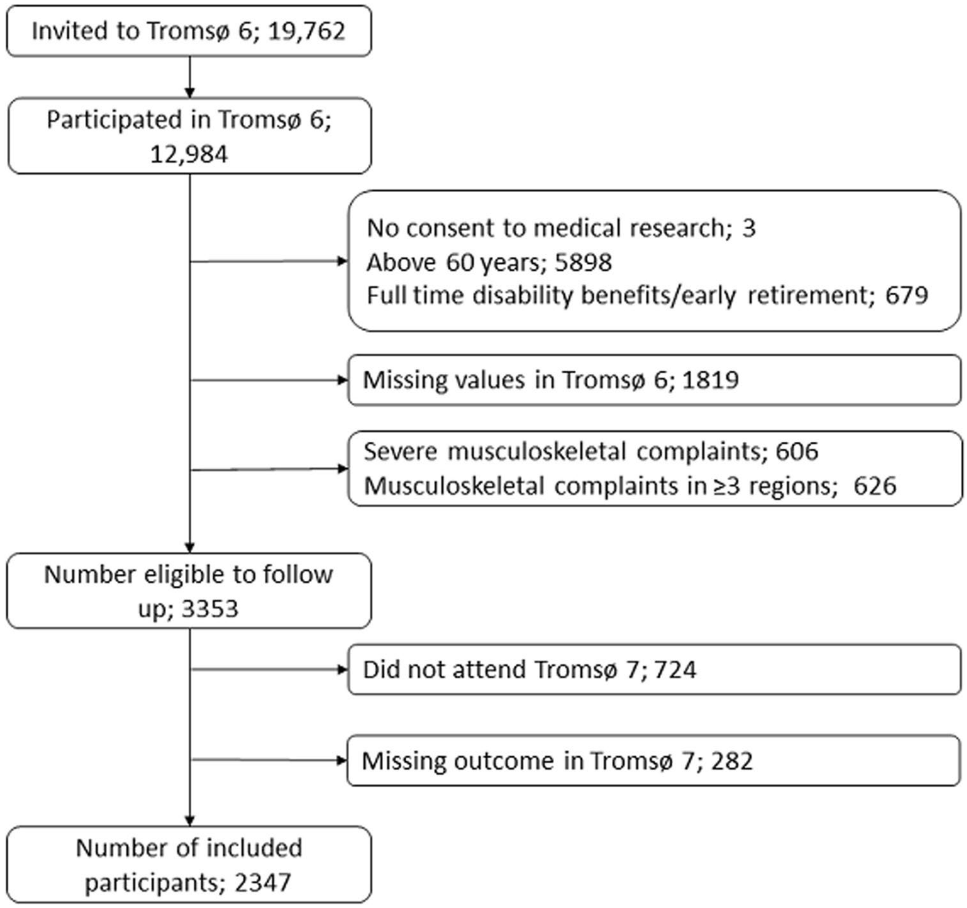

Fig. 1 Flow chart presenting number of subjects invited to Tromsø 6, those who participated in Tromsø 6 and in Tromsø 7, and those excluded and included in the present analysis

MSC in ≥ 3 regions. Poisson regression is recommended when analysing binary outcomes with high prevalence. The effect estimate is incidence rate ratio (IRR) and can be interpreted as relative risk (Zou 2004). All statistical analyses were performed in Stata MP 15.

Sensitivity analysis

A large proportion of participants were excluded due to missing values in Tromsø 6 (Fig. 1). As this could introduce bias, we performed multiple imputation with chained equations. We included the original questions about MSC and all the variables included in the main analysis. To increase the predictive power, we included dichotomous questions about chronic pain from Tromsø 6 and Tromsø 7, as well as pain sites from Tromsø 7. Due to perfect prediction, we used the augment option and imputed 100 datasets. To make the IRRs from the imputed regression models comparable to the IRRs from the main analysis, we included an interaction term between having severe MSC or MSC in ≥ 3 regions in Tromsø 6 and working in a cold environment ≥ 25% of the time in the regression analysis on the imputed datasets.

To investigate possible confounding by occupational factors, we conducted sensitivity analyses using occupational codes obtained from the NAV State Register of Employers and Employees (NREE), which is administrated by Statistics Norway. Employers are required to register all those employed for at least 7 days and who will likely have an average of more than 4 h' work per week in the NREE. Each employee is registered with an industrial classification code using the Norwegian coding system, STYRK-98. The 4 first digits of this system are similar to those in the International Standard Classification of Occupations 88. We used the unique 11-digit identification number assigned to all individuals living in Norway to link the NREE with the data from the Tromsø Study. The NREE was not complete at the time of Tromsø 6; therefore, we restricted sensitivity analyses to the subsample of participants with an existing occupational code in the NREE in 2007. For those missing a code in 2007 but with an existing code in 2008, we used the one from 2008. To assess the possible confounding effect of occupation on the association between working in a cold environment and MSC, we ran three different logistic regression analyses: (1) a model identical to that in the main analysis; (2) a model adjusted for the 10 major occupational groups in the International Standard Classification of Occupations 88; (3) a mixed-effects logistic model with a random intercept for each 4-digit occupational code.

Results

Of the 2347 participants, 258 reported working in a cold environment ≥ 25% of the time in Tromsø 6. The latter participants reported more moderate MSC in Tromsø 6, had less education, were more physically active at work, were more often smokers or former smokers, and a higher BMI than those working in a cold environment < 25% of the time. They also had poorer self-reported health. There were no significant differences in age at the time of Tromsø 6 between those working in a cold environment ≥ 25% of the time and those who did not (Table 1).

Musculoskeletal complaints

In Tromsø 7, those who reported working in a cold environment ≥ 25% of the time in Tromsø 6 had a higher prevalence of both moderate and severe MSC (Table 2). The prevalence of participants with MSC in 1–2 and ≥ 3 regions was higher in the exposed group. These differences were evident among those who had no MSC in Tromsø 6, while there were no significant differences among those reporting moderate MSC in Tromsø 6.

Those working in a cold environment ≥ 25% of the time had a significantly increased risk of any MSC in Tromsø 7, after adjustment for age, sex and number of moderate MSC in Tromsø 6 [IRR 1.13; 95% confidence interval (CI)

Table 1 Characteristics of the study population in Tromsø 6 (baseline)

	Working in a cold environment ≥ 25% of the time				
	No, *n* = 2089		Yes, *n* = 258		t/χ^2
	n	%	*n*	%	*p*
Age[a]	47.1	6.9	46.7	6.9	0.396
Sex					
Female	1041	50	52	20	
Male	1048	50	206	80	< 0.001
Number of moderate musculoskeletal complaints					
0	1260	60.3	123	47.7	
1	483	23.1	66	25.6	
2	346	16.6	69	26.7	< 0.001
Education					
Primary/secondary	154	7.4	61	23.6	
Technical school	370	17.7	107	41.5	
High school	196	9.4	37	14.3	
College/university less than 4 years	559	26.7	41	15.9	
College/university 4 years or more	810	38.8	12	4.7	< 0.001
Physical activity at work					
Mostly sedentary work	1387	66.4	33	12.8	
Work that requires a lot of walking	474	22.7	71	27.5	
Work that requires a lot of walking and lifting	223	10.7	125	48.5	
Heavy manual labour	5	0.2	29	11.2	< 0.001
Smoking status					
Current	303	14.5	57	22.1	
Former	745	35.7	101	39.1	
Never	1041	49.8	100	38.8	0.001
Body mass index					
Under and normal weight (< 25 kg/m²)	892	42.7	85	32.9	
Overweight (≥ 25 and < 30 kg/m²)	886	42.4	131	50.8	
Obese (≥ 30 kg/m²)	311	17.9	42	16.3	0.01
Self-reported health					
Bad/very bad/neither good nor bad	231	11.1	40	15.5	
Good	1193	57.1	171	66.3	
Excellent	665	31.8	47	18.2	< 0.001

[a]Numbers are mean and standard deviation for age

Table 2 Participants having no or moderate musculoskeletal complaints (MSC) in Tromsø 6, and severity of MSC and MSC in 0, 1–2, or ≥ 3 anatomical regions in Tromsø 7

Tromsø 7	No MSC in Tromsø 6					Moderate MSC in Tromsø 6				
	Working in a cold environment ≥ 25% of the time					Working in a cold environment ≥ 25% of the time				
	No $n=1260$		Yes $n=123$		χ^2	No $n=829$		Yes $n=135$		χ^2
	n	%	*N*	%	*p*	*n*	%	*n*	%	*p*
Severity of MSC										
No	697	55.3	53	43.1		251	30.3	39	28.9	
Moderate	500	39.7	62	50.4		471	56.8	78	57.8	
Severe	63	5.0	8	6.5		107	12.9	18	13.3	
					0.034					0.947
Number of MSC										
0	697	55.3	53	43.1		251	30.3	39	28.9	
1–2	420	33.3	48	39.0		364	43.9	61	45.2	
≥3	143	11.4	22	17.9		214	25.8	35	25.9	
					0.017					0.943

1.02–1.25] (Table 3). This association was slightly stronger after further adjustment for education, physical activity at work, smoking, BMI, and self-reported health in Tromsø 6 (IRR 1.15 95% CI 1.03–1.29).

In the model using severe MSC as an outcome, those working in a cold environment ≥ 25% of the time had no significantly increased risk of MSC after adjustment for age, sex, and number of moderate MSC in Tromsø 6 (Table 3).

The risk of MSC in ≥ 3 regions was higher for those working in a cold environment ≥ 25% of the time in the model adjusted for age, sex, and number of moderate MSC in Tromsø 6 (IRR 1.27; 95% CI 0.98–1.64). However, the association was not significant, and further adjustment attenuated the association (IRR 1.11; 95% CI 0.83–1.49).

The results from the analysis using imputed data gave similar results. In the full model, those working in a cold environment ≥ 25% of the time had an increased risk of any MSC (IRR 1.12; 95% CI 1.03–1.22) and no increased risk of severe MSC (IRR 0.77; 95% CI 0.69–1.38) or MSC in ≥ 3 regions (IRR 1.08; 95% CI 0.88–1.32) (Supplementary Table 1).

Sensitivity analyses with occupational codes

The logistic regression model that adjusted for the 10 major occupational groups did not substantially alter the strength of the association when all other covariates were included, nor did the mixed-effects model with a random intercept for each 4-digit occupational code (Supplementary Table 2). Supplementary Table 3 shows the different occupations in Tromsø 6 for those working in a cold environment ≥ 25% of the time.

Table 3 Incidence rate ratio's (IRR) for any musculoskeletal complaints (MSC), severe MSC, and MSC in ≥ 3 anatomical regions in Tromsø 7

	Working in a cold environment < 25% of the time $n=2089$		Working in a cold environment ≥ 25% of the time $n=258$						
			Crude[a]				Fully adjusted model[b]		
	n	IRR	*n*	IRR	CI		IRR	CI	
Any MSC	1141	Ref	166	1.13	1.02	1.25	1.15	1.03	1.29
Severe MSC	170	–	26	1.14	0.76	1.70	0.95	0.60	1.48
MSC in ≥ 3 anatomical regions	357	–	57	1.27	0.98	1.64	1.11	0.83	1.49

[a]Adjusted for age, sex, and number of moderate MSC in Tromsø 6

[b]Adjusted for age, sex, number of moderate MSC, education, physical activity at work, smoking status, body mass index, and self-reported health in Tromsø 6

Discussion

Key findings

This is the first prospective study of working in a cold environment as a risk factor for future MSC in the general working population. Those working in a cold environment ≥ 25% of the time had a significantly increased risk of experiencing any MSC with a duration of ≥ 3 months 7–8 years later. This association remained significant even after adjustment for baseline characteristics of age, sex, number of moderate MSC, education, physical activity at work, smoking, BMI, and self-reported health in Tromsø 6. The risk of severe MSC or MSC in ≥ 3 regions was not significantly higher for those working ≥ 25% of the time in a cold environment.

One previous study found an increased incidence of Achilles paratendinitis among recruits who completed their basic training in winter compared to summer (Milgrom et al. 2003). Another study of meat-house workers noted that the only noticeable difference between two groups with different incidences of tenosynovitis was a colder workplace environment (Kurppa et al. 1991). Other cross-sectional studies have found a higher prevalence of musculoskeletal pain among workers exposed to a cold environment. The studied populations were storehouse workers, construction workers, mine workers and seafood industry workers, and the general working population (Aasmoe et al. 2008; Burstrom et al. 2012; Dovrat and Katz-Leurer 2007; Farbu et al. 2019; Skandfer et al. 2014). In our previous study, we found an association between working in a cold environment and chronic pain at ≥ 3 anatomical sites (Farbu et al. 2019), but in the current study, we did not find any significant increased risk of MSC in ≥ 3 regions. The higher resolution of the outcome measure in our previous study could explain some of this difference, as the previous study investigated 14 different sites with chronic pain versus 6 regions with MSC in the current study, which means that a participant with pain in the neck, shoulder, and arm would have been classified differently in the two studies. However, since the outcomes in this study concern how much the participants are "affected by pain and/or stiffness", and we do not know how many have stiffness without pain, direct comparison with our earlier research is precarious.

Among participants without MSC in Tromsø 6, those working ≥ 25% of the time in a cold environment had a significantly higher prevalence of MSC in Tromsø 7. However, there was no such difference among those with moderate MSC in Tromsø 6. This indicates that working in a cold environment could contribute to developing MSC, but not aggravate already existing MSC. This is consistent with the lack of significant associations for severe MSC and MSC in ≥ 3 regions. One explanation could be that those working in a cold environment are more prone to transient MSC, like tendinopathies, which often have quite a good prognosis even if left untreated (Smidt et al. 2002).

There was a high prevalence of MSC in the present study, with over 50% of the study population reporting moderate or severe MSC in Tromsø 7. This high prevalence could indicate that any MSC includes complaints that are more of a nuisance; not MSC that have a serious impact on quality of life. In this regard, severe MSC or having pain in ≥ 3 regions are likely more discriminant. In Tromsø 7, the prevalences of severe MSC and MSC in ≥ 3 regions were 11% and 18%, respectively. Nevertheless, pain is a strong risk factor for more pain, and even moderate pain is associated with a lack of labour force participation and absenteeism (Bergman et al. 2002; Elliott et al. 2002; Langley et al. 2010).

Self-reported working in a cold environment ≥ 25% of the time is an imprecise measure of cold exposure. Even though the question used to assess exposure specified outdoors, cold stores, or industry buildings, participants might have answered that they worked in a cold building simply because they considered their office to be cold. Some participants with occupations that are most likely performed in an office reported working in a cold environment, i.e. executive officers and customer service officers in banking (Supplementary Table 3). Consequently, we are at risk of classifying participants with minimal exposure to cold environments as exposed, which may have led us to underestimate the effect of working in a cold environment. On the other hand, our previous cross-sectional analysis showed that feeling cold was strongly associated with chronic pain (Farbu et al. 2019). Thus, the measure of cold exposure in this study might, to some degree, represent perceived thermal stress or an underlying trait that increases the likelihood of both feeling cold and developing MSC. Thus, misclassification of exposure might lead to both over- and underestimation of the effect. It should be mentioned that the high number of childcare workers who reported working in a cold environment is plausible, as most kindergarten classes in Norway spend some hours outdoors every day (Supplementary Table 3).

Plausible causal pathway

Few plausible causal pathways between cold environments and MSC have been suggested in the literature. One possible pathway is the acute effects of cold environments on physiological function. Indeed, the capacity of a muscle to develop force and contraction velocity are reduced as muscular temperature lowers (Racinais and Oksa 2010), and increased co-activation of antagonist muscle can also occur, indicating poorer neuromuscular performance in cold environments. Moreover, the nerve conduction rate decreases, the elasticity of the tendons is decreased (Alegre et al. 2016), and if sufficiently cooled, the viscoelastic properties of the synovial fluid increase and make joints stiffer (Parsons 2014). All these changes increase the strain on the musculoskeletal apparatus and could increase the risk of overuse injuries like tendinopathy, as has been observed in earlier research (Kurppa et al. 1991; Milgrom et al. 2003). Other acute physiological changes could play a role as well; for example, increased muscle activity to produce heat will increase the load to the muscles and vasoconstriction following cold exposure could limit the distribution of important nutrients to cells not involved in thermogenesis (Parsons 2014).

It could be hypothesised that cold exposure contributes to a sensitisation process. A study of Danish slaughterhouse workers found that those who had the most complaints about the indoor climate, including cold temperature and draught, had a lower pressure pain threshold (Sundstrup et al. 2015).

Strengths and limitations

One major strength of this study is its prospective design. Another strength is the reasonably high participation rate of Tromsø 6 and Tromsø 7 (65% in both), which increases the likelihood that the surveys contain a representative sample of the working population. There was a larger proportion of participants working in a cold environment ≥ 25% of the time who were lost to follow-up. Further, in a Norwegian cohort study, common health complaints, such as depression and musculoskeletal pain, increased the likelihood of participation in Tromsø 7 (Langhammer et al. 2012), which could have biased our results. However, the difference in loss to follow-up was not evident after exclusion of those with missing values in Tromsø 6. Thus, the analyses of the imputed datasets are more likely to be biased by loss to follow-up.

Individuals working in a cold environment tend to have more physically demanding work. Other known occupational risk factors for musculoskeletal pain could be unevenly distributed as well, i.e. poor posture or repetitiveness (Neupane et al. 2013). Therefore, our main analyses could be confounded. However, adjusting for occupational codes in the sensitivity analyses did not alter the strength of the association (Supplementary Table 2), making residual confounding by occupational factors less likely. On the other hand, it is possible that even within the same occupational code, those working in a cold environment ≥ 25% of the time are exposed to a different set of risk factors than those working in a cold environment < 25% of the time.

As the question about working in a cold environment was not repeated in Tromsø 7 we do not know if exposure was consistent between Tromsø 6 and Tromsø 7. Differences between exposed and non-exposed participants could have increased the probability of them changing occupations or exiting the work force, either due to health or changes in the labour market. If working in a cold environment in Tromsø 6 caused or aggravated pain, it is possible that some participants ended their exposure to reduce the risk of pain before Tromsø 7. In addition, the youngest participant in Tromsø 6 was 32 years of age, thus participants might have been exposed for over 10 years before even entering the study, and those most easily affected by a cold environment might already have developed MSC in Tromsø 6. Furthermore, they might have changed occupation prior to Tromsø 6 to reduce their exposure, and in turn, their risk of developing or aggravating existing MSC. Consequently, we might have underestimated the possible effect of cold environment due to the healthy-worker effect.

There are several diseases that probably increase the risk of developing MSC (Treede et al. 2015). These could be unevenly distributed between those working in a cold environment ≥ 25% of the time and those that do not. The lack of adjusting for these conditions is a limitation. However, we adjusted for self-reported health, which is thought to be a very inclusive measure of health (Mackenbach et al. 2002). Further, the origin of pain can be difficult to determine, and even though the participants were asked for pain and/or stiffness in muscles or joints, we cannot be sure that the complaints did not have other origins (Treede et al. 2015).

Tromsø is situated at 69° North, but has a moderately cold climate due to the Gulf Stream. The cold exposure is dependent on many factors other than ambient air temperature, i.e. amount of clothing or contact with cold surfaces or liquids. Thus, we expect that the results are relevant for other workers that are at risk of cold stress.

Conclusion

Working in a cold environment ≥ 25% of the time increased the risk of future MSC. The increased risk was small, 15% after adjustment for possible confounders. There was no significantly increased risk of MSC in ≥ 3 regions, and no increased risk of severe MSC. However, the crude exposure measurement and the healthy worker effect might have biased the results. There is a need for prospective studies with a more precise measure of exposure.

Author contributions EHF, ACH, and MS designed the study. EHF conducted the data analysis and wrote the manuscript with the assistance of ACH and MS. TB assisted in the analysis. All authors contributed to the interpretation and revised the manuscript. All authors read and approved the final manuscript.

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Code availability All statistical analyses were performed in Stata MP 15.

Data availability All data are available by applying to the Tromsø Study https://tromsoundersokelsen.uit.no/tromso

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The Regional Committee of Research Ethics approved Tromsø 6 and 7 and this particular analysis.

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

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Supplementary tables

Supplementary table 1 Incidence rate ratio's (IRR) and confidence intervals (CI) from Poisson regression on the imputed data.

	Working in a cold environment <25% of the time n=4247	Working in a cold environment ≥25% of time n=632					
		Crude[a]			Fully adjusted[b]		
	Ref.	IRR	CI		IRR	CI	
Any MSC	-	**1.14**	**1.05**	**1.23**	**1.12**	**1.03**	**1.22**
Severe MSC	-	1.14	0.82	1.60	0.98	0.69	1.39
MSC in ≥3 anatomical regions	-	**1.28**	**1.06**	**1.56**	1.07	0.88	1.30

[a] Adjusted for age, sex, and number of MSC in Tromsø 6. Interaction term between working in a cold environment ≥25% of time and severe MSC/MSC in ≥3 anatomical regions.

[b] Adjusted for age, sex, number of moderate MSC, education, physical activity at work, smoking status, body mass index, and self-reported health at Tromsø 6. Interaction term between working in a cold environment ≥25% of time and severe MSC/MSC in ≥3 anatomical regions.

