

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Working in a cold environment, feeling cold at work and chronic pain: A cross-sectional analysis of The Tromsø Study
<b>AUTHORS</b>	Farbu, Erlend; Skandfer, Morten; Nielsen, Christopher; Brenn, Tormod; Stubhaug, Audun; Höper, Anje

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Tiina Ikäheimo University of Oulu, Center for Environmental and Respiratory Health Research, Oulu, Finland
<b>REVIEW RETURNED</b>	09-May-2019

<b>GENERAL COMMENTS</b>	<p>Reviewers comments BMJ Open-2019-031248</p> <p>General</p> <p>The study examined whether working in a cold environment and feeling cold at work are associated with chronic pain. In addition, the occurrence of other health complaints related to cold exposure were examined. The study observed that working in a cold environment was associated with chronic pain. This association was strongest for pain at musculoskeletal sites and for those who often felt cold at work.</p> <p>It is well established that exposure to cold at work reduces both physical and cognitive performance and aggravates the course of clinical conditions. This has been shown to result in a higher prevalence of symptoms, as well as morbidity, and even mortality, in the winter. The results of the presented study are important, since there are only a few previous population studies which have examined musculoskeletal pain at the population level. Furthermore, to my opinion, none have had a focus on chronic pain. In contrast, the reporting of cold-related complaints have been reported in a few previous population studies. Overall, the topic is significant due to recurrent occupational exposure to cold (in- and outdoor) especially among workers residing in northern climates.</p> <p>The manuscript is, in general, well prepared and written. The statistical analyzes, are appropriate for examining the association between reported exposure to cold and occurrence of chronic pain. Though, to my opinion, there some possible important confounders that are not adjusted for. The results are clearly presented. Overall, the discussion reflects the description of the main finding and their interpretation. The results in the supplement table presenting the overall health-related complaints and effects seem a bit disconnected.</p> <p>Specific</p>
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	<p>Introduction: The authors should present a hypothesis/hypotheses of the study. As the focus of the article is related to cold exposure and chronic pain, the presentation of other health complaints and effects seems a bit arbitrary, and especially since they represent a relatively minor proportion of the manuscript (rather to provide support that the workers experience cold exposure).</p> <p>Methods, page 6, line 34: Please clarify what was the time perspective for the occurrence of chronic pain (e.g. during the past 12 months?). Further was the question concerning with pain formulated as persistent musculoskeletal pain?</p> <p>Methods, page 7, Line 28: (BMI) was calculated</p> <p>Methods: My major concern is related to confounding related to possible health conditions of the respondents. It is not clear to whether information from the mentioned extensive health questionnaire were used for adjusting for the examined association between reported cold exposure/sensations of cold and occurrence of chronic pain. One could speculate that there could be several conditions that could be related to chronic pain. Furthermore, could the authors elaborate why insomnia was chosen as a confounder? It is probably related to experienced pain, but would need to associate with reported cold exposure/sensation of cold in order to be a true confounding factor. Furthermore, as a lifestyle factor, it is likely that the use of alcohol could also be a confounding factor.</p> <p>Results, line 24 onwards, Table 3. Rather than repeating the OR 1 for working less in cold you could indicate that this is the reference point.</p> <p>Results, page 11, line 59 onwards, this sentence should be reformulated to improve clarity.</p> <p>The discussion should aim at better distinguishing for the mechanisms between how the exposure (exposure of more than 25% to cold at work, feeling cold) relates to the effect (chronic pain). In some cases the authors associate the reported pain to be a result of cold exposure, and its physiological responses affecting chronic pain. Though, as the authors correctly indicate, the association between cold exposure and pain has not been established. The effects on thermal thresholds, or sensitization, could provide an explanation, though, not confirmed. Here it would also be important to distinguish between the acute and chronic effects of cold exposure (which are briefly mentioned in the introduction).</p> <p>Another, perhaps more plausible mechanism, would be that these workers have a clinical condition affecting their neural and musculoskeletal functions, and which aggravates their prevailing pain. Estimating these effects is rendered difficult. For example, the defined exposure (e.g. working less or above 25% of working time in cold) is a robust estimate and leaves the question of how much these workers report symptoms of chronic pain without any cold exposure (which was not elaborated here). The authors also correctly indicate that the health status (e.g. musculoskeletal, but also neural) likely reflects a person's thermal state and reported pain sensations. The inability to take this into account in the study is a weakness.</p> <p>Lines 35 onwards: The suggested plausible mechanisms explaining the association between cold exposure and pain needs to be presented in a different way. "such as a change in electromyography, poorer energy-efficiency and increased muscle activity" do not explain the effects of cold on the neuromuscular system adequately. Instead, you should indicate what these responses are (e.g. impaired muscular performance (force,</p>
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	<p>velocity, co-ordination), altered neural and reflex functions) and how they would affect neuromuscular performance.</p> <p>The authors should also acknowledge somewhere in the text that their question of chronic musculoskeletal pain could mean a variety of conditions (Treede et al. 2015). In addition, chronic pain thought to be of musculoskeletal origin, could reflect some other clinical condition. A relatively large emphasis is put on describing pain occurring in different parts of the body. Yet, as both the information of exposure and the health conditions of the workers is either robust or lacking, it is impossible to understand the reasons for the experienced chronic pain occurring in different areas of the body. This could be mentioned.</p> <p>Line 57 onwards: Referring to my previous comment, the part related to cardiovascular or respiratory complaints do not really fit well to the entity of this study. Here their prevalence are only compared with other studies, but their significance is not explained. I understand that the authors want to demonstrate that the higher amount of complaints and reported performance decrements occur more often when working in cold, or while reporting feeling cold, and would provide support for the exposure itself. However, this still remains implicative and is out of the main focus (chronic pain and cold exposure).</p> <p>Limitations: The authors have, in general, acknowledged the limitations of the study well. In addition to these, I would add the lack of information of the health status of the respondents as a limitation. One obvious limitation is also the self-reported cold exposure, sensations of cold, as well as chronic pain, which are rather robust estimates (and cannot be validated) and also subject to recollection bias.</p> <p>Useful references: Treede et al. Pain. 2015 Jun; 156(6): 1003–1007.</p>
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<b>REVIEWER</b>	Qihong Deng Central South University, Changsha, China
<b>REVIEW RETURNED</b>	15-Jun-2019

