Prevalence and Risk Factors of Multi-type Post-COVID Pain in a Cohort of Previously Hospitalized COVID-19 Survivors: A Danish Cross-Sectional Survey

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--Manuscript Draft--

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Abstract:	This population-based study investigated the prevalence of de novo, multi-type, post-COVID pain and its associated risk factors in previously hospitalized COVID-19 survivors. The nationwide, cross-sectional study included a cohort of Danish residents previously hospitalized due to SARS-CoV-2 infection between March 2020 and December 2021. Demographic data, pre-existing medical comorbidities, previous pain-related symptoms, medication use for pain management, pain intensity (4-point scale), and development of de novo, multi-type, post-COVID pain were collected by a self-reported survey distributed via e-Boks (a secured national digital mail system used in Denmark to provide public information to residents). The sample comprised 4,712 previously hospitalized COVID-19 survivors (48.6% women, mean age: 60.1±15.6 years). At the time of the study (21±6 months after hospitalization), 18.0% (847) reported the presence of de novo, multi-type, post-COVID pain, and 38.6% of any pain. A multivariate analysis revealed that female sex (OR 1.711, 95%CI 1.444-2.023), higher body mass index (OR 1.032, 95%CI 1.019-1.045), intensive care unit admission (OR 1.597, 95%CI 1.324-1.926), previous history of whiplash (OR 2.471, 95%CI 1.004-6.081), anxiety (OR 3.626, 95%CI 1.335-9.708), and younger age (OR 0.982, 95%CI 0.976-0.987) were factors associated with development of de novo, multi-type, post-COVID pain. High income (OR 0.635, 95%CI 0.494-0.817) and high educational level (OR 0.774, 95%CI 0.609-0.984) were protective factors. In conclusion, multi-type pain as a de novo post-COVID symptom was present in 18.0% of previously hospitalized COVID-19 survivors more than one year after hospital discharge and as such can be considered as adding to the global burden of chronic pain.

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Date 19 December 2023

Dear Editor-in-chief for Journal of Pain,
Dr. Tonya Palermo

We hereby submit the manuscript entitled:

Prevalence and Risk Factors of Widespread Post-COVID Pain in a Cohort of Previously Hospitalized COVID-19 Survivors: A Danish Cross-Sectional Survey

for your consideration of publication as an original article in Journal of Pain.

Authors: Brian D. Ebbesen, Rocco Giordano, Jakob Nebeling Hedegaard, Juan A. Valera Calero, César Fernández-de-las-Peñas, Bodil Steen Rasmussen, Henrik Nielsen, Berit Schiøttz-Christensen, Pernille Lykke Petersen, Matteo Castaldo, Lars Arendt-Nielsen

Synopsis:
The prevalence of long-term pain post-COVID-19 (post-COVID pain) is well established. However, due to the heterogeneity of existing literature, the prevalence of post-COVID pain is still not fully elucidated. Depending on the pain assessment of individuals suffering from post-COVID pain, the pain can be local or widespread, with the latter potentially resembling nociplastic phenotype features with a possibility of pain chronification.

In this manuscript, we map the prevalence of de novo widespread post-COVID pain in 4,712 previously hospitalized COVID-19 survivors. Data is collected via an online questionnaire, registered data from medical hospitalization journals, and socio-economic data.

Interestingly, with a follow-up period over 21 months after the initial hospitalization, we find that 38.6% report pain, and 19.3% report de novo widespread post-COVID pain. Additionally, female sex, younger age, higher body mass index, and a previous history of whiplash and anxiety are risk factors associated with the development of de novo widespread post-COVID pain. A high income and educational level are considered protective factors.

These results provide a unique insight into how previously hospitalized COVID-19 survivors are prone to the development of painful symptoms long after having recovered from a SARS-CoV-2 infection. We believe these results will be relevant to the readers of Journal of Pain, as they elucidate the need for additional attention towards this new pain group.

Technical information:
The study was registered and approved by the Danish Data Protection Agency (approval #F2022-004) in compliance with the Danish Health Care Act (approval #2022-056227) and has been granted access to sensitive data of residents from the Danish Health Data Agency and Statens Serum Institute (approval #FSEID-00006572).

Anonymized questionnaire data relevant to the present work will be available upon request to the corresponding author. Due to the legal limitations of the Danish Health Act, § 42, subsection 1,

registered data is subject to sensitive microdata that must not be exported or shared from the secure research server from Statistics Denmark, used in the current research project. This concerns medical journal records and socio-economic data.