MSC=musculoskeletal complaints

Supplementary table 2 Sensitivity analysis for any musculoskeletal complaints (MSC), severe MSC, and MSC in ≥3 anatomical regions. Three different approaches are shown: a logistic regression, logistic regression adjusted for the 10 major occupational groups in the Norwegian version of the International Standard Classification of Occupations 88 (ISCO-88), and a model with a random intercept for each 4-digit occupational code. The odds ratio (OR), confidence intervals (CI) and Akaike information criterion (AIC) are shown for each model.

n=1982	Crude[a]				Fully adjusted model[b]			
	OR	CI		AIC	OR	CI		AIC
Any MSC								
Logistic model	**1.69**	**1.22**	**2.32**	2578	**1.79**	**1.23**	**2.60**	2566
Logistic model adjusted for the 10 major occupational groups	**1.52**	**1.07**	**2.16**	2589	**1.73**	**1.17**	**2.54**	2579
Mixed-effects logistic model with 4-digit occupational code	**1.66**	**1.20**	**2.31**	2580	**1.79**	**1.22**	**2.61**	2568
Severe MSC								
Logistic model	1.46	0.90	2.36	1079	1.18	0.66	2.12	1065
Logistic model adjusted for the 10 major occupational groups	1.03	0.60	1.76	1082	1.06	0.58	1.95	1070
Mixed-effects logistic model with 4-digit occupational code	1.46	0.90	2.36	1079	1.18	0.66	2.12	1065
MSC in ≥3 anatomical regions								
Logistic model	**1.71**	**1.16**	**2.51**	1725	1.43	0.93	2.21	1714
Logistic model adjusted for the 10 major occupational groups	**1.69**	**1.17**	**2.43**	1725	1.43	0.93	2.21	1714
Mixed-effects logistic model with 4-digit occupational code	1.40	0.93	2.10	1724	1.45	0.93	2.27	1722

[a] Adjusted for age and number of moderate MSC at Tromsø 6.

[b] Adjusted for age, number of moderate MSC, education, physical activity at work, smoking status, body mass index, and self-reported health at baseline.

Supplementary table 3 Occupations for which participants reported to work 25% of the time in cold environment at the time of Tromsø 6. Sorted by frequency of workers in the occupation.

Occupation	Working in a cold environment ≥25% of the time Yes
Child-care workers	21
Carpenters and joiners	13
Stock clerks	10
Road workers and construction workers	10
Earth-moving and related plant operators	8
Mail carriers and sorting clerks	7
Fishery workers	7
Ships deck officers and pilots	6
Fish-processing-machine operators	6
Pre-primary education teaching associate professionals	5
Electricians, electrical and electronic equipment mechanics and fitters	5
Civil engineering technicians	4
Helpers and cleaners in offices and other establishments	4
Directors and chief executives	3
Nursing assistants and care	3
Shop salespersons and other salespersons (retail)	3
Dairy and livestock producers	3
Welders	3
Motor vehicle mechanics and fitters	3
Aircraft engine mechanics and fitters	3
Electrical line installers, repairers, and cable jointers	3
Heavy truck and lorry drivers	3
Shipsdeck crews	3
Labourers in construction and maintenance, etc.	3
Officers (above the rank of captain)	2
Other public service administrative associate professionals	2
Police officers	2
Clerical officers	2
Caretakers	2
Bricklayers and stonemasons	2
Concrete workers and site labourers	2
Telegraph and telephone installers and servicers	2
Bus- and tram drivers	2
Garbage collectors and related labourers	2
Production and operations department managers in manufacturing, mining and quarrying, electricity, gas and water supply	1
Production and operations department managers in education, health and social security	1
Production and operations department managers in personal care, cleaning and related services	1
Supply and distribution department managers	1
Other department managers not elsewhere classified	1

Transport clerks	1
General managers in construction	1
General managers in wholesale and retail trade	1
General managers in business services	1
Mining engineers, metallurgists, and related professionals	1
Biologists, botanists, zoologists, and related professionals	1
Nursing and midwifery professionals	1
Secondary education teaching professionals	1
Other public service administrative professionals	1
Electrical engineering technicians	1
Electronics and telecommunications engineering technicians	1
Oil, mining and metallurgical technicians	1
Fire inspectors	1
Nurses	1
Primary education teaching associate professionals	1
Estate agents	1
Technical and commercial sales representatives	1
Appraisers, valuers, and auctioneers	1
Bank associate professionals	1
Athletes, sportspersons and coaches	1
Radio and television announcers	1
Transport clerks	1
Dentists secretaries	1
Fire-fighters	1
Salespersons (wholesale)	1
Fish farmers, etc.	1
Plumbers	1
Painters and related workers	1
Chimney sweepers	1
Tinsmiths, etc.	1
Industrial mechanics and fitters	1
Technical illustrators	1
Oil- and gas-processing-plant operators	1
Fishing tackles-machine operators	1
Car, taxi, and van drivers	1
Labourers in manufacturing	1
Storing and goods handling labourers	1

Paper 3

Farbu EH, Rypdal M, Skandfer M, Steingrímsdóttir ÓA, T Brenn, Stubhaug A, Sivert Nielsen C, Höper, AC.

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

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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^{th} or below 10^{th} 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 7was 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.

Ackknowledgments

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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://tromsoundersokelsen.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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Figure legends

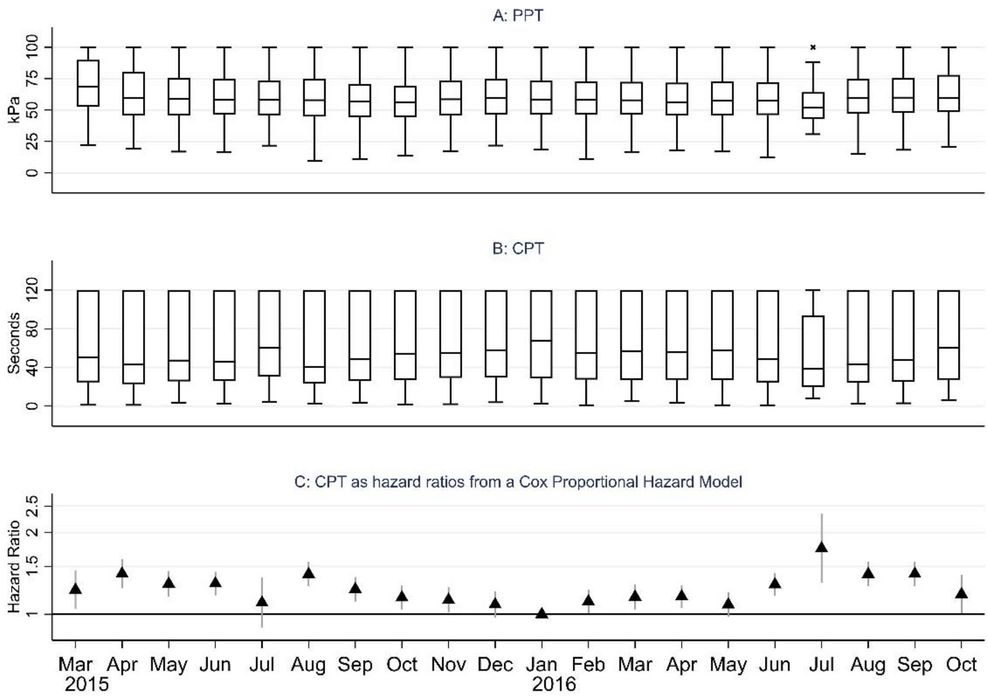
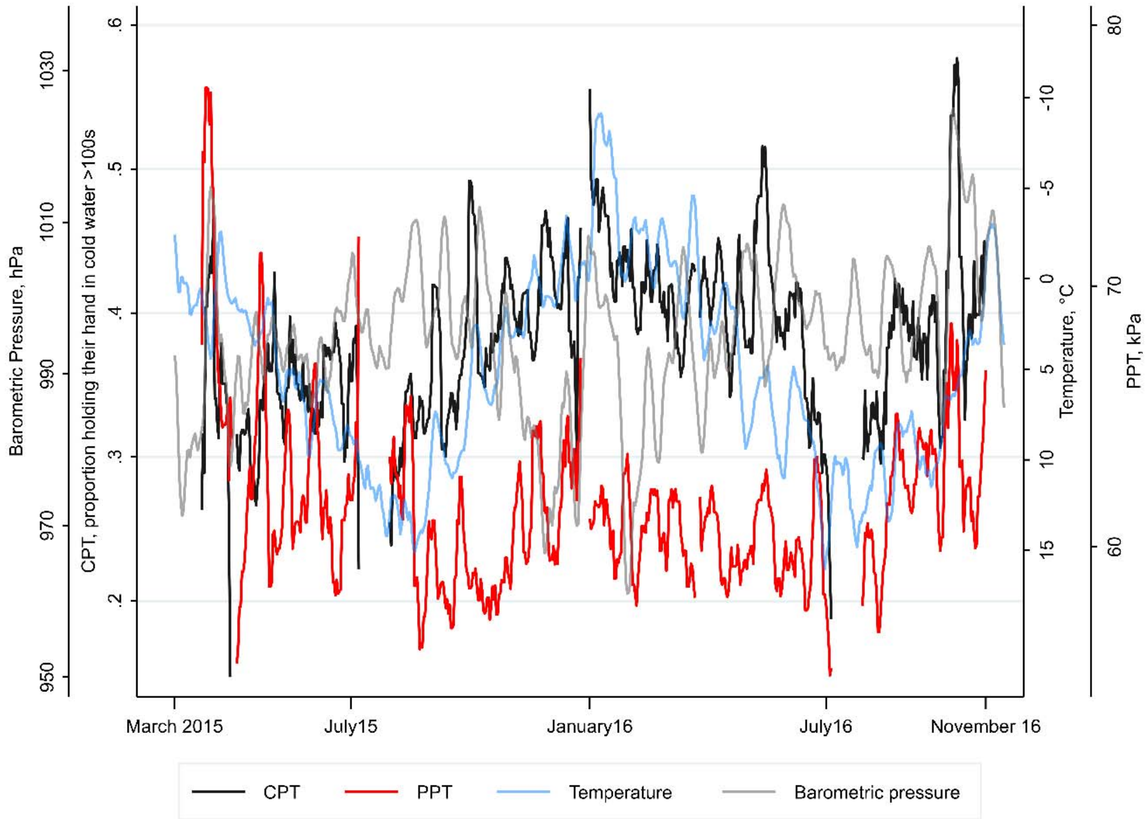


Figure 1: Monthly variation in pressure pain tolerance (PPT) and cold pain tolerance (CPT) **a:** Box-plot of monthly PPT, **b:** CPT as time to withdrawal in the cold pressor test and **c:** CPT as hazard ratios from a Cox proportional hazard model using time to withdrawal in the cold pressor test as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



Figur 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

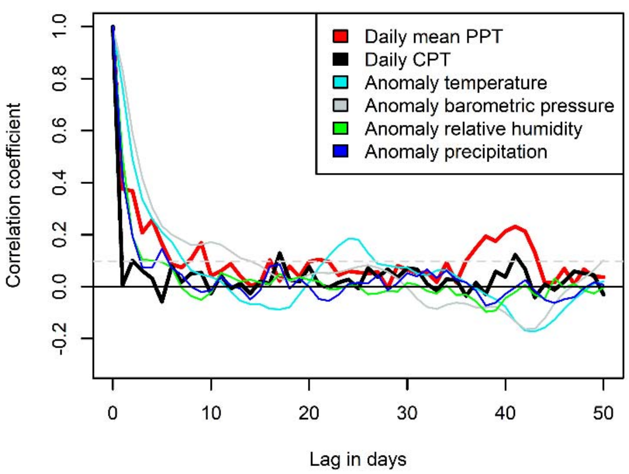


Figure 3: Autocorrelations for pressure pain tolerance (PPT), daily cold pain tolerance (CPT) after removal of seasonality, and meteorological anomalies

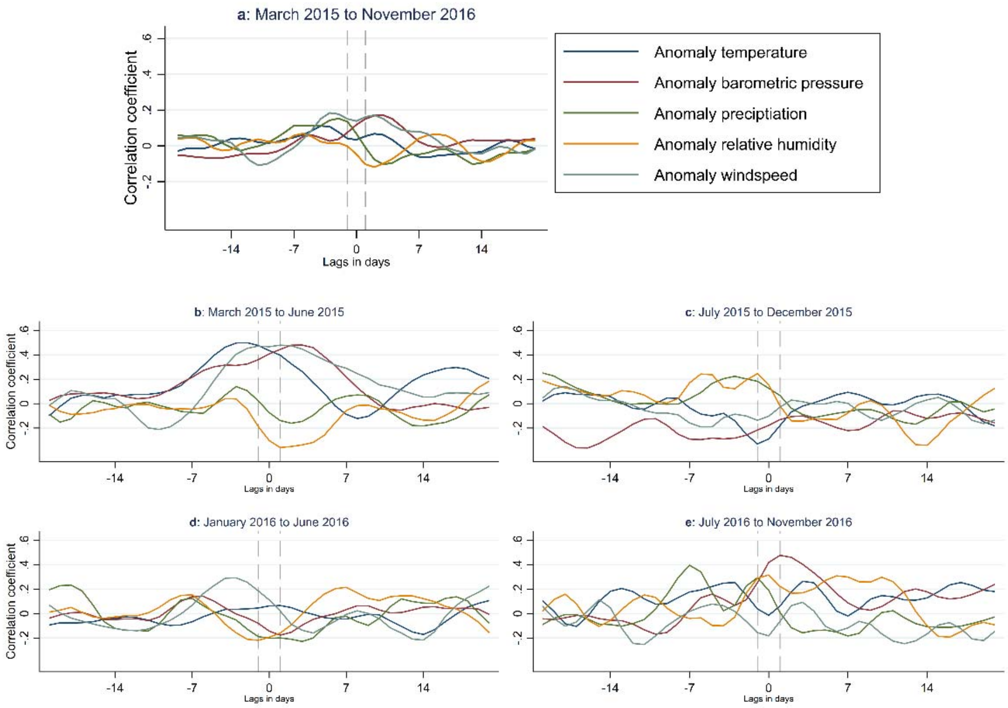


Figure 4: Cross-correlation of 3-day moving averages of pressure pain tolerance (PPT) and meteorological anomalies. The correlation at day 0 should be interpreted as the correlation between the 3-day moving averages, of PPT and the meteorological anomalies, centered at day 0. At day -7 (seven days before 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

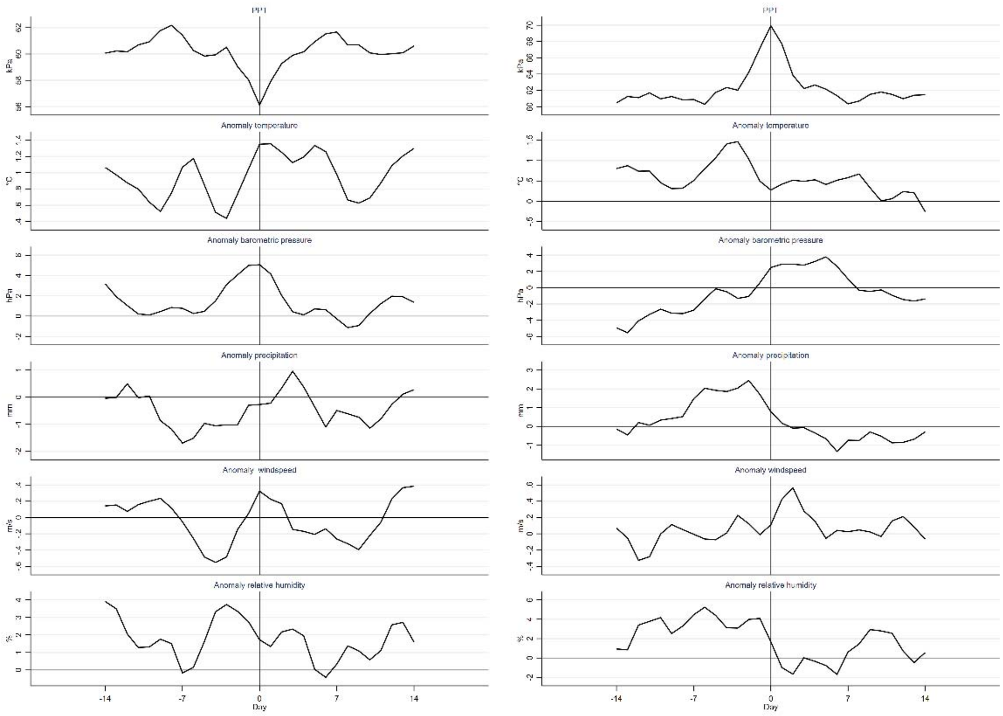


Figure 5: Mean of 3-day moving averages of pressure pain tolerance (PPT) and meteorological anomalies at local minima and maxima of PPT, which were below 10th or above the 90th percentile, and in the 14 days before and after

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

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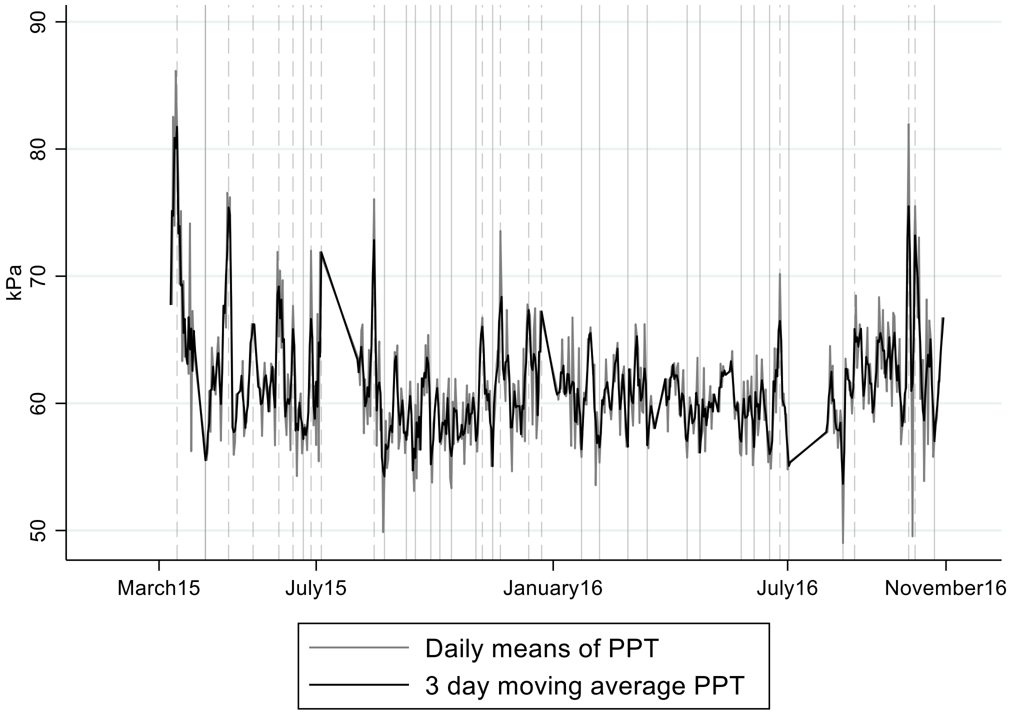
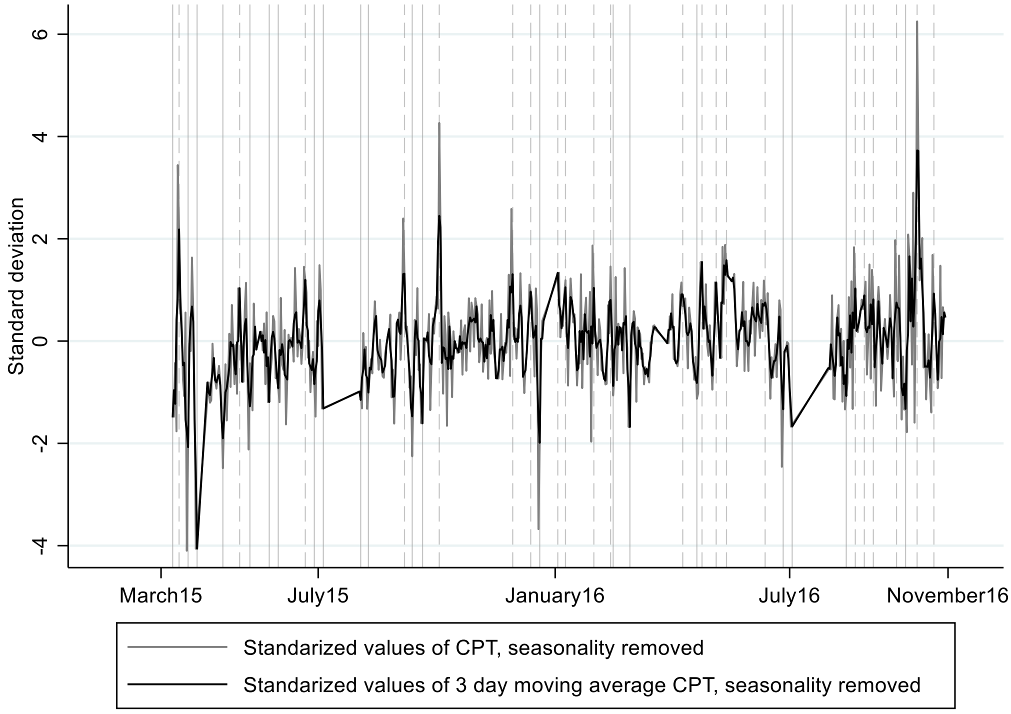
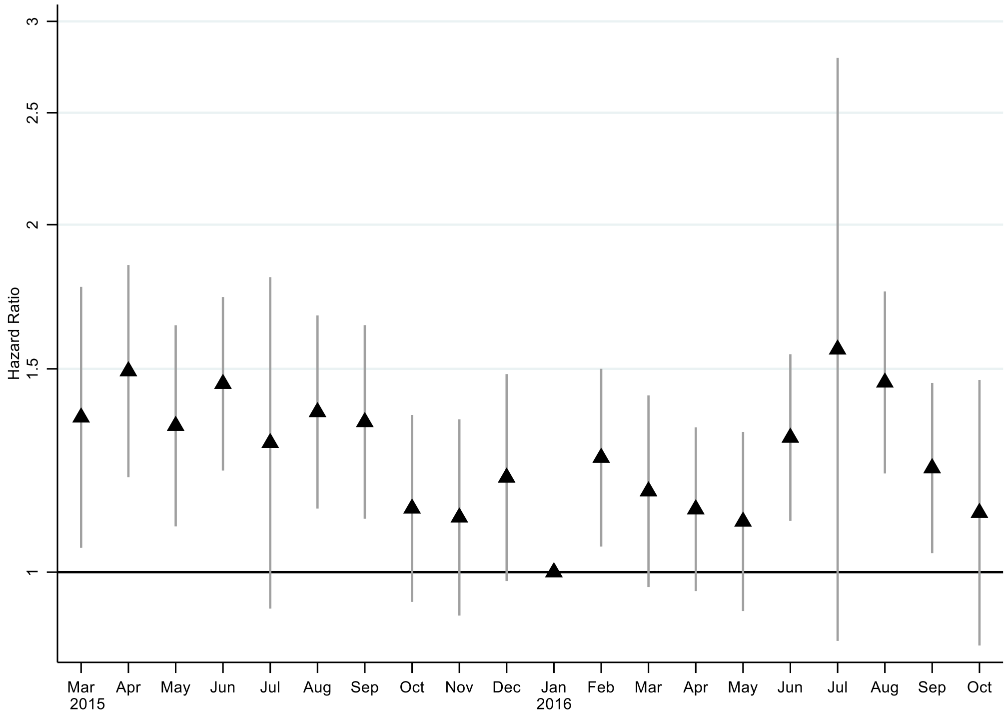
Tables S1 to S2