<b>GENERAL COMMENTS</b>	<p>This work is really good, simple and clear. The topic is also very attractive. The health effect of cold exposure may be even stronger than, or at least as strong as, that of heat exposure, but it has received much less attention. I recommend this work to be accepted for publication as soon as possible.</p> <p>One literature for the authors' reference: Zheng et al. An epidemiological assessment of the effect of ambient temperature on the incidence of preterm births: Identifying windows of susceptibility during pregnancy. Journal of Thermal Biology, Volume 74, May 2018, Pages 201-207. This reference indicated that exposure to cold environment during pregnancy may increase the risk of preterm birth.</p>
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### VERSION 1 – AUTHOR RESPONSE

First reviewers comment:

Introduction: The authors should present a hypothesis/hypotheses of the study.

Reply:

As suggested, we have stated a hypothesis at the end of introduction. Page 5, line 26 in the manuscript with marked changes.

First reviewers comment:

As the focus of the article is related to cold exposure and chronic pain, the presentation of other health complaints and effects seems a bit arbitrary, and especially since they represent a relatively minor proportion of the manuscript (rather to provide support that the workers experience cold exposure).

Reply:

We agree that the aim to describe cold-related complaints is thematically disconnected from the main focus of the paper. We have therefore removed those parts. In the manuscript with marked changes: Abstract, page 2, line 8. Introduction, page 5, line 23. Methods, page 6, line 48 and page 7, line 3. Results: page 12, line 59 and onward. Discussion, page 15, line 21 and page 16, line 32. We have also removed the supplementary file.

First reviewers comment:

Methods, page 6, line 34: Please clarify what was the time perspective for the occurrence of chronic pain (e.g. during the past 12 months?). Further was the question concerning with pain formulated as persistent musculoskeletal pain?

Reply:

Chronic pain was defined as pain lasting 3 months or more, without a defined time frame such as i.e. for the past 12 months. It was asked for persisting or recurrent pain. We have included the original phrasing of the question concerning pain in the methods section. Page 6, Line 34 in the manuscript with marked changes.

First reviewers comment:

Methods, page 7, Line 28: (BMI) was calculated

Reply:

We thank the reviewer for pointing out our misspelling which is now corrected. Page 7, line 30 in the manuscript with marked changes.

First reviewers comment:

Methods: My major concern is related to confounding related to possible health conditions of the respondents. It is not clear to whether information from the mentioned extensive health questionnaire were used for adjusting for the examined association between reported cold exposure/sensations of cold and occurrence of chronic pain. One could speculate that there could be several conditions that could be related to chronic pain.

Reply:

We agree that existing health conditions can be confounders of the observed associations, especially for frequency of feeling cold. We could have used self-reported health or measures of psychological distress as additional confounders. However, both self-reported health and psychological health are difficult to disentangle from pain as they probably are risk factors for onset of chronic pain, but also highly influenced by existing pain. Further, this project does not have the variables on existing clinical conditions and can therefore not adjust for them. We have included the lack of adjusting for these conditions as a limitation in the discussion, see page 17 line 3 in the manuscript with marked changes.