All authors were involved in designing the study or discussing, revising, and approving the manuscript. The authors have no conflicts of interest.

Yours faithfully and on behalf of the authors,

Lars Arendt-Nielsen

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Date 30 April 2024

Dear Professor Tonya Palermo,

JPAIN-D-23-01009
Title: Prevalence and Risk Factors of Multi-type Post-COVID Pain in a Cohort of Previously Hospitalized COVID-19 Survivors: A Danish Cross-Sectional Survey

Authors: Brian Duborg Ebbesen, Rocco Giordano, Jakob Nebeling Hedegaard, Juan Antonio Valera Calero, César Fernández-de-las-Peñas, Bodil Steen Rasmussen, Henrik Nielsen, Berit Schiøttz-Christensen, Pernille Lykke Petersen, Matteo Castaldo, Lars Arendt-Nielsen

Thank you for providing your extensive help to improve the manuscript. The points raised are very appropriate and highly appreciated. We have been working on these data for almost a year and hence it is evident to us how data were analysed and reported. We are therefore thankful for your and the reviewers' help in explaining the findings and characterization in a much better and more understandable way.
We have to our best abilities addressed all points raised by you and the reviewer.

All the changes are marked with red in the manuscript and tables. Looking forward to your final decision. On behalf of the authors

Lars Arendt-Nielsen,
Prof., dr. med., ph d

We thank you for the very constructive review of our manuscript to strengthen the overall communication and validity of the research project.

Comment 1.1.
It could be interesting to include the question “Does pain affect your everyday life” to help to understand the potential impact of de novo widespread pain in your patient population.

Response 1.1.
We added to the manuscript the results from this question along with the wording ‘Even if the pain has now resolved, did your pain affect your daily life before it disappeared?’. The results clearly show that the participants with post-COVID muscle pain have impacted quality of life. Among others, Nicholl et al. (2009) likewise showed in their systematic review that widespread pain affects the quality of life, particularly in those with new-onset chronic widespread pain (similar to the long-COVID pain population). Also, psychosocial factors (e.g. anxiety) affect the quality of life which is in line with the results of the present study and suggested as possible risk factors for the development of post-COVID muscle pain (see Table 2). This is further supported by the IASP ICD-11 classification of chronic widespread pain, where emotional distressers such as anxiety and depressed mood are associated with widespread pain (IASP ICD-11, 2024). The results have been added to Table 2 and the following text added to the results section:

“The quality of life information was collected for all responders with pain (**Table 2**) by the question: ”Even if the pain has now resolved, did your pain affect your daily life before it disappeared?”. The responses showed that 88.9% of the COVID-19 survivors with current muscle pain had reduced quality of life compared to those without muscle pain ($p<0.001$) while 73.9% of individuals with previous pain, but with post-COVID muscle pain resolved, reported reduced quality of life (**Table 2**).”.

Comment 1.2.
The definition of de novo widespread pain is crucial in interpreting the results and implications of this study and still requires further clarity. There are some discrepancies between how this is defined in the last paragraph of the introduction and in the methods. In the introduction, it states 'one or more pain conditions reflecting pain from more regions', whereas in the methods it states 'new painful symptoms in regions not involved prior to acute infection more than six months post-infection' and 'two different types of pain conditions and pain in more regions'.

Response 1.2.
When we designed the questionnaire to be distributed to the approx. 600,000 citizens, it was unfortunately not possible to include pain drawings so we had to find surrogates to estimate the distribution and pattern of the muscle pain. The definition of chronic widespread pain as suggested by Wolfe et al. (2016) and the ICD-11 introduction of chronic widespread pain

definition (IASP ICD-11, 2024) obviously are not, as you correctly hinted, the most appropriate wording to be used in the present paper focusing on self-reported data. We have, according to your input, changed the term in our paper to **"de novo multi-type pain**". We have created a diagram to be added as supplementary figure 1 explaining the coding on how we collected data about the number of pain types reported by the participants. For further details about Figure 1, please refer to response 1.3, below. Our definition of **de novo multi-type pain** is characterized by participants reporting more than one pain type. We have therefore analyzed the number of de novo pain types (1, 2, …, 11+) reported (Table 1). Data show that 93.4%% of the responders reported more than one de novo post-COVID pain type. The corrections on terminology have been implemented throughout the manuscript and fit with our previous reports that post-covid muscle pain can be experienced as many types of pain in different regions such as in the neck, back, leg, and arm (Fernández-de-Las-Peñas C et al., 2022). In the results section we have added:

"Of those, 18.0% (847) reported the de novo pain to be of multi-type character. Of the participants reporting de novo post-COVID pain, 93.4% reported more than one pain type (Table 1). Further, 76.8% reported 3 or more types of pain.".