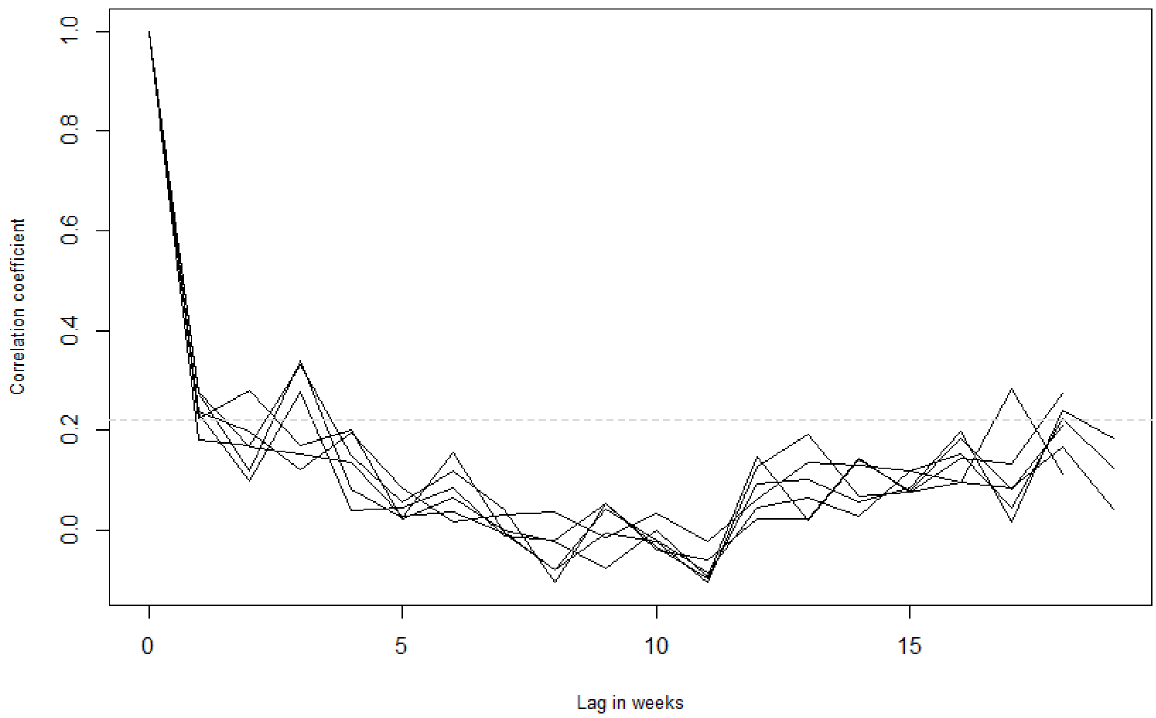
Supplementary figure 1: Daily means of pressure pain tolerance (PPT) and the 3-day moving average of the daily means of PPT. The local minima and maxima in PPT were chosen from the moving average. Solid vertical lines indicate minima and dashed vertical lines indicate maxima



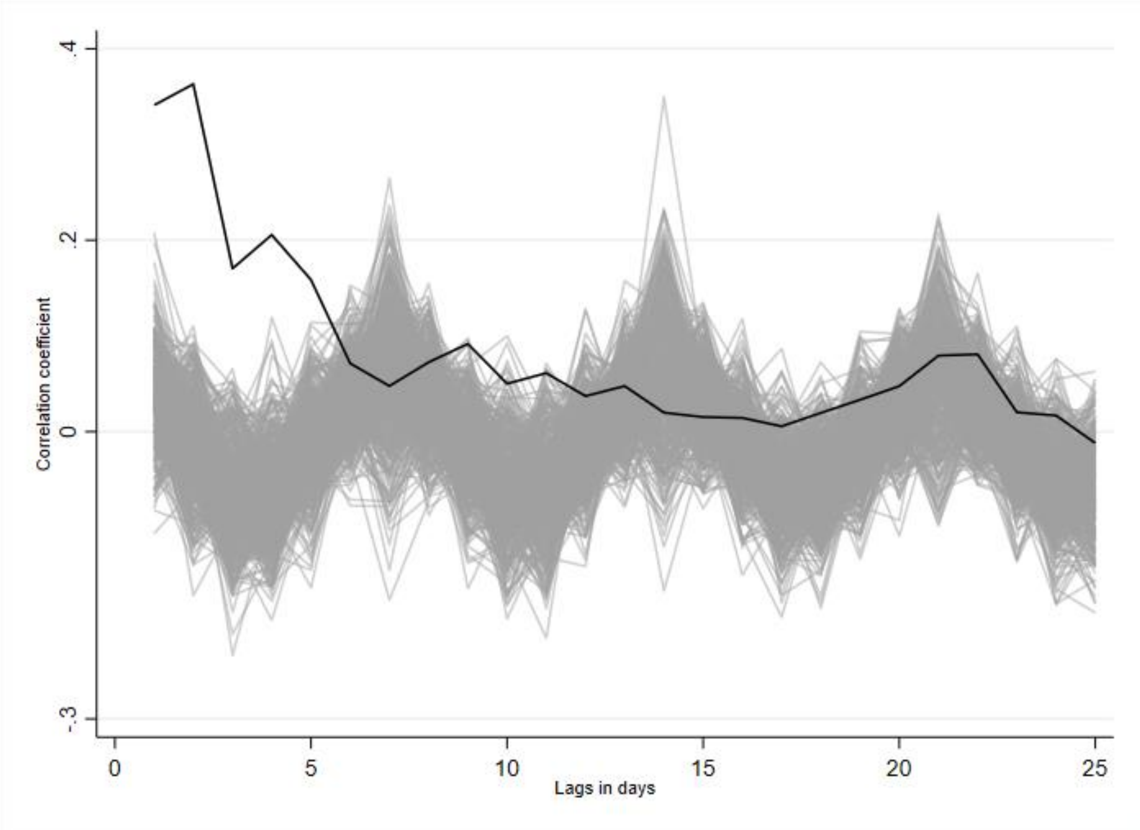
Supplementary figure 2: Standardized values of cold pain tolerance (CPT) after removal of seasonal variation and the 3-day moving average of the standardized values of CPT. The local minima and maxima in CPT were chosen from the moving average. Solid vertical lines indicate minima and dashed vertical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



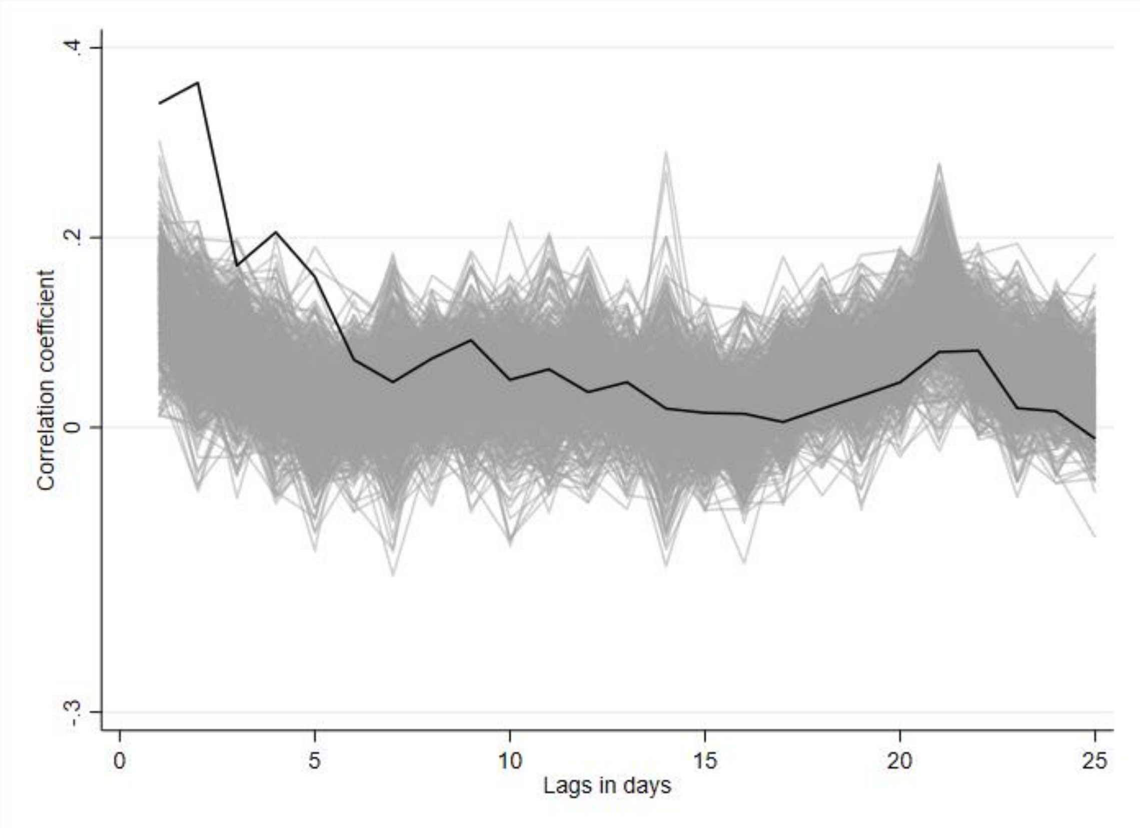
Supplementary figure 3: Hazard ratio's from a Cox proportional model using time to withdrawal in the cold pressor test as survival time. Only participants with an acclimatization time (time between physical examination and the cold pressor test) >60 min are included. January 2016 was used as the reference.



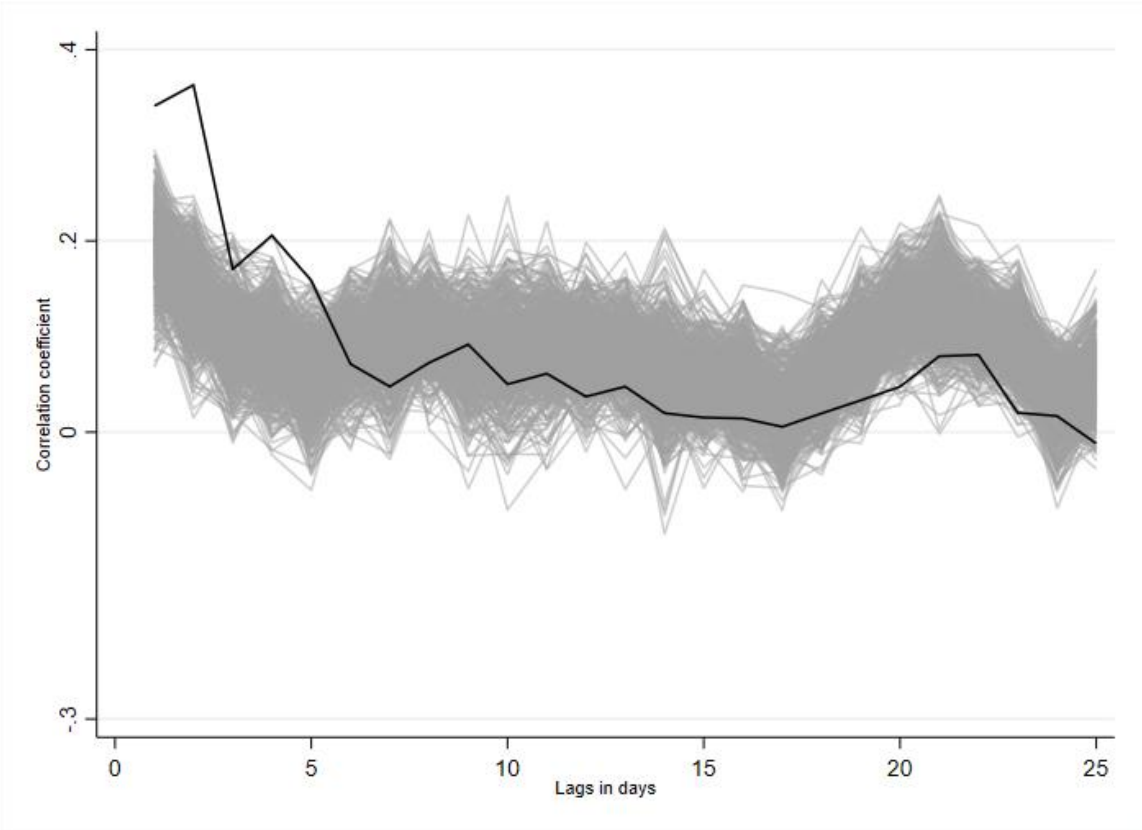
Supplementary figure 4: Autocorrelation for 7 different weekly averages of cold pain tolerance after removal of seasonality



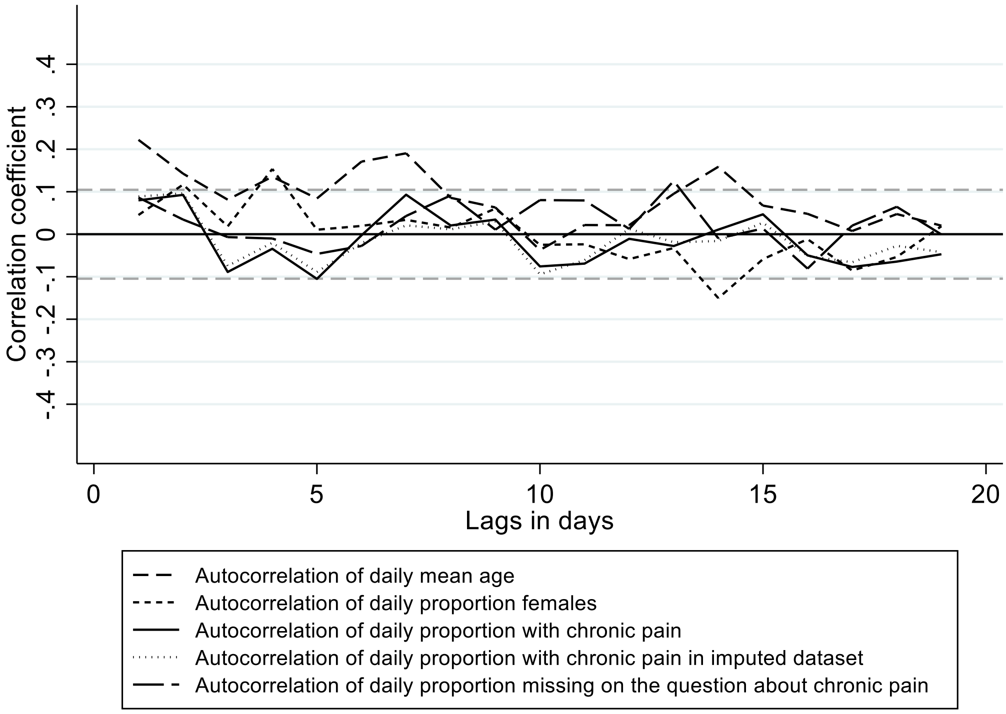
Supplementary figure 5: Autocorrelation for pressure pain tolerance (PPT) and autocorrelation for 500 randomly shuffled copies of PPT with a simulated effect of day of the week on pain tolerance. The size of the effect is two times the observed differences between days of the week in the full dataset



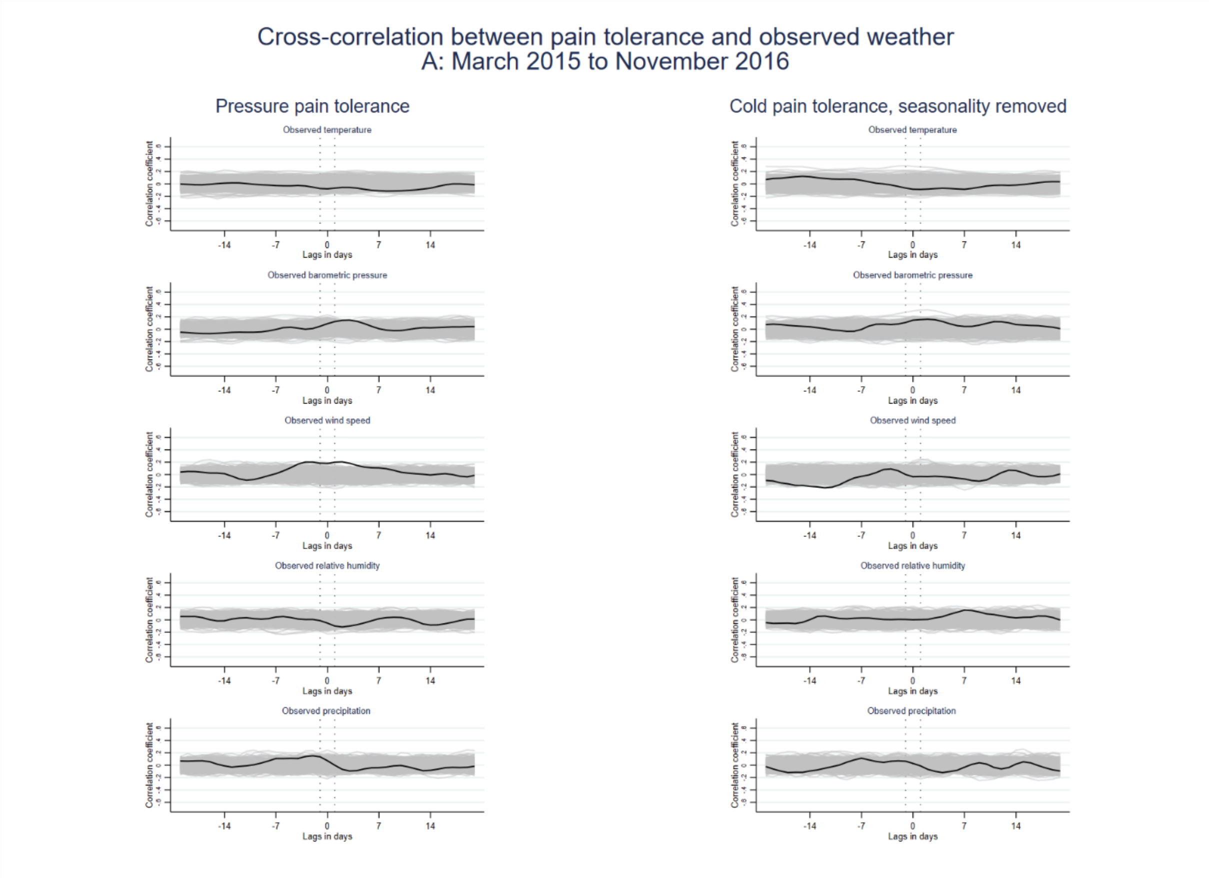
Supplementary figure 6: Autocorrelation for pressure pain tolerance (PPT) and autocorrelation for 500 randomly shuffled copies of PPT with a simulated effect of study technician rotation on pain tolerance. The effect is two times the observed difference between study technicians in the full dataset