First reviewers comment:

Furthermore, could the authors elaborate why insomnia was chosen as a confounder? It is probably related to experienced pain, but would need to associate with reported cold exposure/sensation of cold in order to be a true confounding factor.

Reply:

Insomnia is included as a possible confounder because it is a risk factor for chronic pain. In our study, we also see an association with cold exposure, as those working in a cold environment in this study have a lower prevalence of insomnia (Table 1). A large proportion of those working in cold environment in the Tromsø area work outdoors, and one could speculate that working outdoors will give more exposure to sun/daylight and consequently less insomnia, especially during the dark season.

First reviewers comment:

Furthermore, as a lifestyle factor, it is likely that the use of alcohol could also be a confounding factor.

Reply:

We have explored the possibility of alcohol use as a possible confounder. We have tried it as a continuous variable, in quartiles and as excessive drinking. There is a minimal difference which is on the level of the second decimal in the OR's, depending on how we adjust. We therefore suggest that alcohol is not included in the final analysis. However, if the reviewer or editor find it necessary, we will include alcohol in the analysis and change the figures accordingly. Please see the attached excel file for all the analyses.

First reviewers comment:

Results, line 24 onwards, Table 3. Rather than repeating the OR 1 for working less in cold you could indicate that this is the reference point.

Reply:

We have changed the table according to the reviewer's comment.

First reviewers comment:

Results, page 11, line 59 onwards, this sentence should be reformulated to improve clarity.

Reply:

We have rewritten this sentence which is now situated on page 11 line 58 and onward in the manuscript with marked changes.

First reviewers comment:

The discussion should aim at better distinguishing for the mechanisms between how the exposure (exposure of more than 25% to cold at work, feeling cold) relates to the effect (chronic pain). ..... Here it would also be important to distinguish between the acute and chronic effects of cold exposure (which are briefly mentioned in the introduction).

Lines 35 onwards: The suggested plausible mechanisms explaining the association between cold exposure and pain needs to be presented in a different way. "such as a change in electromyography, poorer energy-efficiency and increased muscle activity" do not explain the effects of cold on the neuromuscular system adequately.

Reply:

The first reviewer correctly points out that the Discussion chapter is vague on the physiological effects of cold. We have thus rewritten parts of the Discussion chapter with a stronger emphasis on the acute versus chronic effects of cold. Page 15, line 48 and onwards in the manuscript with marked changes.

First reviewers comment:

The authors should also acknowledge somewhere in the text that their question of chronic musculoskeletal pain could mean a variety of conditions (Treede et al. 2015). In addition, chronic pain thought to be of musculoskeletal origin, could reflect some other clinical condition. ....This could be mentioned

Reply:

We acknowledge that we do not know the origin of the pain. We have written in the discussion that many conditions can cause chronic pain or increase the risk of pain and that we cannot determine the origin of the pain. We thank the reviewer for pointing out the paper by Treede et al. 2015 which is now included as a reference. See Discussion, page 14 Line 25 in the manuscript with marked changes.

First reviewers comment:

Another, perhaps more plausible mechanism, would be that these workers have a clinical condition affecting their neural and musculoskeletal functions ..... The inability to take this into account in the study is a weakness.

Limitations: ..... I would add the lack of information of the health status of the respondents as a limitation. One obvious limitation is also the self-reported cold exposure, sensations of cold, as well as chronic pain, which are rather robust estimates (and cannot be validated) and also subject to recollection bias.

Reply:

Please also see reply above. We have included the lack of adjusting for clinical conditions as a weakness in the study.

We acknowledge the challenges with self-reported data for our exposure and outcome. The challenges of cold as an exposure measure, whether as temperature or as self-reported experience, are discussed in the Discussion chapter (page 15 line3 in the manuscript with marked changes). As pain is commonly defined as a subjective experience, asking the participants is our best tool, and thus we have to accept the bias implied. We were uncertain whether the reviewer wished us to include the nature of our self-reported data as a source of recall bias and thus weakness of the study. Since pain studies in general have the challenge of an outcome based on self-reported data, we found it unnatural to explicitly state this in our paper. However, if the reviewer or editor find it necessary, we will include this in the discussion chapter.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Tiina Ikkäheimo University of Oulu, Center for Environmental and Respiratory Health Research, Oulu, Finland
<b>REVIEW RETURNED</b>	18-Oct-2019
<b>GENERAL COMMENTS</b>	I consider that the authors have addressed the issues that I raised while reviewing this manuscript.