Comment 1.3.

Please elaborate on the measurement and coding of the de novo widespread pain variables to enhance reader understanding and transparent reporting. To adequately convey the coding the reader needs to know how many regions of bodily pain you are using from the survey (noting that the survey responses contain a mixture of regions of pain and pain conditions) and the definition for assignment of yes/no to whether the patient developed de novo widespread pain.

Response 1.3.

To visualize the pain group stratification and de novo multi-type characterization a new diagram is prepared including the relevant questions from the survey along with possible answers. This has now been added to the supplementary material (Figure 1). Further, this stratification has been elaborated on in the methods section where the following is added:

"Participants were stratified into four pain groups: (Group 1) No pain pre- or post-COVID, (Group 2) pre-COVID pain but no post-COVID pain, (Group 3) no pre-COVID pain but post-COVID pain, and (Group 4) both pre- and post-COVID pain. For a full overview of this group characterization, please refer to Supplementary Figure 1. Participants were asked if they had a pre-COVID diagnosis (from a medical doctor) of long-term pain. If not, they would fall into either group 1 or 3, and if yes group 2 or 4. Groups 2 and 4 were asked about 16 types of long-term pain conditions as well as a free-text option, and other previous diseases that included 17 pre-defined diseases and a free-text option. To further stratify the groups, the participants were asked if they had developed post-COVID pain. Participants with pre-COVID pain were asked if they had developed any new pain symptoms. Groups 3 and 4 were asked about the new post-

COVID pain types development. These participants were stratified into either ‘no multi-type pain. when reporting one pain type or ‘multi-type pain’ when reporting more than one new pain type.”.

Comment 1.4.

Clarify how new conditions and/or symptoms were identified, as long-term diagnosis pre-COVID (mixture of diagnoses and pain associated with different regions) and new pains post-COVID (pain in different regions) answers are different.

Response 1.4.

The focus of this study is the development of de novo post-COVID pain. Referring to the diagram mentioned in response 1.3, the question about other disease diagnoses is used in the calculation of potential risk factors for Table 3. This is also the case with the pre-COVID question about previous long-term pain conditions. Hence, the question concerning post-COVID de novo pain development is different from those of pre-COVID questions. We have addressed the inherited limitations of self-reported questionnaire data in the limitations section:

“As it has been anticipated that all answered the questions to their best abilities, misunderstandings could occur when asked about new pain caused by the COVID-19 infection. Newer painful events (back pain, knee pain, or neck pain) occurring after the infection (e.g. by accidents) could directly or indirectly influence the responses.”.

Comment 1.5.

Please clarify how you know that this was more than six months following acute infections, as the duration of the new symptoms does not appear to have been asked (although you did ask how long before it got better).

Response 1.5.

Despite the limitation of self-reported data we have tried to highlight to the participants that the new pain must have followed and persisted after the initial COVID-19 infection and not something more recently acquired (e.g. by an accident) (see also response. 1.4). It is however not possible to rule out that some responses could be caused by newer events after the COVID infection. This has now been added to the limitations (see also response 1.4).

Further, when the questionnaire was sent out and participants at least 8 months (on average 21.0 months) after the initial COVID infection, only very few participants (3.4% of those with post-COVID pain) indicated that their pain arising after COVID had disappeared by the time of the survey. The following is added to the limitations:

"When the questionnaire was sent out to participants asking about the new pain development, it was at least 8 months (on average 21.0 months) after the initial COVID infection and hence it can be termed at least long-term. However, if participants had a pre-COVID pain condition, there could be a possibility that the pain was reported as a new pain simply due to a worsening of existing pain. It is known that in up to 50% of post-COVID patients, a worsening of pre-COVID existing muscle pain has been reported (Fernández-de-las-Peñas et al., 2022)".

Comment 1.6.
Please clarify how many symptoms was needed to be classed as widespread pain.

Response 1.6.
De novo post-COVID, multi-type pain is defined as participants reporting more than one pain type in the post-COVID pain question from the Supplementary Figure 1 diagram. The following is added to the methods section:

"Groups 3 and 4 were asked about the new post-COVID pain types development. These participants were stratified into either 'no multi-type pain. when reporting one pain type or 'multi-type pain' when reporting more than one new pain type.".