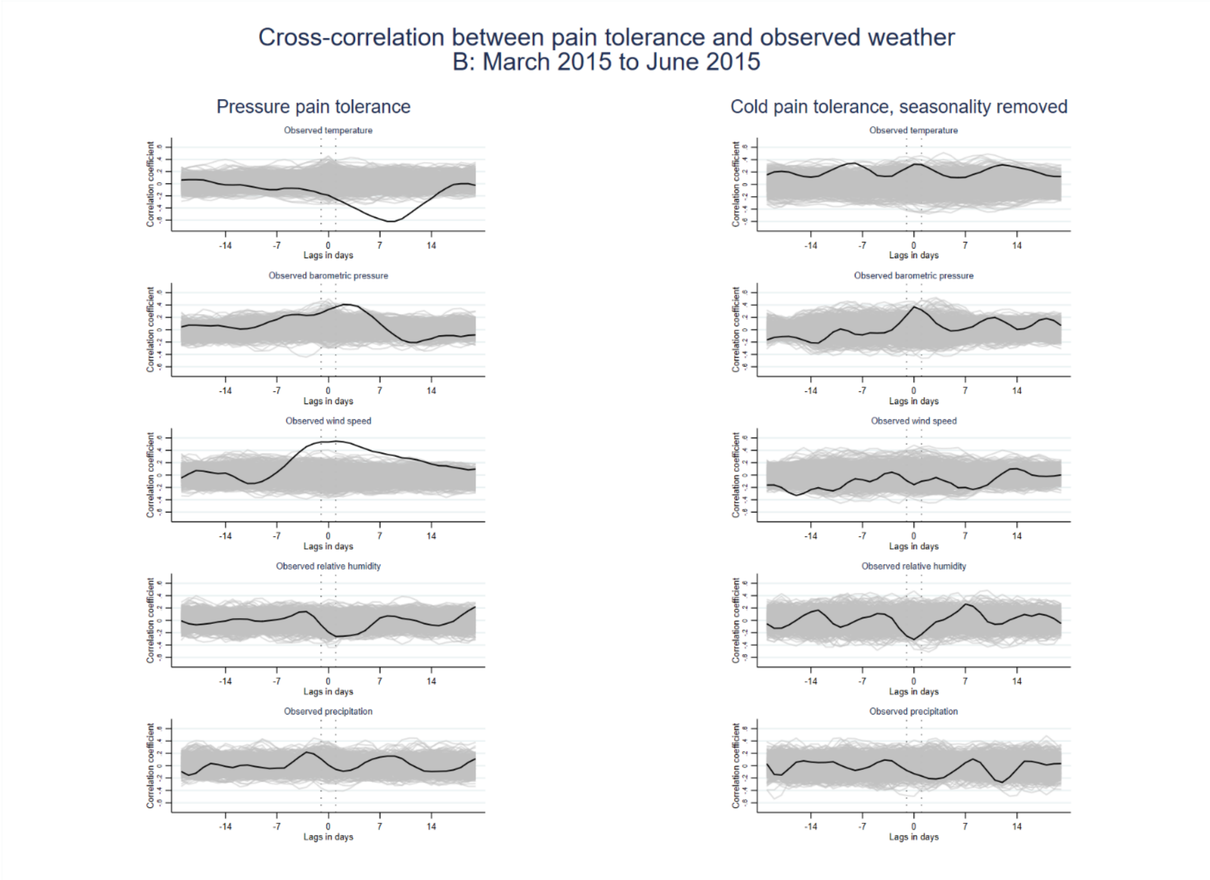
Supplementary figure 7: Autocorrelation for pressure pain tolerance (PPT) and autocorrelation for 500 randomly shuffled copies of PPT with a simulated combined effect of mean age, proportion of females, and study technician rotation on pain tolerance. The effect is two times the observed differences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



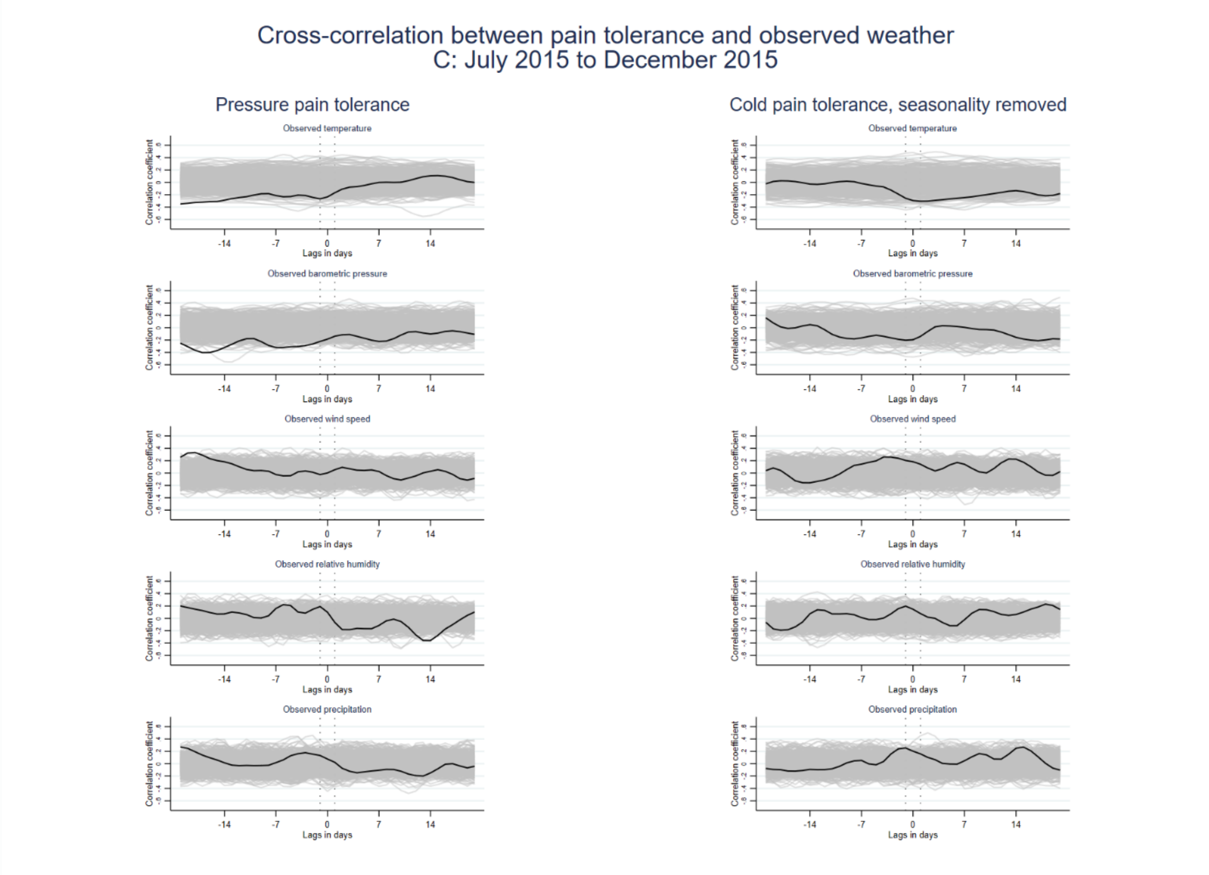
Supplementary figure 8: Autocorrelation for the daily mean age, daily proportion of females, daily proportion of participants reporting chronic pain, daily proportion with chronic pain in an imputed dataset, and the daily proportion missing on the question about chronic pain. Dashed grey lines indicate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



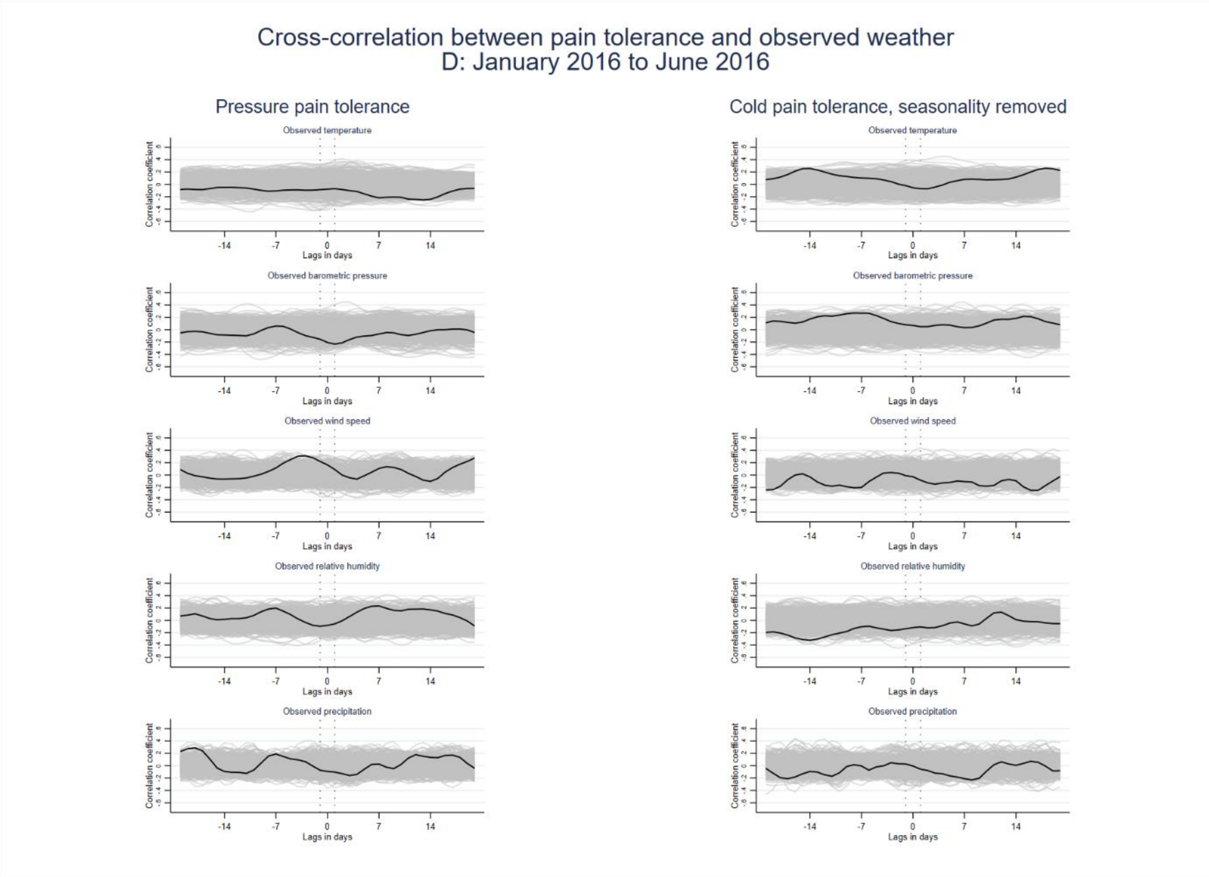
Supplementary figure 9: 3-day moving average of daily mean pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



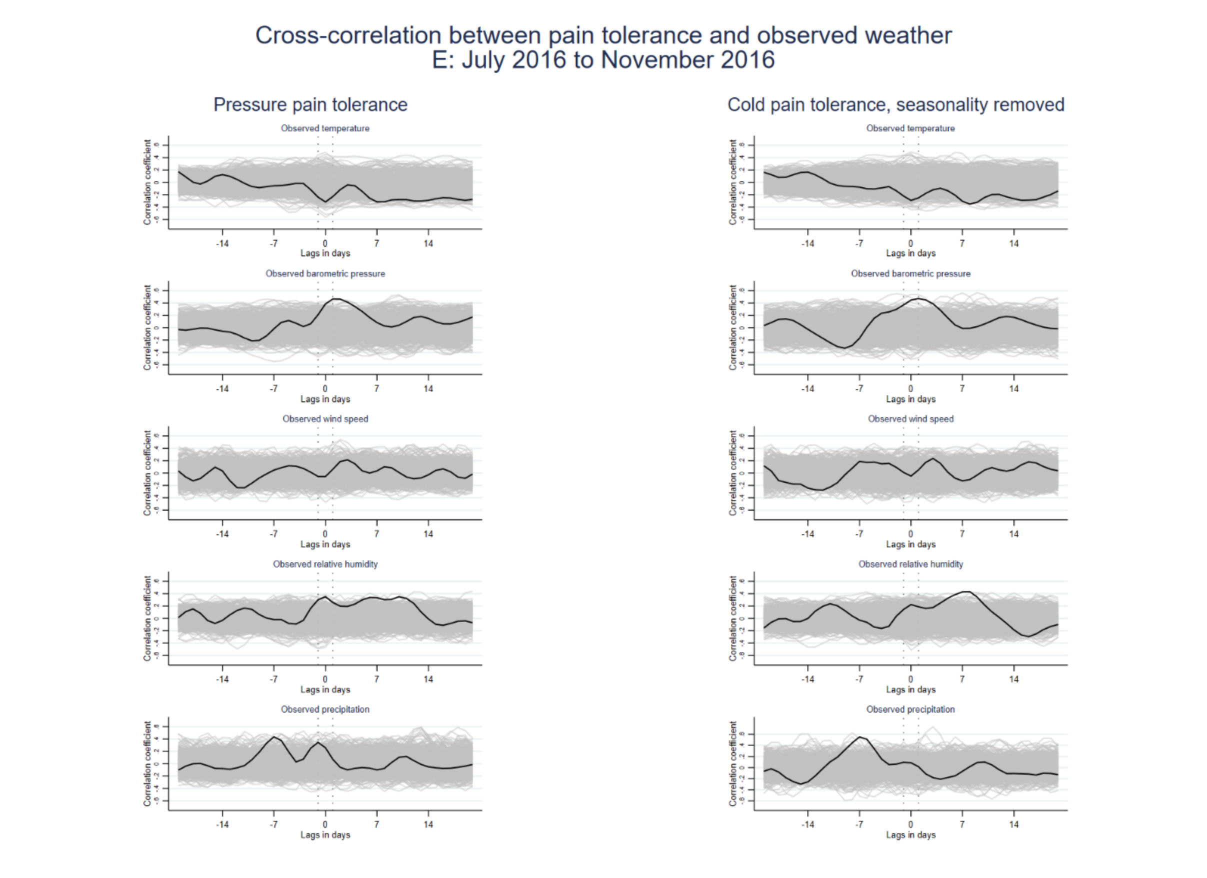
Supplementary figure 10: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



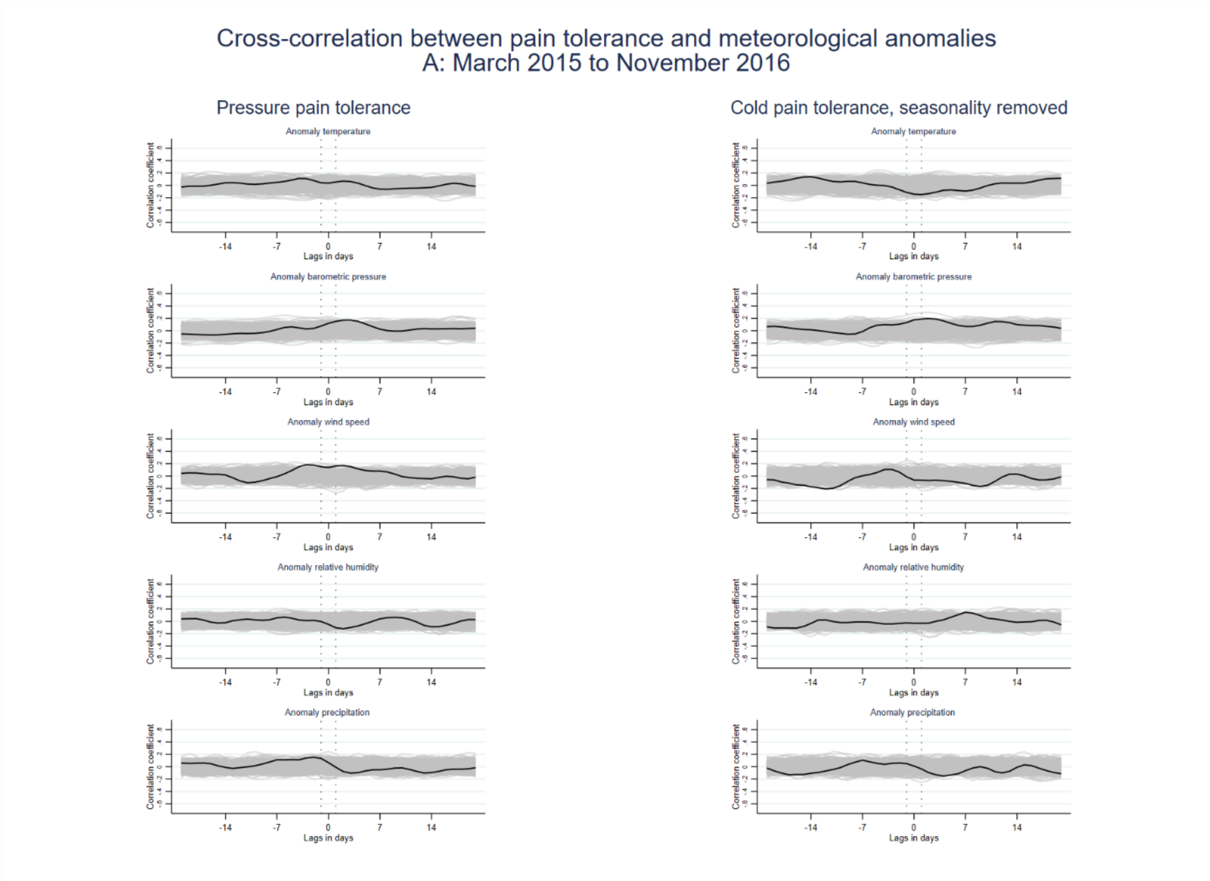
Supplementary figure 11: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



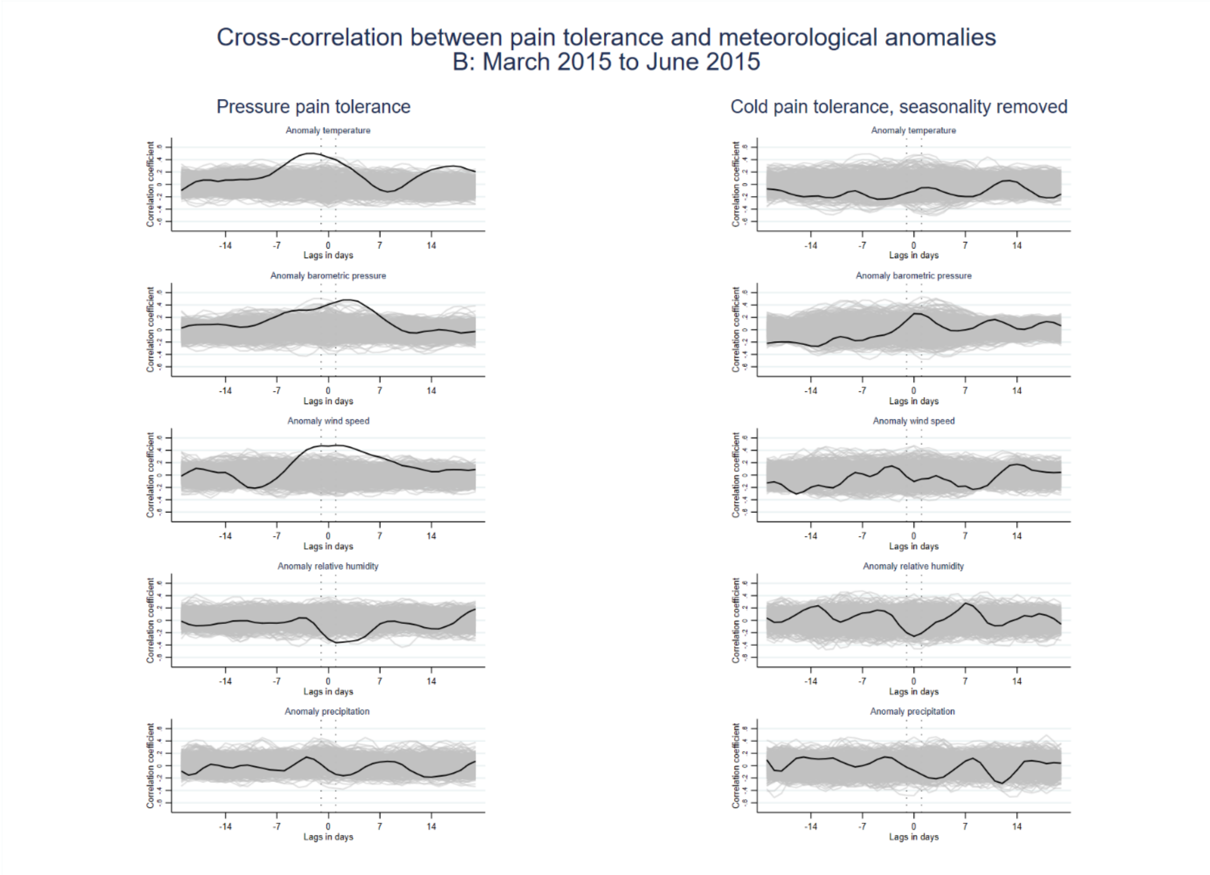
Supplementary figure 12: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