Comment 1.7.
Why was muscle pain excluded from the multivariate model?

Response 1.7.
Muscle pain was the initial focus of interest in the current study and all 907 participants in the pain group reported muscle pain. Muscle pain was the outcome factor. Thus, we used muscle pain as the dependent variable in the multivariate model, therefore it is not reported along with the other predictor variables. The following clarification has been elaborated in the method section:

"Muscle pain was the only variable not included as participants not having muscle pain was the primary condition, thus muscle pain was the outcome factor and dependent variable in the multivariate model.".

References relevant to this response letter.

Nicholl BI, Macfarlane GJ, Davies KA, Morriss R, Dickens C, McBeth J. Premorbid psychosocial factors are associated with poor health-related quality of life in subjects with new onset of chronic widespread pain - results from the EPIFUND study
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Wolfe F, Clauw DJ, Fitzcharles M, Goldenberg DL, Häuser W, Katz RL et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*, 46(3), 319-329, 2016. https://doi.org/10.1016/j.semarthrit.2016.08.012

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Highlights

- Almost a fifth of previously hospitalized COVID-19 survivors suffer from new pain
- De novo multi-type post-COVID pain persists for at least 21 months on average
- Risk factors for the development of post-COVID pain are multifaceted
- Post-COVID pain phenotype could resemble pain patterns of nociplastic conditions
- De novo post-COVID pain is only one of multiple pain symptoms

Prevalence and Risk Factors of Multi-type Post-COVID Pain in a Cohort of Previously Hospitalized COVID-19 Survivors: A Danish Cross-Sectional Survey

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Number of figures and tables: 4 tables and 3 figures

Abstract

This population-based study investigated the prevalence of *de novo, multi-type,* post-COVID pain and its associated risk factors in previously hospitalized COVID-19 survivors. The nationwide, cross-sectional study included a cohort of Danish residents previously hospitalized due to SARS-CoV-2 infection between March 2020 and December 2021. Demographic data, pre-existing medical comorbidities, previous pain-related symptoms, medication use for pain management, pain intensity (4-point scale), and development of *de novo, multi-type,* post-COVID pain were collected by a self-reported survey distributed via e-Boks (a secured national digital mail system used in Denmark to provide public information to residents). The sample comprised 4,712 previously hospitalized COVID-19 survivors (48.6% women, mean age: 60.1±15.6 years). At the time of the study (21±6 months after hospitalization), 18.0% (847) reported the presence of *de novo, multi-type,* post-COVID pain, and 38.6% of any pain. A multivariate analysis revealed that female sex (OR 1.711, 95%CI 1.444-2.023), higher body mass index (OR 1.032, 95%CI 1.019-1.045), intensive care unit admission (OR 1.597, 95%CI 1.324-1.926), previous history of whiplash (OR 2.471, 95%CI 1.004-6.081), anxiety (OR 3.626, 95%CI 1.335-9.708), and younger age (OR 0.982, 95%CI 0.976-0.987) were factors associated with development of *de novo, multi-type,* post-COVID pain. High income (OR 0.635, 95%CI 0.494-0.817) and high educational level (OR 0.774, 95%CI 0.609-0.984) were protective factors. In conclusion, multi-type pain as a *de novo* post-COVID symptom was present in 18.0% of previously hospitalized

COVID-19 survivors more than one year after hospital discharge and as such can be considered as adding to the global burden of chronic pain.

Perspective

The study investigates the prevalence of de novo, multi-type, post-COVID pain in previously hospitalized COVID-19 survivors. This article presents potential risk factors associated with developing new pain symptoms. The results will contribute to understanding the possibility of predicting post-infectious pain from COVID-19 for future analysis.

Short-running title: Post-COVID Pain after Hospitalization

Keywords: COVID-19, multi-type pain, long-term pain, post-COVID, risk factors, hospitalization.

Introduction

Long-term pain has been reported to be prevalent in individuals who survived the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and, in addition to several other symptoms, is termed post-COVID-19 condition or long-COVID[19,22,39,44]. The reported prevalence of post-COVID pain in previously hospitalized patients by coronavirus disease, 2019 (COVID-19) is highly heterogeneous and depends on the study design, the follow-up period, and the pain definitions used. The prevalence of post-COVID pain during the first six months has been estimated to be between 4.6% and 23.6%[20]. Peter et al. identified a "musculoskeletal pain cluster" in up to 16% of individuals with post-COVID symptoms[48]. However, the prevalence rate of post-COVID

pain can reach 60% in some studies depending on the time of assessment[3,9,34,55]. Hence, the prevalence of post-COVID pain is not fully elucidated and depends e.g. on time of observation after the infection and severity (hospitalized versus non-hospitalized).