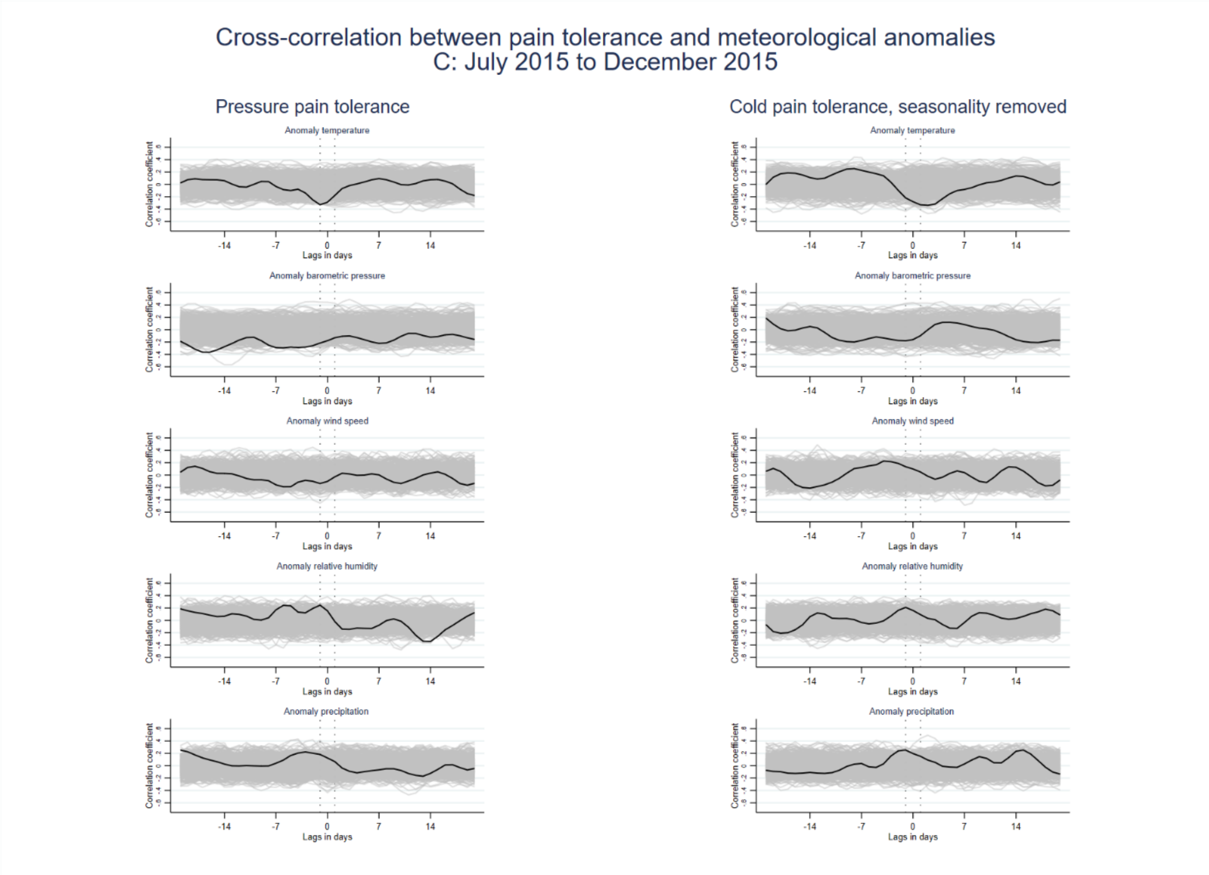
Supplementary figure 13: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of observed temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



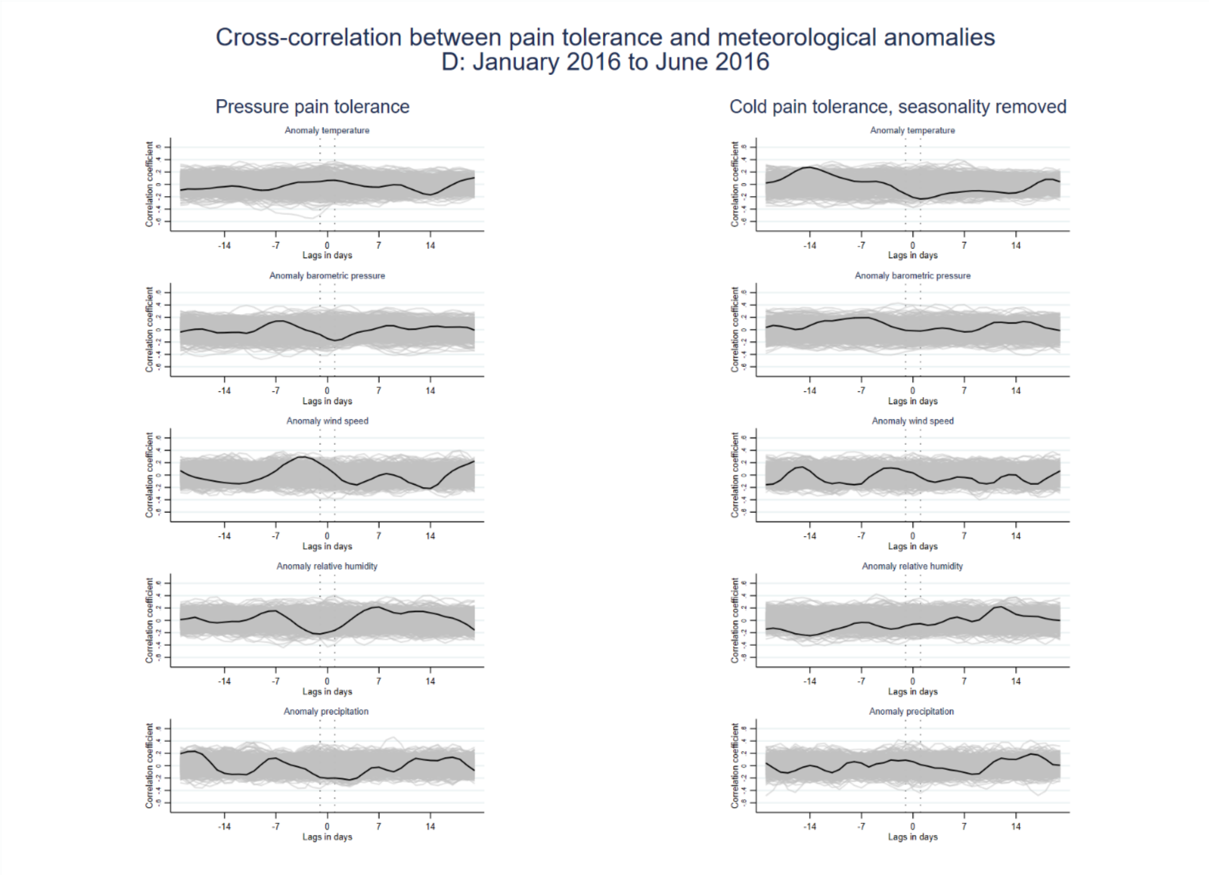
Supplementary figure 14: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



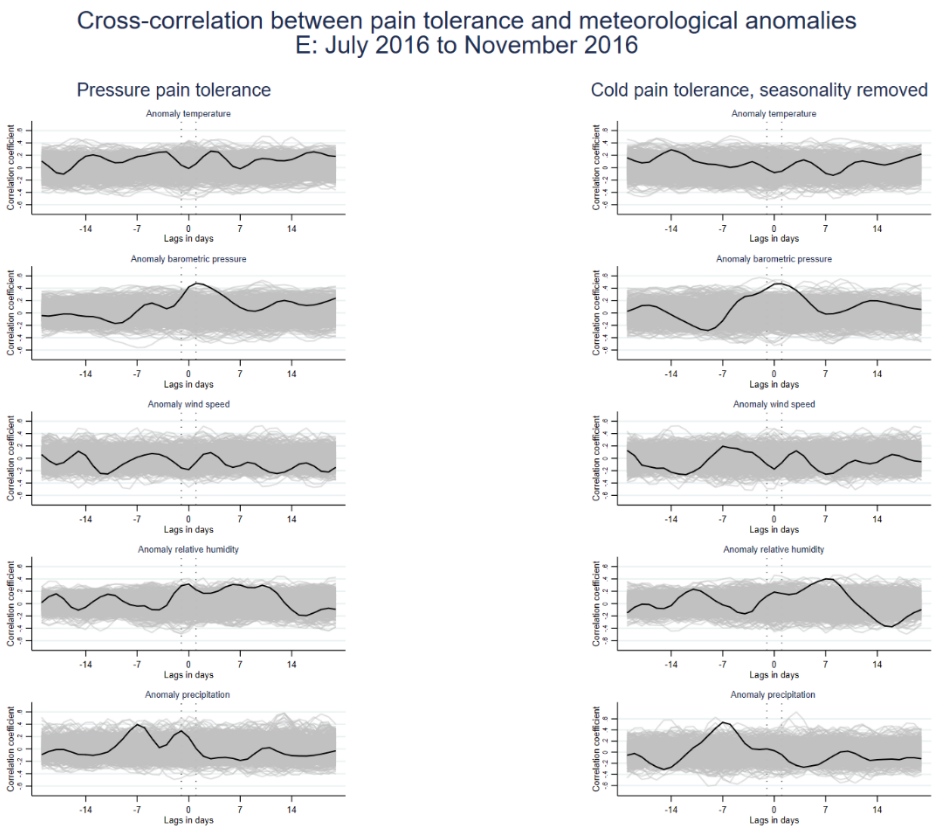
Supplementary figure 15: : 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



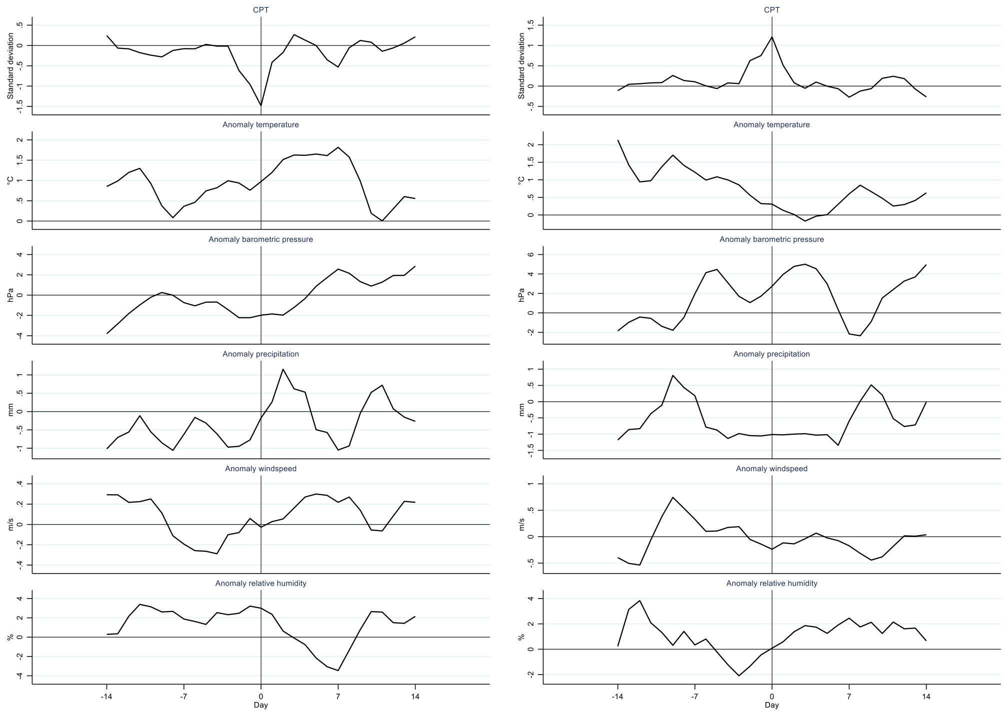
Supplementary figure 16: 3-day moving average of daily mean of pressure cuff-algometry values and daily proportion of participants holding their hand in cold water >100s cross-correlated with the 3-day moving averages of anomaly temperature, barometric pressure, wind speed, relative humidity and precipitation. 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



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



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



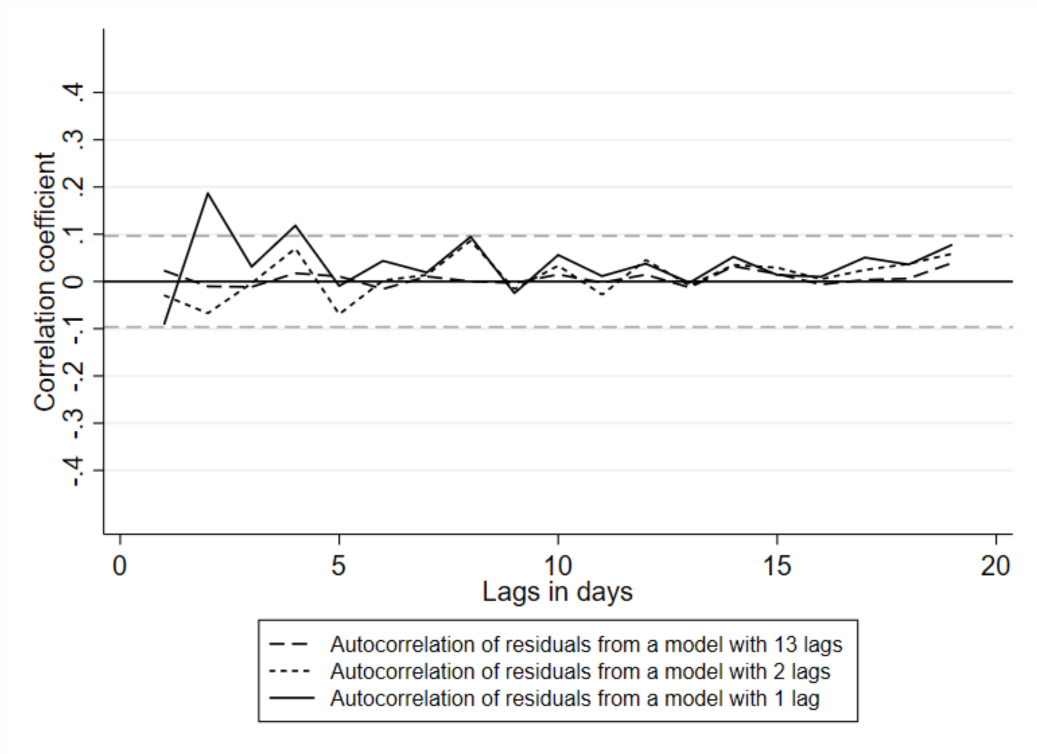
Supplementary figure 19: Mean of 3-day moving averages of cold pain tolerance (CPT) after removal of seasonal variation and meteorological anomalies at local minima and maxima of CPT, which were below 10th or above the 90th percentile, and in the 14 days before and after

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

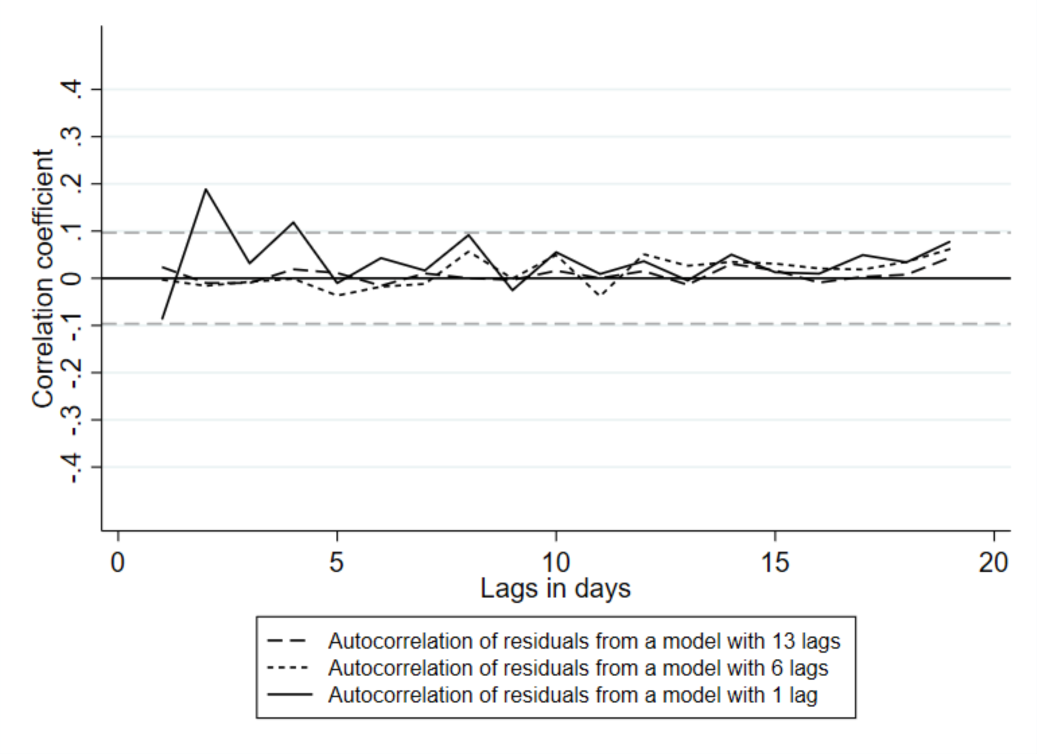
	Mean lifetime in days	95% CI	
		Lower	Upper
PPT	5.1	4.0	7.2
Anomaly temperature	2.9	2.8	3.2
Anomaly barometric pressure	6.2	5.5	7.2
Anomaly relative humidity	3.8	3.5	4.3
Anomaly precipitation	2.6	1.9	4.0

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
Anomalies						
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
Observed						
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.

Appendix 1

First questionnaire in the Tromsø Study 6

Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

- ☐ Meget god
- ☐ God
- ☐ Verken god eller dårlig
- ☐ Dårlig
- ☐ Meget dårlig

2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

- ☐ Mye bedre
- ☐ Litt bedre
- ☐ Omtrent lik
- ☐ Litt dårligere
- ☐ Mye dårligere

3 **Har du eller har du hatt?**

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐	☐	
Angina pectoris *(hjertekrampe)*	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	
Hjerteflimmer *(atrieflimmer)*	☐	☐	
Høyt blodtrykk	☐	☐	
Beinskjørhet *(osteoporose)*	☐	☐	
Astma	☐	☐	
Kronisk bronkitt/emfysem/KOLS	☐	☐	
Diabetes	☐	☐	
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	
Lavt stoffskifte	☐	☐	
Nyresykdom, unntatt urinveisinfeksjon	☐	☐	
Migrene	☐	☐	

4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i <u>3 måneder eller mer</u>?**

☐ Ja ☐ Nei

5 **Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?**

- ☐ Aldri, eller noen få ganger
- ☐ 1-3 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn 1 gang i uken

6 **Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?** (Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐

BRUK AV HELSETJENESTER

7 **Har du i løpet av de siste 12 måneder vært hos:**
Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege	☐	☐	
Psykiater/psykolog	☐	☐	
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	
Fysioterapeut	☐	☐	
Kiropraktor	☐	☐	
Annen behandler *(homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l)*	☐	☐	
Tannlege/tannpleier	☐	☐	

8 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Ja	Nei	Ant ggr
Innlagt på sykehus	☐	☐	
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk	☐	☐	
Ved annen sykehuspoliklinikk	☐	☐	

9 **Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?**

☐ Ja ☐ Nei

BRUK AV MEDISINER

10 **Bruker du, eller har du brukt, noen av følgende medisiner?** (Sett ett kryss for hver linje)

	Aldri brukt	Nå	Før	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Medisin mot hjertesykdom	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Medisin mot beinskjørhet *(osteoporose)*	☐	☐	☐	
Insulin	☐	☐	☐	
Diabetesmedisin *(tabletter)*	☐	☐	☐	
Stoffskiftemedisinene Thyroxin/levaxin	☐	☐	☐	

11 **Hvor ofte har du i løpet av <u>de siste 4 ukene</u> brukt følgende medisiner?** (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende reseptfrie	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

12 **Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode.** (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

13 **Hvem bor du sammen med?** (Sett kryss for hvert spørsmål og angi antall)

	Ja	Nei	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

14 **Kryss av for de slektninger som har eller har hatt**

	Foreldre	Barn	Søsken
Hjerteinfarkt	☐	☐	☐
Hjerteinfarkt før fylte 60 år	☐	☐	☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐
Hjerneslag/hjerneblødning	☐	☐	☐
Beinskjørhet *(osteoporose)*	☐	☐	☐
Magesår/tolvfingertarmsår	☐	☐	☐
Astma	☐	☐	☐
Diabetes	☐	☐	☐
Demens	☐	☐	☐
Psykiske plager	☐	☐	☐
Rusproblemer	☐	☐	☐

15 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

16 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

17 **Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?**

- ☐ Aldri, eller noen få ganger i året
- ☐ 1-2 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

18 **Hva er din høyeste fullførte utdanning?** (Sett ett kryss)

- ☐ Grunnskole, framhaldsskole eller folkehøyskole
- ☐ Yrkesfaglig videregående, yrkesskole eller realskole
- ☐ Allmennfaglig videregående skole eller gymnas
- ☐ Høyskole eller universitet, mindre enn 4 år
- ☐ Høyskole eller universitet, 4 år eller mer

19 **Hva er din hovedaktivitet?** (Sett ett kryss)

- ☐ Yrkesaktiv heltid
- ☐ Yrkesaktiv deltid
- ☐ Arbeidsledig
- ☐ Hjemmeværende
- ☐ Pensjonist/trygdet
- ☐ Student/militærtjeneste

20 **Mottar du noen av følgende ytelser?**

- ☐ Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
- ☐ Sykepenger (er sykemeldt)
- ☐ Rehabiliterings-/attføringspenger
- ☐ Uføreytelse/pensjon, hel
- ☐ Uføreytelse/pensjon, delvis
- ☐ Dagpenger under arbeidsledighet
- ☐ Overgangstønad
- ☐ Sosialhjelp/-stønad

21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

☐ Under 125 000 kr	☐ 401 000-550 000 kr
☐ 125 000-200 000 kr	☐ 551 000-700 000 kr
☐ 201 000-300 000 kr	☐ 701 000 -850 000 kr
☐ 301 000-400 000 kr	☐ Over 850 000 kr

22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**

☐ Ja ☐ Nei

FYSISK AKTIVITET

23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**

- ☐ For det meste stillesittende arbeid
  (f.eks. skrivebordsarbeid, montering)
- ☐ Arbeid som krever at du går mye
  (f.eks ekspeditørarbeid, lett industriarbeid, undervisning)
- ☐ Arbeid der du går og løfter mye
  (f.eks postbud, pleier, bygningsarbeider)
- ☐ Tungt kroppsarbeid

24 **Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f eks mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.** (Sett kryss i den ruta som passer best)

- ☐ Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
- ☐ Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka

25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uken
- ☐ En gang i uken
- ☐ 2-3 ganger i uken
- ☐ omtrent hver dag

26 **Hvor hardt mosjonerer du da i gjennomsnitt?**

- ☐ Tar det rolig uten å bli andpusten eller svett.
- ☐ Tar det så hardt at jeg blir andpusten og svett
- ☐ Tar meg nesten helt ut

27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**

☐ Mindre enn 15 minutter	☐ 30 minutter – 1 time
☐ 15-29 minutter	☐ Mer enn 1 time

ALKOHOL OG TOBAKK

28 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2-4 ganger hver måned
- ☐ 2-3 ganger pr. uke
- ☐ 4 eller flere ganger pr.uke

29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**

☐ 1-2	☐ 5-6	☐ 10 eller flere
☐ 3-4	☐ 7-9	

30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ aldri
- ☐ sjeldnere enn månedlig
- ☐ månedlig
- ☐ ukentlig
- ☐ daglig eller nesten daglig

31 **Røyker du av og til, men ikke daglig?**

☐ Ja ☐ Nei

32 **Har du røykt/røyker du daglig?**

☐ Ja, nå ☐ Ja, tidligere ☐ Aldri

33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**

Antall år ☐☐

34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**

Antall sigaretter ☐☐

35 **Hvor gammel var du da du begynte å røyke daglig?**

Antall år ☐☐

36 **Hvor mange år til sammen har du røykt daglig?**

Antall år ☐☐

37 **Bruker du, eller har du brukt, snus eller skrå?**

☐ Nei, aldri	☐ Ja, av og til
☐ Ja, men jeg har sluttet	☐ Ja, daglig

KOSTHOLD

38 **Spiser du vanligvis frokost hver dag?**

☐ Ja ☐ Nei

39 **Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag?** (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter ☐☐

40 **Hvor mange ganger i uken spiser du varm middag?**

Antall ☐☐

41 **Hvor ofte spiser du vanligvis disse matvarene?**
(Sett ett kryss pr linje)

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Kjøtt *(ikke kvernet)*	☐	☐	☐	☐	☐
Kvernet kjøtt *(pølser, hamburger o.l)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk	☐	☐	☐	☐	☐
Feit fisk	☐	☐	☐	☐	☐

(f.eks.laks, ørret, makrell, sild, kveite,uer)

42 **Hvor mye drikker du vanligvis av følgende?**
(Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker med sukker	☐	☐	☐	☐	☐

43 **Hvor mange kopper kaffe og te drikker du daglig?**
(sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe	☐☐
Kokekaffe/presskanne	☐☐
Annen kaffe	☐☐
Te	☐☐

44 **Hvor ofte spiser du vanligvis fiskelever?**
(For eksempel i mølje)

☐ Sjelden/aldri ☐ 1-3 g i året ☐ 4-6 g i året
☐ 7-12 g i året ☐ Oftere

45 **Bruker du følgende kosttilskudd?**

	Daglig	Iblant	Nei
Tran, trankapsler	☐	☐	☐
Omega 3 kapsler *(fiskeolje,selolje)*	☐	☐	☐
Kalktabletter	☐	☐	☐

SPØRSMÅL TIL KVINNER

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Usikker

47 **Hvor mange barn har du født?**

Antall ☐☐

48 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.**
(Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **Har du i forbindelse med svangerskap hatt for høyt blodtrykk?**

☐ Ja ☐ Nei

50 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

51 **Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?**

☐ Ja ☐ Nei

52 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

53 **Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?**

☐ Ja ☐ Nei

54 **Hvis Ja, hvilke(t) barn**

Barn 1	Barn 2	Barn 3	Barn 4	Barn 5	Barn 6
☐	☐	☐	☐	☐	☐

55 **Hvor gammel var du da du fikk menstruasjon første gang?**

Antall år ☐☐

56 **Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?**

P-pille, hormonspiral eller lignende ☐ Ja ☐ Nei
Hormonpreparat for overgangs-alderen ☐ Ja ☐ Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

LUNDBLAD MEDIA AS, TROMSØ, 77 75 32 50 - ONR 082222

Appendix 2

Second questionnaire in the Tromsø Study 6

Tromsø 6

- en del av Tromsøundersøkelsen

SLIK FYLLER DU UT SKJEMAET:

Skjemaet vil bli lest maskinelt, det er derfor viktig at du krysser av riktig:

☒ Riktig

☑ Galt

☒ Galt

■ Om du krysser feil, retter du ved å fylle boksen slik

Skriv tydelige tall 1 2 3 4 5 6 7 8 9 0

7,4 Riktig

7,4 Galt

Bruk kun sort eller blå penn, bruk ikke blyant eller tusj

1. BESKRIVELSE AV DIN HELSETILSTAND

Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette ett kryss i en av rutene utenfor hver av de fem gruppene nedenfor:

1.01 **Gange**

- ☐ Jeg har ingen problemer med å gå omkring
- ☐ Jeg har litt problemer med å gå omkring
- ☐ Jeg er sengeliggende

1.02 **Personlig stell**

- ☐ Jeg har ingen problemer med personlig stell
- ☐ Jeg har litt problemer med å vaske meg eller kle meg
- ☐ Jeg er ute av stand til å vaske meg eller kle meg

1.03 **Vanlige gjøremål** (f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

- ☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål
- ☐ Jeg har litt problemer med å utføre mine vanlige gjøremål
- ☐ Jeg er ute av stand til å utføre mine vanlige gjøremål

1.04 **Smerte og ubehag**

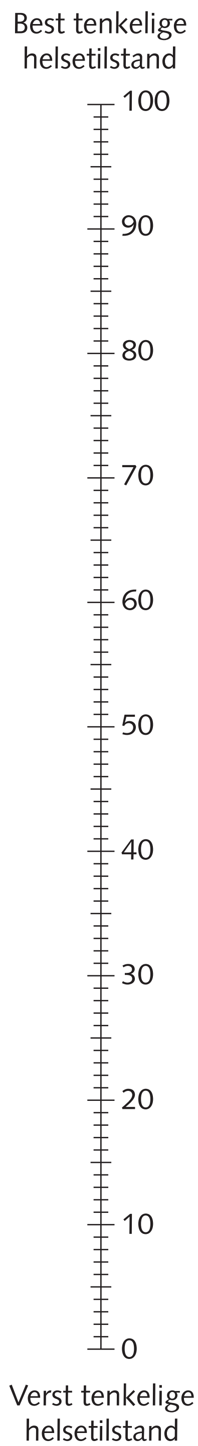
- ☐ Jeg har verken smerte eller ubehag
- ☐ Jeg har moderat smerte eller ubehag
- ☐ Jeg har sterk smerte eller ubehag

1.05 **Angst og depresjon**

- ☐ Jeg er verken engstelig eller deprimert
- ☐ Jeg er noe engstelig eller deprimert
- ☐ Jeg er svært engstelig eller deprimert

1.6 For at du skal kunne vise oss hvor god eller dårlig din helsetilstand er, har vi laget en skala (nesten som et termometer), hvor den beste helsetilstanden du kan tenke deg er markert med 100 og den dårligste med 0. Vi ber om at du viser din helsetilstand ved å trekke ei linje fra boksen nedenfor til det punkt på skalaen som passer best med din helsetilstand.

Nåværende helsetilstand



2. OPPVEKST OG TILHØRIGHET

2.01 **Hvor bodde du da du fylte 1 år?**

- ☐ I Tromsø *(med dagens kommunegrenser)*
- ☐ I Troms, men ikke i Tromsø
- ☐ I Finnmark fylke
- ☐ I Nordland fylke
- ☐ Annet sted i Norge
- ☐ I utlandet

2.02 **Hvordan var de økonomiske forhold i familien under din oppvekst?**

- ☐ Meget gode
- ☐ Gode
- ☐ Vanskelige
- ☐ Meget vanskelige

2.03 **Hvilken betydning har religion i ditt liv?**

- ☐ Stor betydning
- ☐ En viss betydning
- ☐ Ingen betydning

2.04 **Hva regner du deg selv som?** (Kryss av for ett eller flere alternativ)

- ☐ Norsk
- ☐ Samisk
- ☐ Kvensk/Finsk
- ☐ Annet

2.05 **Hvor mange søsken og barn har du/har du hatt?**

Antall søsken .... ☐☐

Antall barn .... ☐☐

2.06 **Lever din mor?**

☐ Ja ☐ Nei

Hvis NEI: hennes alder ved død .... ☐☐

Lever din far?

☐ Ja ☐ Nei

Hvis NEI: hans alder ved død .... ☐☐

2.07 **Hva var/er den høyeste fullførte utdanning til dine foreldre og din ektefelle/samboer?**
(sett ett kryss i hver kolonne)

	Mor	Far	Ektefelle/ samboer
Grunnskole 7-10 år, framhaldsskole eller folkehøyskole	☐	☐	☐
Yrkesfaglig videregående, yrkesskole eller realskole	☐	☐	☐
Allmennfaglig videregående skole eller gymnas	☐	☐	☐
Høyskole eller universitet (mindre enn 4 år)	☐	☐	☐
Høyskole eller universitet (4 år eller mer)	☐	☐	☐

3. TRIVSEL OG LIVSFORHOLD

3.01 **Nedenfor står tre utsagn om tilfredshet med livet som et hele. Deretter står to utsagn om syn på din egen helse. Vis hvor enig eller uenig du er i hver av påstandene ved å sette et kryss i rubrikken for det tallet du synes stemmer best for deg.** (sett ett kryss for hvert utsagn)

	Helt uenig	1	2	3	4	5	6	7	Helt enig
På de fleste måter er livet mitt nær idealet mitt		☐	☐	☐	☐	☐	☐	☐	
Mine livsforhold er utmerkede		☐	☐	☐	☐	☐	☐	☐	
Jeg er tilfreds med livet mitt		☐	☐	☐	☐	☐	☐	☐	
Jeg ser lyst på min framtidige helse		☐	☐	☐	☐	☐	☐	☐	
Ved å leve sunt kan jeg forhindre alvorlige sykdommer		☐	☐	☐	☐	☐	☐	☐	

3.02 **Nedenfor står fire utsagn om syn på forhold ved din nåværende jobb, eller hvis du ikke er i arbeid nå, den jobben du hadde sist** (sett ett kryss for hvert utsagn)

	Helt uenig	1	2	3	4	5	6	7	Helt enig
Arbeidet mitt er for belastende, fysisk eller følelsesmessig		☐	☐	☐	☐	☐	☐	☐	
Jeg har tilstrekkelig innflytelse på når og hvordan arbeidet mitt skal utføres		☐	☐	☐	☐	☐	☐	☐	
Jeg blir mobbet eller trakassert på arbeidsplassen min		☐	☐	☐	☐	☐	☐	☐	
Jeg blir rettferdig behandlet på arbeidsplassen min		☐	☐	☐	☐	☐	☐	☐	

3.03 **Jeg opplever at yrket mitt har følgende sosiale status i samfunnet:** (dersom du ikke er i arbeid nå, tenk på det yrket du hadde sist)

☐ Meget høy status
☐ Ganske høy status
☐ Middels status
☐ Ganske lav status
☐ Meget lav status

3.04 **Har du over lengre tid opplevd noe av det følgende?** (sett ett eller flere kryss for hver linje)

	Nei	Ja, som barn	Ja, som voksen	Ja, siste år
Blitt plaget psykisk, eller truet med vold	☐	☐	☐	☐
Blitt slått, sparket eller utsatt for annen type vold	☐	☐	☐	☐
Noen i nær familie har brukt rusmidler på en slik måte at dette har vært til *bekymring* for deg	☐	☐	☐	☐

Dersom du har opplevd noen av disse forholdene, hvor mye plages du av dette nå?

☐ Ingen plager ☐ Noen plager ☐ Store plager

4.01 **Har du i løpet av den siste måneden følt deg syk eller hatt en skade?**

☐ Ja ☐ Nei

Hvis JA: har du i den samme perioden?
(sett ett kryss for hver linje)

	Ja	Nei
Vært hos allmennlege/fastlege	☐	☐
Vært hos spesialist	☐	☐
Vært på legevakt	☐	☐
Vært innlagt i sykehus	☐	☐
Vært hos alternativ behandler *(kiropraktor, homøopat eller lignende)*	☐	☐

4.02 **Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året?**

☐ Ja ☐ Nei

4.03 **Blir du tungpustet i følgende situasjoner?**
(sett ett kryss for hvert spørsmål)

	Ja	Nei
Når du går hurtig på flatmark eller svak oppoverbakke	☐	☐
Når du spaserer i rolig tempo på flatmark	☐	☐
Når du vasker deg eller kler på deg	☐	☐
Når du er i hvile	☐	☐

4.04 **Hoster du omtrent daglig i perioder av året?**

☐ Ja ☐ Nei

Hvis JA: Er hosten vanligvis ledsaget av oppspytt?

☐ Ja ☐ Nei

Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste årene?

☐ Ja ☐ Nei

4.05 **Hvor ofte er du plaget av søvnløshet?**
(sett ett kryss)

☐ Aldri, eller noen få ganger i året
☐ 1-3 ganger i måneden
☐ Omtrent 1 gang i uka
☐ Mer enn 1 gang i uka

Hvis du er plaget av søvnløshet månedlig eller oftere, når på året er du mest plaget?
(sett ett eller flere kryss)

☐ Ingen spesiell tid
☐ Mørketida
☐ Midnattsoltida
☐ Vår og høst

4.06 **Har du i de siste par ukene hatt vansker med å sove?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.07 **Har du de siste par ukene følt deg ulykkelig og nedtrykt (deprimert)?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.08 **Har du i de siste par ukene følt deg ute av stand til å mestre dine vanskeligheter?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.09 **Nedenfor ber vi deg besvare noen spørsmål om din hukommelse:** (sett ett kryss for hvert spørsmål)

	Ja	Nei
Synes du at din hukommelse har blitt dårligere?	☐	☐
Glemmer du ofte hvor du har lagt tingene dine?	☐	☐
Har du problemer med å finne vanlige ord i en samtale?	☐	☐
Har du fått problemer med daglige gjøremål som du mestret tidligere?	☐	☐
Har du vært undersøkt for sviktende hukommelse?	☐	☐

Hvis JA på minst ett av de fire første spørsmålene ovenfor: Er det et problem i hverdagen?

☐ Ja ☐ Nei

4.10 **Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?** (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

4.11 **Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 4 ukene?** (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

4.12 **Har du noen gang hatt:**

	Ja	Nei	Alder siste gang
Brudd i håndledd/ underarm?	☐	☐	☐☐
Lårhalsbrudd?	☐	☐	☐☐

4.13 **Har du fått stilt diagnosen slitasjegikt av lege?**

☐ Ja ☐ Nei

4.14 **Har eller har du hatt noen av følgende:**

	Aldri	Litt	Mye
Nikkelallergi	☐	☐	☐
Pollenallergi	☐	☐	☐
Andre allergier	☐	☐	☐

4.15 **Har du opplevd ufrivillig barnløshet i mer enn 1 år?**

☐ Ja ☐ Nei

Hvis JA, skyldtes dette:

	Ja	Nei	Vet ikke
Forhold hos deg selv?	☐	☐	☐
Forhold hos partneren?	☐	☐	☐

4.16 **I hvilken grad har du hatt følgende plager i de siste 12 måneder?**

	Aldri	Litt	Mye
Kvalme	☐	☐	☐
Halsbrann/sure oppstøt	☐	☐	☐
Diare	☐	☐	☐
Treg mage	☐	☐	☐
Vekslende treg mage og diare	☐	☐	☐
Oppblåsthet	☐	☐	☐
Smerter i magen	☐	☐	☐

4.17 **Hvis du har hatt smerter i eller ubehag fra magen siste året:**

	Ja	Nei
Er disse lokalisert øverst i magen?	☐	☐
Har du hatt plagene så ofte som 1 dag i uka eller mer de siste 3 måneder?	☐	☐
Blir plagene bedre etter avføring?	☐	☐
Har plagene sammenheng med hyppigere eller sjeldnere avføring enn vanlig?	☐	☐
Har plagene noen sammenheng med løsere eller fastere avføring enn vanlig?	☐	☐
Kommer plagene etter måltid?	☐	☐

4.18 **Har du noen gang hatt:**

	Ja	Nei	Alder siste gang
Sår på magesekken	☐	☐	☐☐
Sår på tolvfingertarmen	☐	☐	☐☐
Magesår-operasjon	☐	☐	☐☐

4.19 **Til kvinnen: Har du spontanabortert?**

☐ Ja ☐ Nei ☐ Vet ikke

Hvis JA, antall ganger ☐☐

4.20 **Til mannen: Har din partner noen gang spontanabortert?**

☐ Ja ☐ Nei ☐ Vet ikke

Hvis JA, antall ganger ☐☐

4.21 **Bruker du glutenfri diett?**

☐ Ja ☐ Nei ☐ Vet ikke

4.22 **Har du fått stilt diagnosen Dermatitis Herpetiformis (DH)?**

☐ Ja ☐ Nei ☐ Vet ikke

4.23 **Har du fått stilt diagnosen cøliaki på bakgrunn av en vevsprøve fra tynntarmen tatt under en undersøkelse der du svelget en slange (gastroskopi)?**

☐ Ja ☐ Nei ☐ Vet ikke

4.24 **Har du egne tenner?**

☐ Ja ☐ Nei

4.25 **Hvor mange amalgamfyllinger har du/har du hatt?**

☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Har du vært plaget av hodepine det siste året?**

☐ Ja ☐ Nei

Hvis NEI, gå til del 5, kosthold

4.27 **Hva slags hodepine er du plaget av?**

☐ Migrene ☐ Annen hodepine

4.28 **Omtrent hvor mange dager per måned har du hodepine?**

☐ Mindre enn 1 dag
☐ 1-6 dager
☐ 7-14 dager
☐ Mer enn 14 dager

4.29 **Er hodepinen vanligvis:**
(sett et kryss for hver linje)

	Ja	Nei
Bankende/dunkende smerte	☐	☐
Pressende smerte	☐	☐
Ensidig smerte *(høyre eller venstre)*	☐	☐

4.30 **Hvor sterk er hodepinen vanligvis?**

☐ Mild *(hemmer ikke aktivitet)*
☐ Moderat *(hemmer aktivitet)*
☐ Sterk *(forhindrer aktivitet)*

4.31 **Hvor lenge varer hodepinen vanligvis?**

☐ Mindre enn 4 timer
☐ 4 timer – 1 døgn
☐ 1-3 døgn
☐ Mer enn 3 døgn

4.32 **Dersom du er plaget av hodepine, når på året er du plaget mest?** (sett ett eller flere kryss)

☐ Ingen spesiell tid
☐ Mørketida
☐ Midnattsoltida
☐ Vår og/eller høst

4.33 **Før eller under hodepinen, kan du da ha forbigående:**

	Ja	Nei
Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐	☐
Nummenhet i halve ansiktet eller i hånden?	☐	☐
Forverring ved moderat fysisk aktivitet	☐	☐
Kvalme og /eller oppkast	☐	☐

4.34 **Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:**

Antall dager ☐☐

5. KOSTHOLD

5.01 **Hvor ofte spiser du vanligvis følgende?** (sett ett kryss i hver linje)

	0-1 g per mnd	2-3 g per mnd	1-3 g per uke	Mer enn 3 g per uke
Ferskvannsfisk *(ikke oppdrett)*	☐	☐	☐	☐
Saltvannsfisk *(ikke oppdrett)*	☐	☐	☐	☐
Oppdrettsfisk *(laks, røye, ørret)*	☐	☐	☐	☐
Tunfisk *(fersk eller hermetisert)*	☐	☐	☐	☐
Fiskepålegg	☐	☐	☐	☐
Skjell	☐	☐	☐	☐
Den brune innmaten i krabbe	☐	☐	☐	☐
Hvalkjøtt/sel/kobbekjøtt	☐	☐	☐	☐
Innmat fra rein eller elg	☐	☐	☐	☐
Innmat fra rype	☐	☐	☐	☐

5.02 **Hvor mange ganger i året spiser du/spiste du vanligvis følgende?** (antall ganger)

	Som voksen	I din barndom
Mølje *(Antall ganger i året)*	☐☐	☐☐
Måsegg *(Antall egg i året)*	☐☐	☐☐
Reinsdyrkjøtt *(Antall ganger i året)*	☐☐	☐☐
Selvplukket sopp og bær *(blåbær/tyttebær/multe) (Antall ganger i året)*	☐☐☐	☐☐☐

5.03 **Hvor mange ganger i måneden spiser du hermetiske matvarer (fra metallbokser)?**

Antall ☐☐

5.04 **Bruker du vitaminer og/eller mineraltilskudd?**

☐ Ja, daglig ☐ Iblant ☐ Aldri

5.05 **Hvor ofte spiser du?**

	Aldri	1-3 g per mnd	1-3 g per uke	4-6 g. per uke	1-2 g. per dag	3 g. per dag eller mer
Mørk sjokolade	☐	☐	☐	☐	☐	☐
Lys sjokolade/melkesjokolade	☐	☐	☐	☐	☐	☐
Sjokoladekake	☐	☐	☐	☐	☐	☐
Andre søtsaker	☐	☐	☐	☐	☐	☐

5.06 **Hvis du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang?**
Tenk deg størrelsen på en Kvikk- Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.

¼	½	1	1 ½	2	Mer enn 2
☐	☐	☐	☐	☐	☐

5.07 **Hvor ofte drikker du kakao/varm sjokolade**

Aldri	1-3 g per mnd	1-3 g per uke	4-6 g. per uke	1-2 g. per dag	3 g. per dag eller mer
☐	☐	☐	☐	☐	☐

6. ALKOHOL

6.01 **Hvor ofte har du <u>det siste året</u>:**	Aldri	Sjeldnere enn månedlig	Månedlig	Ukentlig	Daglig, eller nesten daglig
Ikke klart å stoppe og drikke alkohol når du først har begynt?	☐	☐	☐	☐	☐
Ikke klart å gjøre det som normalt forventes av deg fordi du har drukket?	☐	☐	☐	☐	☐
Trengt en drink om morgenen for å få komme i gang etter en rangel?	☐	☐	☐	☐	☐
Følt skyld eller anger etter at du har drukket?	☐	☐	☐	☐	☐
Ikke klart å huske hva som skjedde kvelden før på grunn av at du hadde drukket?	☐	☐	☐	☐	☐

	Aldri	Ja, men ikke det siste året	Ja, det siste året
6.02 **Har du eller andre noen gang blitt skadet på grunn av at du har drukket?**	☐	☐	☐
Har en slektning, venn, lege, eller annet helsepersonell vært bekymret for din drikking, eller foreslått at du reduserer inntaket?	☐	☐	☐

7. VEKT

7.01 **Har du ufrivillig gått ned i vekt <u>siste 6 måneder</u>?**

☐ Ja ☐ Nei

Hvis JA: Hvor mange kilo? ____

7.02 **Anslå din vekt da du var 25 år gammel:**

Antall hele kg ____

7.03 **Er du fornøyd med vekta di nå?**

☐ Ja ☐ Nei

7.04 **Hvilken vekt ville du være tilfreds med (din trivselsvekt):**

Antall kg ____

8. LØSEMIDLER

8.01 **Hvor mange timer i uka driver du med følgende <u>fritids- eller yrkesaktiviteter:</u>**
Bilreparasjoner/lakkering, keramikkarbeid, maling/lakkering/løsemidler, frisør, glassmester, elektriker (Sett 0 om du ikke driver med slike fritids eller yrkesaktiviteter)

Antall timer per uke i gjennomsnitt ____

8.02 **Bruker du hårfargemidler?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger per år? ____

9.01 **Har du noen gang opplevd at sykdom er blitt mangelfullt undersøkt eller behandlet, og at dette har gitt alvorlige følger?**

- ☐ Ja, det har rammet meg selv
- ☐ Ja, det har rammet en nær pårørende *(barn, foreldre, ektefelle/samboer)*
- ☐ Nei

Hvis JA, hvor mener du årsaken ligger? (sett ett eller flere kryss):

- ☐ hos fastlege/allmennlege
- ☐ hos legevaktslege
- ☐ hos privatpraktiserende spesialist
- ☐ hos sykehuslege
- ☐ hos annet helsepersonell
- ☐ hos alternativ behandler
- ☐ hos flere på grunn av svikt i rutiner og samarbeid

9.02 **Har du noen gang følt deg overtalt til å godta undersøkelse eller behandling som du selv ikke ønsket?**

☐ Ja ☐ Nei

Hvis JA, mener du dette har hatt uheldige helsemessige følger?

☐ Ja ☐ Nei

9.03 **Har du noen gang klaget på behandling du har fått?**

- ☐ Har aldri vært aktuelt
- ☐ Har vurdert å klage, men ikke gjort det
- ☐ Har klaget muntlig
- ☐ Har klaget skriftlig

9.04 **Hvor lenge har du hatt din nåværende fastlege/annen lege?**

- ☐ Mindre enn 6 måneder
- ☐ 6 til 12 måneder
- ☐ 12 til 24 måneder
- ☐ Mer enn 2 år

9.05 **Ved siste legebesøk hos fastlegen, snakket legen(e) til deg slik at du forsto dem?** Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.06 **Hvordan vil du karakterisere behandlingen eller rådgivingen du fikk siste gang du var hos lege?** Svar på en skala fra 0 til 10, hvor 0= meget dårlig behandling og 10 = meget god behandling

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.07 **Har du i løpet av de siste 12 måneder opplevd at det har vært vanskelig å bli henvist til spesielle undersøkelser (som røntgen eller liknende) eller til spesialisthelsetjenesten (privatpraktiserende spesialist eller ved sykehus)?**

- ☐ Ikke aktuelt
- ☐ Intet problem
- ☐ Noe problem
- ☐ Stort problem

9.08 **Har du i løpet av de siste 12 måneder opplevd at det er vanskelig å bli henvist til fysioterapeut, kiropraktor eller liknende?**

- ☐ Ikke aktuelt
- ☐ Intet problem
- ☐ Noe problem
- ☐ Stort problem

9.09 **Alt i alt, har du opplevd at det er vanskelig eller enkelt å bli henvist til spesialisthelsetjenesten?**

- ☐ Ikke aktuelt
- ☐ Meget vanskelig
- ☐ Noe vanskelig
- ☐ Rimelig enkelt
- ☐ Meget enkelt

9.10 **Har du i løpet av de siste 12 måneder vært til undersøkelse eller behandling i spesialist-helsetjenesten?**

☐ Ja ☐ Nei

Hvis JA, snakket legen(e) til deg slik at du forstod dem? Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.11 **Hvordan vil du karakterisere behandlingen eller rådgivningen du fikk siste gang du var hos spesialist?** Svar på en skala fra 0 til 10, hvor 0=meget dårlig og 10=meget god

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.12 **Har du noen gang før 2002 gjennomgått en operasjon på sykehus eller spesialist-klinikk?**

☐ Ja ☐ Nei

9.13 **Har du i løpet av de siste 12 måneder brukt urtemedisin , naturmidler eller naturlegemidler?**

☐ Ja ☐ Nei

9.14 **Har du i løpet av de siste 12 måneder brukt meditasjon, yoga, qi gong eller thai chi som egenbehandling?**

☐ Ja ☐ Nei

10. BRUK AV ANTIBIOTIKA

10.01 **Har du brukt antibiotika i løpet av de siste 12 måneder?** (all penicillinliknende medisin i form av tabletter, mikstur eller sprøyter)

☐ Ja ☐ Nei ☐ Husker ikke

Hvis JA, hva fikk du behandling mot? Har du tatt flere antibiotikakurer, sett ett kryss for hver kur.

	Kur 1	Kur 2	Kur 3	Kur 4	Kur 5	Kur 6
· Urinveisinfeksjon *(blærebetennelse, blærekatarr)*	☐	☐	☐	☐	☐	☐
· Luftveisinfeksjon *(øre-, bihule- hals- eller lungebetennelse, bronkitt)*	☐	☐	☐	☐	☐	☐
· Annet	☐	☐	☐	☐	☐	☐
Antall dagers antibiotika kur						

Hvordan skaffet du deg antibiotikakuren? Har du tatt flere kurer, sett ett kryss for hver kur.

	Kur 1	Kur 2	Kur 3	Kur 4	Kur 5	Kur 6
Etter resept fra lege/tannlege	☐	☐	☐	☐	☐	☐
Uten kontakt med lege/uten resept:						
· Kjøp direkte fra apotek i utlandet	☐	☐	☐	☐	☐	☐
· Kjøp gjennom Internett	☐	☐	☐	☐	☐	☐
· Rest fra tidligere kur tilgjengelig hjemme	☐	☐	☐	☐	☐	☐
· Fått av familie/venner	☐	☐	☐	☐	☐	☐
· Andre måter	☐	☐	☐	☐	☐	☐

10.02 **Har du antibiotika hjemme?**

☐ Ja ☐ Nei

Hvis JA, er dette etter avtale med lege for å behandle kronisk eller hyppig tilbakevendende sykdom?

☐ Ja ☐ Nei

Hvis Nei, hvordan skaffet du deg dette legemiddelet? (Flere kryss er mulig)

- Kjøpt direkte fra apotek i utlandet ☐
- Kjøpt over Internett ☐
- Rest fra tidligere kur ☐
- Fått av familie/venner ☐
- Andre måter ☐

10.03 **Kan du tenke deg å bruke antibiotika uten å kontakte lege først?**

☐ Ja ☐ Nei

Hvis JA, hvilke tilstander vil du i så fall behandle? (Flere kryss mulig)

- Forkjølelse ☐
- Hoste ☐
- Bronkitt ☐
- Halsbetennelse ☐
- Bihulebetennelse ☐
- Feber ☐
- Influensa ☐
- Ørebetennelse ☐
- Diaré ☐
- Blærebetennelse ☐
- Andre infeksjoner ☐

11. DIN DØGNRYTME

Vi vil stille deg noen spørsmål som handler om dine søvnvaner.

11.01 **Har du hatt skiftarbeid de tre siste månedene?**

☐ Ja ☐ Nei

11.02 **Antall dager i løpet av uken hvor du ikke kan velge fritt når du vil sove (f.eks arbeidsdager)?**

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

Da går jeg til sengs klokken ....

Jeg gjør meg klar til å sove klokken ....

Antall minutter jeg trenger på å sovne ....

Jeg våkner klokken ....

Ved hjelp av: ☐ Vekkeklokke ☐ annen ytre påvirkning *(støy, familie etc)* ☐ av meg selv

Antall minutter jeg trenger på å stå opp ....

11.03 **Antall dager i løpet av uken hvor du fritt kan velge når du vil sove** (f.eks helger eller fridager)

0	1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐	☐

Da går jeg til sengs klokken ....

Jeg gjør meg klar til å sove klokken ....

Antall minutter jeg trenger på å sovne ....

Jeg våkner klokken ....

Ved hjelp av: ☐ Vekkeklokke ☐ annen ytre påvirkning *(støy, familie etc)* ☐ av meg selv

Antall minutter jeg trenger på å stå opp ....

12.01 **Hvor ofte dusjer eller bader du vanligvis?** (sett ett kryss)

- ☐ 2 eller flere ganger daglig
- ☐ 1 gang daglig
- ☐ 4-6 ganger per uke
- ☐ 2-3 ganger per uke
- ☐ 1 gang per uke
- ☐ sjeldnere enn 1 gang per uke

12.02 **Hvor ofte vasker du vanligvis hendene med såpe i løpet av en dag?** (sett ett kryss)

- ☐ 0 ganger
- ☐ 1-5 ganger
- ☐ 6-10 ganger
- ☐ 11-20 ganger
- ☐ Mer enn 20 ganger

12.03 **Har du noen gang fått antibiotikakur (penicillin og liknende medisin) på grunn av en hudlidelse, for eksempel betent eksem, kviser, leggsår som ikke vil gro, tilbakevendende verkebyll?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger i gjennomsnitt per år fikk du antibiotika i den perioden du var mest plaget (sett ett kryss)

☐ 1-2 ☐ 3-4 ☐ Mer enn 4 ganger

12.04 **Har du eller har du noen gang hatt følgende hudlidelser?** (sett ett kryss for hver linje)

	Ja	Nei
Psoriasis	☐	☐
Atopisk eksem (barneeksem)	☐	☐
Tilbakevendende håndeksem	☐	☐
Tilbakevendende kviser over flere måneder	☐	☐
Legg- eller fotsår som ikke ville gro i løpet av 3-4 uker	☐	☐

Hvis JA på spørsmål om legg-og/eller fotsår, har du leggsår i dag?

☐ Ja ☐ Nei

12.05 **Har du ofte eller bestandig noen av følgende plager?** (sett ett kryss for hver linje)

	Ja	Nei
Hevelse i ankler og legger, særlig om kvelden	☐	☐
Åreknuter	☐	☐
Eksem (rødt, kløende utslett) på leggene	☐	☐
Smerter i beina når du går, men som forsvinner når du står stille	☐	☐

12.06 **Har du noen gang fått følgende diagnoser av lege?** (sett ett kryss for hver linje)

	Ja	Nei
Psoriasis	☐	☐
Atopisk eksem	☐	☐
Rosacea	☐	☐

12.07 **Har du tilbakevendende store kviser/verkebyller som er ømme/smertefulle og som ofte tilheler med arr på følgende steder?** (sett ett kryss for hver linje)

	Ja	Nei
Armhulene	☐	☐
Under brystene	☐	☐
Magefolden/navlen	☐	☐
Rundt kjønnsorganet	☐	☐
Rundt endetarmsåpningen	☐	☐
Lyskene	☐	☐

Hvis JA, har du noen gang oppsøkt lege på grunn av verkebyller?

☐ Ja ☐ Nei

Hvis JA, fikk du da noen av følgende behandlinger? (sett ett kryss for hver linje)

	Ja	Nei
Antibiotika salve/krem	☐	☐
Antibiotika tabletter	☐	☐
Kirurgisk åpning/tømming	☐	☐
Større kirurgisk inngrep med fjerning av hud	☐	☐
Kirurgisk laserbehandling	☐	☐

Oppfølgingsspørsmål

INFORMASJON TIL OPPFØLGINGSSPØRSMÅL

De neste sidene med spørsmål skal ikke besvares av alle. Dersom du har svart ja på ett eller flere av spørsmålene under, ber vi deg om å gå videre til oppfølgingsspørsmål om emnet eller emnene du har svart ja på. De fire første emnene er fra det første spørreskjemaet og det siste spørsmålet er fra dette skjemaet.

Vi har for enkelhetsskyld markert emnene med ulike farger slik at du lett skal finne frem til de spørsmålene som gjelder for deg.

Dersom du svarte JA på at du har: langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer, ber vi deg svare på spørsmålene på side 19 og 20. Margen er markert med grønn.

Dersom du svarte JA på at du har gjennomgått noen form for operasjon i løpet av de siste 3 årene, ber vi deg svare på spørsmålene på side 21 og 22. Margen er markert med lilla.

Dersom du svarte JA på at du arbeider utendørs minst 25% av tiden, eller i lokaler med lav temperatur, som for eksempel lager/industrihaller, ber vi deg svare på spørsmålene på side 23. Margen er markert med rød.

Dersom du svarte JA på at du har brukt reseptfrie smertestillende medisiner, ber vi deg svare på spørsmålene på side 24. Margen er markert med orange.

Dersom du svarte JA på at du har eller noen gang har hatt plager med hud (som psoriasis, atopisk eksem, legg- eller fotsår som ikke vil gro, tilbakevendende håndeksem, kviser eller verkebyll), ber vi deg svare på spørsmålene på side 25. Margen er markert med gul.

Har du svart **NEI** på disse fem spørsmålene, er du ferdig med besvarelsen din. Spørreskjemaet returneres i svarkonvolutten du fikk utlevert på undersøkelsen. Portoen er allerede betalt.

Skulle du ønske å gi oss en skriftlig tilbakemelding om enten spørreskjema eller Tromsøundersøkelsen generelt, er du hjertelig velkommen til det på side 26.

Har du noen spørsmål, kan du ta kontakt med oss på telefon eller på e-post. Du finner kontaktinformasjon på baksiden av skjemaet. **TUSEN TAKK** for at du tok deg tid til undersøkelsen og til å svare på spørsmålene fra oss.

13. OPPFØLGINGSSPØRSMÅL OM SMERTE

Du svarte i det første spørreskjemaet at du har langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer. Her ber vi deg beskrive de smertene litt nærmere.

13.01 **Hvor lenge har du hatt disse smertene?**

Antall år........... [|] måneder........... [|]

13.02 **Hvor ofte har du vanligvis disse smertene?**

- ☐ Hver dag
- ☐ En eller flere ganger i uken
- ☐ En eller flere ganger i måneden
- ☐ Sjeldnere enn 1 gang i måneden

13.03 **Hvor er det vondt?** (Kryss av for alle steder der du har langvarige eller stadig tilbakevendende smerter)

- ☐ Hode/ansikt
- ☐ Kjeve/kjeveledd
- ☐ Nakke
- ☐ Rygg
- ☐ Skulder
- ☐ Arm/albue
- ☐ Hånd
- ☐ Hofte
- ☐ Lår/kne/legg
- ☐ Ankel/fot
- ☐ Bryst
- ☐ Mage
- ☐ Underliv/kjønnsorganer
- ☐ Hud
- ☐ Annet sted

13.04 **Hva mener du er årsaken til smertene?** (Kryss av for alle kjente årsaker)

- ☐ Ulykke/akutt skade
- ☐ Langvarig belastning
- ☐ Kirurgisk inngrep/operasjon
- ☐ Skiveutglidning *(prolaps)*/lumbago
- ☐ Nakkesleng *(whiplash)*
- ☐ Migrene/hodepine
- ☐ Slitasjegikt *(artrose)*
- ☐ Leddgikt
- ☐ Bechterews sykdom
- ☐ Fibromyalgi
- ☐ Angina pectoris *(hjertekrampe)*
- ☐ Dårlig blodsirkulasjon
- ☐ Kreft
- ☐ Nerveskade/nevropati
- ☐ Infeksjon
- ☐ Helvetesild
- ☐ Annen årsak *(beskriv under)*
- ☐ Vet ikke

Beskriv annen årsak:

....

13.05 **Hvilke former for behandling har du fått for smertene?** (Kryss av for alle typer smertebehandling du har mottatt)

- ☐ Ingen behandling
- ☐ Smertestillende medisiner
- ☐ Fysioterapi/kiropraktikk
- ☐ Behandling ved smerteklinikk
- ☐ Operasjon
- ☐ Smerteskole/avspenning/psykoterapi
- ☐ Akupunktur
- ☐ Alternativ behandling *(homøopati, healing, aromaterapi, m.m.)*
- ☐ Annen behandling

13.06 **På en skala fra 0 til 10, der 0 tilsvarer ingen smerte og 10 tilsvarer den verst tenkelige smerten du kan forestille deg:**

		0	1	2	3	4	5	6	7	8	9	10	
Hvor sterke vil du si at smertene vanligvis er?	Ingen smerte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Verst tenkelige smerte
Hvor sterke er smertene når de er på sitt sterkeste?	Ingen smerte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Verst tenkelige smerte
I hvor stor grad påvirker smertene søvnen din?	Påvirker ikke	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig å få sove
I hvor stor grad hindrer smertene deg i å utføre vanlige aktiviteter hjemme og i arbeid?	Påvirker ikke	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Kan ikke gjøre noe

14. OPPFØLGINGSSPØRSMÅL OM OPERASJON

I det første spørreskjemaet svarte du at du har gjennomgått en operasjon i løpet av de siste 3 årene.

14.01 **Hvor mange operasjoner har du totalt gjennomgått de siste 3 årene?**

Antall .... ☐☐

Nedenfor ber vi deg beskrive operasjonen. Dersom du har gjennomgått flere operasjoner i løpet av de siste 3 årene gjelder disse spørsmålene den siste operasjonen du gjennomgikk.

14.02 **Hvor i kroppen ble du operert?** (Dersom du samtidig ble operert flere steder i kroppen, settes flere kryss)

Operasjon i hode/nakke/rygg

- Hode/ansikt ☐
- Nakke/hals ☐
- Rygg ☐

Operasjon i brystregionen

- Hjerte ☐
- Lunger ☐
- Bryster ☐
- Annen operasjon i brystregionen ☐

Operasjon i mage/underliv

- Mage/tarm ☐
- Lyskebrokk ☐
- Urinveier/kjønnsorganer ☐
- Galleblære/galleveier ☐
- Annen operasjon i mage/underliv ☐

Operasjon i hofte/ben

- Hofte/lår ☐
- Kne/legg ☐
- Ankel/fot ☐
- Amputasjon ☐

Operasjon i skulder og arm

- Skulder/overarm ☐
- Albue/underarm ☐
- Hånd ☐
- Amputasjon ☐

14.03 **Bakgrunn for operasjonen:**

Akutt sykdom/skade ☐
Planlagt ikke-kosmetisk operasjon ☐
Planlagt kosmetisk operasjon ☐

14.04 **Hvor ble du operert?**

Sykehuset i Tromsø ☐
Sykehuset i Harstad ☐
Annet offentlig sykehus ☐
Privat klinikk ☐

14.05 **Hvor lenge er det siden du gjennomgikk operasjonen?**

Antall år ☐☐ måneder ☐☐

14.06 **Har du nedsatt følsomhet i et område nær operasjonsarret?**

☐ Ja ☐ Nei

14.07 **Er du overfølsom for berøring, varme eller kulde i et område nær operasjonsarret?**

☐ Ja ☐ Nei

14.08 **Kan lett berøring av klær, dusj og lignende fremkalle ubehag/smerte?**

☐ Ja ☐ Nei

14.09 **Hvis du hadde smerter på operasjonsstedet før du ble operert, har du samme type smerte nå?**

☐ Ja ☐ Nei

14.10 **Smerte fra operasjonsstedet:** Svar på en skala fra 0 til 10, hvor 0=ingen smerte og 10=verst tenkelige smerte

	Ingen smerte	0	1	2	3	4	5	6	7	8	9	10	Verst tenkelige smerte
Hvor sterke smerter hadde du fra operasjonsstedet før operasjonen		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Hvor sterke smerter har du vanligvis fra operasjonsstedet nå		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Hvor sterke smerter har du nå fra operasjonsstedet når smertene er på det sterkeste		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

15. OPPFØLGINGSSPØRSMÅL OM ARBEID I KALDT KLIMA

I det første spørreskjemaet svarte du ja på at du arbeidet i kaldt klima. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

15.01 **Fryser du på jobb?**

☐ Ja, ofte
☐ Ja, noen ganger
☐ Nei, aldri

15.02 **Hvor lenge har du vært utsatt for kalde omgivelser under 0°C sist vinter?**

Fritid/hobby *(timer/uke)* ☐☐
Arbeid *(timer/uke)* ☐☐
Utendørs, godt kledd *(timer/uke)* ☐☐
Utendørs, tynnkledd *(timer/uke)* ☐☐
Innendørs, uten oppvarming *(timer/uke)* ☐☐
I kalde omgivelser, med våte klær *(timer/uke)* ☐☐
Kontakt med kalde gjenstander/verktøy *(timer/uke)* ☐☐

15.03 **Hvilken omgivelsestemperatur forhindrer deg i å:**

	Under °C
Arbeide utendørs	☐☐☐
Trene utendørs	☐☐☐
Utføre andre aktiviteter utendørs	☐☐☐

15.04 **Har du hatt forfrysninger siste 12 måneder, med blemmer, sår eller skader i huden?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger? ☐☐

15.05 **Har du opplevd kløe og/eller utslett i forbindelse med kulde?**

☐ Ja ☐ Nei

15.06 **Har du i løpet av de siste 12 måneder vært involvert i ulykke som krevde medisinsk behandling der kulde var en viktig faktor?**

	Ja	Nei
På arbeid	☐	☐
I fritiden	☐	☐

15.07 **Opplever du noen av følgende symptomer mens du oppholder deg i kalde omgivelser? I så fall, ved hvilken temperatur oppstår symptomene?**

	Ja	Nei	Under °C
Pusteproblemer	☐	☐	☐☐☐
Pipende pust	☐	☐	☐☐☐
Slim fra lungene	☐	☐	☐☐☐
Brystsmerter	☐	☐	☐☐☐
Forstyrrelse i hjerterytmen	☐	☐	☐☐☐
Nedsatt blodsirkulasjon i hender/føtter	☐	☐	☐☐☐
Synsforstyrrelse *(kortvarig/forbigående)*	☐	☐	☐☐☐
Migrene *(kortvarig/forbigående)*	☐	☐	☐☐☐
Hvite fingre *(kortvarig/forbigående)*	☐	☐	☐☐☐
Blå, blå-røde fingre *(kortvarig/forbigående)*	☐	☐	☐☐☐

15.08 **Hvordan påvirker kalde omgivelser og kulderelaterte symptomer din yteevne?**

	Nedsatt	Uforandret	Forbedret
Konsentrasjon	☐	☐	☐
Hukommelse	☐	☐	☐
Fingerfølsomhet *(følelse)*	☐	☐	☐
Fingerferdighet *(motorikk)*	☐	☐	☐
Kontroll av bevegelse *(for eksempel skjelving)*	☐	☐	☐
Tungt fysisk arbeid	☐	☐	☐
Langvarig fysisk arbeid	☐	☐	☐

16. BRUK AV RESEPTFRIE SMERTESTILLENDE LEGEMIDLER

I det første spørreskjemaet svarte du at du hadde brukt reseptfrie smertestillende legemidler de siste 4 ukene. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

16.01 **Hvilke typer reseptfrie smertestillende legemidler har du brukt?**

Paracetamol: *(Pamol, Panodil, Paracet, Paracetamol, Pinex)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter, stikkpiller) .... ☐☐

Acetylsalisylsyre: (*Aspirin,Dispril, Globoid)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)........ ☐☐

Ibuprofen: *(Ibumetin, Ibuprofen, Ibuprox, Ibux)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter, stikkpiller) .... ☐☐

Naproksen: *(Ledox, Naproxen)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)........ ☐☐

Fenazon med koffein: *(Antineuralgica ,Fanalgin Fenazon-koffein, Fenazon-koffein sterke)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)........ ☐☐

16.02 **Mot hvilke plager bruker du reseptfrie smertestillende midler:** (Flere kryss er mulig)

- ☐ Hodepine
- ☐ Menssmerter
- ☐ Migrene
- ☐ Ryggsmerter
- ☐ Muskelsmerter/leddsmerter
- ☐ Tannsmerter
- ☐ Annet

16.03 **Mener du å ha opplevd bivirkninger av noen av legemidlene?** (sett ett kryss for hver linje)

	Ja	Nei
Paracetamol	☐	☐
Acetylsalisylsyre	☐	☐
Ibuprofen	☐	☐
Naproksen	☐	☐
Fenazon med koffein	☐	☐

16.04 **Hvor pleier du å kjøpe slike legemidler?**

- ☐ Apotek
- ☐ Dagligvare
- ☐ Bensinstasjon
- ☐ Utenlands
- ☐ Internett

16.05 **Kombinerer du behandlingen med bruk av reseptbelagte smertestillende midler?**

☐ Ja ☐ Nei

17. OPPFØLGINGSSPØRSMÅL OM HUDSYKDOMMER

På side 15 i dette spørreskjemaet svarte du at du har eller har hatt en hudsykdom. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

Svar på en skala fra 0 til 10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager. Dersom du svarte JA på at du har eller har hatt:

	Ingen plager 0	1	2	3	4	5	6	7	8	9	10 Verst tenkelige plager
17.01 **Psoriasis**											
· Hvor mye plaget er du av din psoriasis i dag?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
· Hvor mye plaget er du av din psoriasis når den er som verst?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17.02 **Atopisk eksem**											
· Hvor mye plaget er du av ditt atopiske eksem i dag?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
· Hvor mye plaget er du av ditt atopiske eksem når det er som verst?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17.03 **Håndeksem**											
· Hvor mye plaget er du av ditt håndeksem i dag?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
· Hvor mye plaget er du av ditt håndeksem når det er som verst?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17.04 **Kviser**											
· Hvor mye plaget er du av dine kviser i dag?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
· Hvor mye plaget er du av dine kviser når de er som verst?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17.05 **Verkebyller**											
· Hvor mye plaget er du av dine verkebyller i dag?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
· Hvor mye plaget er du av dine verkebyller når de er som verst?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

17.06 **Her er en liste over faktorer som kan tenkes å utløse eller forverre verkebyller, kryss av for hva du synes gjelder for deg:**

	Ja	Nei
Stress/psykisk påkjenning	☐	☐
Trange/tette klær	☐	☐
Menstruasjonssyklus	☐	☐
Svangerskap	☐	☐
Annet	☐	☐

17.07 **Hvor mange utbrudd av verkebyller har du vanligvis i løpet av ett år?** (sett ett kryss)

☐ 0-1 ☐ 4-6
☐ 2-3 ☐ Mer enn 6

17.08 **Hvor gammel var du da du fikk verkebyller første gang?**

☐ 0-12 år ☐ 26-35 år
☐ 13-19 år ☐ 36-50 år
☐ 20-25 år ☐ Over 50 år

17.09 **Dersom du ikke lenger har verkebyller, hvor gammel var du da plagene forsvant?**

☐ 0-12 år ☐ 26-35 år
☐ 13-19 år ☐ 36-50 år
☐ 20-25 år ☐ Over 50 år

TILBAKEMELDING

Skulle du ønske å gi oss en skriftlig tilbakemelding om enten spørreskjema eller Tromsøundersøkelsen generelt, er du hjertelig velkommen til det her:

Takk for hjelpen!

Tromsø-undersøkelsen

Tromsøundersøkelsen
Institutt for samfunnsmedisin, Universitetet i Tromsø
9037 TROMSØ
telefon: 77 64 48 16
telefaks: 77 64 48 31
epost: tromsous@ism.uit.no
www.tromso6.no

LUNDBLAD MEDIA AS · FOTO: TORGER GRYTÅ

Appendix 3

First questionnaire in the Tromsø Study 7

Tromsø-undersøkelsen
2015–2016

KONFIDENSIELT

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Bruk blokkbokstaver. Du kan ikke bruke komma.

Dato for utfylling: ☐☐☐☐☐☐

HELSE OG SYKDOMMER

1.1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

Meget god	God	Verken god eller dårlig	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

1.2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

Mye bedre	Litt bedre	Omtrent lik	Litt dårligere	Mye dårligere
☐	☐	☐	☐	☐

1.3 **Har du eller har du hatt?**
Sett ett kryss per linje.

	Nei	Ja nå	Før, ikke nå	Alder første gang
Høyt blodtrykk	☐	☐	☐	☐☐
Hjerteinfarkt	☐		☐	☐☐
Hjertesvikt	☐	☐	☐	☐☐
Atrieflimmer *(hjerteflimmer)*	☐	☐	☐	☐☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐	☐☐
Hjerneslag/hjerneblødning	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Nyresykdom *(unntatt urinveisinfeksjon)*	☐	☐	☐	☐☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐	☐☐
Astma	☐	☐	☐	☐☐
Kreft	☐	☐	☐	☐☐
Revmatoid artritt *(leddgikt)*	☐	☐	☐	☐☐
Artrose *(slitasjegikt)*	☐	☐	☐	☐☐
Migrene	☐	☐	☐	☐☐
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	☐	☐☐

1.4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?**

☐ Nei ☐ Ja

TANNHELSE

2.1 **Hvordan vurderer du din egen tannhelse?**

	1	2	3	4	5	
Svært dårlig	☐	☐	☐	☐	☐	Svært god

2.2 **Hvor fornøyd eller misfornøyd er du med tennene eller protesene dine?**

	1	2	3	4	5	
Svært misfornøyd	☐	☐	☐	☐	☐	Svært fornøyd

BRUK AV HELSETJENESTER

3.1 **Har du, grunnet egen helse, i løpet av de siste 12 måneder vært hos:**

	Nei	Ja	Antall ganger
Fastlege/allmennlege	☐	☐	☐☐
Legevakt	☐	☐	☐☐
Psykiater/psykolog	☐	☐	☐☐
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	☐☐
Tannlege/tannpleier	☐	☐	☐☐
Apotek *(for kjøp/råd om medisiner/behandling)*	☐	☐	☐☐
Fysioterapeut	☐	☐	☐☐
Kiropraktor	☐	☐	☐☐
Akupunktør	☐	☐	☐☐
Alternativ behandler *(homøopat, soneterapeut, healer etc)*	☐	☐	☐☐
Tradisjonell helbreder *(hjelper, «læser» etc)*	☐	☐	☐☐
Har du kommunisert via internett med noen av tjenestene over?	☐	☐	☐☐

3.2 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Nei	Ja	Antall ganger
Innlagt på sykehus	☐	☐	☐☐
Konsultasjon ved sykehus uten innleggelse:			
Ved psykiatrisk poliklinikk	☐	☐	☐☐
Ved annen sykehuspoliklinikk	☐	☐	☐☐

BRUK AV MEDISINER

4.1 **Bruker du, eller har du brukt, noen av følgende medisiner?** *Sett ett kryss per linje.*

	Aldri	Nå	Før, ikke nå	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Annen medisin mot hjertesykdom *(f.eks. blodfortynnende, rytmestabiliserende, nitroglycerin)*	☐	☐	☐	
Insulin	☐	☐	☐	
Tabletter mot diabetes	☐	☐	☐	
Stoffskiftemedisin *(Levaxin/thyroxin)*	☐	☐	☐	

4.2 **Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?** *Sett ett kryss per linje.*

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende uten resept	☐	☐	☐	☐
Magesyrehemmende medisiner	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

4.3 **Skriv alle medisiner (reseptfrie og reseptbelagte) du har brukt regelmessig siste 4 uker.** *Ikke regn med reseptfrie vitamin-, mineral- og kosttilskudd, urter, naturmedisin etc.*

Får du ikke plass til alle medisinene, bruk eget ark.

KOSTHOLD

5.1 **Spiser du vanligvis frokost hver dag?**

☐ Nei ☐ Ja

5.2 **Hvor mange porsjoner frukt og grønnsaker spiser du i gjennomsnitt per dag?** *Med porsjon menes f.eks. et eple, en salatbolle.*

Antall porsjoner

5.3 **Hvor ofte spiser du vanligvis disse matvarene?** *Sett ett kryss per linje.*

	0–1 pr. mnd.	2–3 pr. mnd.	1–3 pr. uke	4–6 pr. uke	1 eller mer pr. dag
Rødt kjøtt *(alle produkter av storfe, får, svin)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei)*	☐	☐	☐	☐	☐
Feit fisk *(laks, ørret, uer makrell, sild, kveite)*	☐	☐	☐	☐	☐

5.4 **Hvor mange glass/beger drikker/spiser du vanligvis av følgende?** *Sett ett kryss per linje.*

	Sjelden/ aldri	1–6 pr. uke	1 pr. dag	2–3 pr. dag	4 eller mer pr. dag
Melk/yoghurt tilsatt probiotika *(Biola, Cultura, Activia, Actimel, BioQ)*	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker:					
med sukker	☐	☐	☐	☐	☐
med kunstig søtning	☐	☐	☐	☐	☐

5.5 **Hvor mange kopper kaffe og te drikker du daglig?** *Sett 0 for de typene du ikke drikker daglig.*

	Antall kopper
Filterkaffe *(trakterkaffe)*	
Kokekaffe og/eller presskannekaffe	
Pulverkaffe	
Espressobasert kaffe *(fra kaffemaskin, kapsler etc)*	
Sort te *(f.eks. Earl Grey)*	
Grønn/hvit/oolong te	
Urtete *(f.eks. nype, kamille, Rooibos)*	

HELSEBEKYMRING

	Ikke i det hele tatt	Litt	Noe	En hel del	Svært mye
6.1 **Tror du at det er noe alvorlig galt med kroppen din?**	☐	☐	☐	☐	☐
6.2 **Er du svært bekymret over helsen din?**	☐	☐	☐	☐	☐
6.3 **Er det vanskelig for deg å tro på legen din dersom hun/han forteller deg at det ikke er noe å bekymre seg for?**	☐	☐	☐	☐	☐
6.4 **Er du ofte bekymret for muligheten for at du har en alvorlig sykdom?**	☐	☐	☐	☐	☐
6.5 **Hvis du blir gjort oppmerksom på en sykdom (f.eks. via TV, radio, internett, avis eller noen du kjenner), bekymrer du deg da for selv å få sykdommen?**	☐	☐	☐	☐	☐
6.6 **Opplever du at du plages av mange ulike symptomer?**	☐	☐	☐	☐	☐
6.7 **Har du tilbakevendende tanker (som er vanskelig å bli kvitt) om at du har en sykdom?**	☐	☐	☐	☐	☐

FYSISK AKTIVITET

7.1 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?** *Sett kryss i den ruta som passer best.*

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks. ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks. pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

7.2 **Angi bevegelse og kroppslig anstrengelse i din fritid det siste året.** *Hvis aktiviteten varierer gjennom året, ta et gjennomsnitt. Sett kryss i den ruta som passer best.*

- ☐ Leser, ser på TV / skjerm eller annen stillesittende aktivitet
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka *(inkludert gang eller sykling til arbeidsstedet, søndagsturer etc)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking etc minst 4 timer i uka
- ☐ Trener hardt eller driver konkurranseidrett regelmessig flere ganger i uka

7.3 **Siste uka, omtrent hvor lang tid tilbrakte du sittende på en typisk hverdag og fridag?** *F.eks. ved arbeidsbord, hos venner, mens du så på TV / skjerm.*

☐☐ timer sittende på en hverdag *(både jobb og fritid)*

☐☐ timer sittende på en fridag

ALKOHOL

8.1 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2–4 ganger hver måned
- ☐ 2–3 ganger per uke
- ☐ 4 eller flere ganger per uke

8.2 **Hvor mange enheter alkohol (flaske øl, glass vin eller drink) tar du vanligvis når du drikker?**

1–2	3–4	5–6	7–9	10 eller flere
☐	☐	☐	☐	☐

8.3 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ Aldri
- ☐ Sjeldnere enn månedlig
- ☐ Månedlig
- ☐ Ukentlig
- ☐ Daglig eller nesten daglig

RØYK OG SNUS

9.1 **Har du røykt/røyker du daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

9.2 **Har du brukt/bruker du snus eller skrå daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

SPØRSMÅL OM KREFT

10.1 **Har du noen gang fått**

	Nei	Ja	**Hvis ja:** alder første gang	**Hvis ja:** alder siste gang
Utført mammografi	☐	☐		
Målt PSA (prostataspesifikt antigen)	☐	☐		
Utført tykktarmsundersøkelse (koloskopi, avføringsprøve)	☐	☐		

10.2 **Har noen i din nære biologiske familie hatt**

	Egne barn	Mor	Far	Mormor	Morfar	Farmor	Farfar	Tante	Onkel	Søsken
Brystkreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostatakreft	☐		☐		☐		☐		☐	☐
Tykktarmskreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

UTDANNING OG INNTEKT

11.1 **Hva er din høyeste fullførte utdanning?** *Sett ett kryss.*

☐ Grunnskole/framhaldsskole/folkehøyskole inntil 10 år

☐ Fagutdanning/realskole/videregående/gymnas minimum 3 år

☐ Høyskole/universitet mindre enn 4 år

☐ Høyskole/universitet 4 år eller mer

11.2 **Hva var din husstands samlede bruttoinntekt siste år?**
Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

☐ Under 150 000 kr

☐ 150 000–250 000 kr

☐ 251 000–350 000 kr

☐ 351 000–450 000 kr

☐ 451 000–550 000 kr

☐ 551 000–750 000 kr

☐ 751 000 –1 000 000 kr

☐ Over 1 000 000 kr

FAMILIE OG VENNER

12.1 **Hvem bor du sammen med?**

	Nei	Ja	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

12.2 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

12.3 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

12.4 **Hvor ofte deltar du vanligvis i foreningsvirksomhet som syklubb, idrettslag, politiske, religiøse eller andre foreninger?**

Aldri, eller noen få ganger i året	1–2 ganger i måneden	Omtrent 1 gang i uka	Mer enn 1 gang i uka
☐	☐	☐	☐

SPØRSMÅL TIL KVINNER

13.1 **Hvor gammel var du da du fikk menstruasjon første gang?**

Alder

13.2 **Er du gravid nå?**

☐ Nei ☐ Ja ☐ Usikker

13.3 **Hvor mange barn har du født?**

Antall barn

13.4 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.** *Angi så godt du kan. Hvis flere barn, bruk ekstra ark.*

	Fødselsår	Fødselsvekt i gram	Ammet ant. mnd.
Barn 1			
Barn 2			
Barn 3			
Barn 4			
Barn 5			
Barn 6			

SPØRSMÅL TIL MENN

14.1 **Har du fått behandling for betennelse i prostata eller urinblæra?**

☐ Nei ☐ Ja

14.2 **Har du fått utført steriliseringsoperasjon?**

☐ Nei ☐ Ja **Hvis ja:** hvilket år

Tusen takk for ditt bidrag.