Most studies investigating post-COVID pain have included relatively small cohorts of previously hospitalized COVID-19 survivors[3,9,34,55]. A large cohort study including 1,969 previously hospitalized COVID-19 survivors found post-COVID musculoskeletal pain symptoms related to the musculoskeletal system (i.e., post-COVID musculoskeletal pain) in 45% of the patients eight months after hospital discharge[18]. Large-scale population-based epidemiological studies focusing specifically on post-COVID pain are scarce[2]. Two nationwide, large cohort surveys, conducted in Denmark analyzed the overall presence of post-COVID symptoms; however, these were non-hospitalized cohorts[57,66] and based only on data collected during the first year of the pandemic in 2021.

The prevalence of post-COVID pain depends on whether the pain is assessed as a local or widespread problem[3,9,20,34,48,55]. Data suggests that a subgroup of individuals with post-COVID pain develop a multi-type pain pattern like fibromyalgia syndrome[25]. This suggests that some post-COVID pain patients may exhibit a pain-related phenotype characterized by nociplastic features involving pain sensitization[21]. However, no studies have specifically investigated the development of *de novo* (a new pain symptom appearing after the SARS-CoV-2 infection) multi-type post-COVID pain in a large cohort of previously hospitalized COVID-19 survivors. In addition, the possible risk factors for developing this specific disabling pain symptomatology are largely unknown.

The aims of this nationwide, population-based study were 1) to investigate the prevalence of *de novo, multi-type,* post-COVID pain (defined as more than one pain type) in a large cohort of previously hospitalized COVID-19 survivors, and 2) to investigate risk factors associated with the development of this specific pain symptomatology.

Methods

Study design

This nationwide, exploratory, cross-sectional, questionnaire-based survey included a cohort of residents from Denmark who were previously hospitalized due to an acute SARS-CoV-2 infection from March 2020 to December 2021. In Denmark, mass testing via reverse transcription-polymerase chain reaction (RT-PCR) was used in the management of the COVID-19 pandemic. Data was handled by the COVID-19 Surveillance System at Statens Serum Institut to control how the COVID-19 pandemic has developed over time in Denmark[60]. The current cohort study was registered and approved by the Danish Data Protection Agency (approval #F2022-004) in compliance with the Danish Health Data Act (approval #2022-056227) and has been granted access to sensitive data of residents from the Danish Health Data Agency and Statens Serum Institut (approval #FSEID-00006572). The extent of participation in the survey and the rights of the participants were explained in a preceding information letter distributed with the questionnaire and, hence, informed consent was obtained from all participants before starting data collection. According to Danish legislation, approval from the Scientific Ethics Committee was not required.

Participants

From a population of 593,741 adult residents registered by the COVID-19 surveillance system received our questionnaire. A total of 137,260 completed the full questionnaire. Of those, a total sample of 4,833 residents had previously been hospitalized. All participants had been previously hospitalized and registered by the COVID-19 Surveillance System at Statens Serum Institut because of a positive RT-PCR test between 1 March 2020 and 31 December 2021. However, 121 participants were

excluded due to erroneous data entries (i.e., negative or unrealistic values for demographic features, or microdata issues) or erroneous administrative hospitalization data. **Figure 1** depicts the final sample size of 4,712.

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Figure 1 near here

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Participants were included in the invitation list if they: (1) were ≥18 years old, (2) had a confirmed SARS-CoV-2 infection (RT-PCR+) and had been hospitalized due to the acute infection, (3) consented to participate in the study, (4) were resident in Denmark with a valid social security number, (5) had access to the official, secure, national, digital mailing system (e-Boks), in use in Denmark, at the time of data collection[14], and (6) received pre-defined clinical COVID-19 codes (International Statistical Classification of Diseases and Related Health Problems; ICD-10) as the main diagnosis during the hospital admission. Survey respondents were excluded if they did not complete the questionnaire or if reported demographic data were considered outliers. The cohort included individuals infected during the period in Denmark with circulating SARS-CoV-2 of the historical Wuhan strain, Alpha, or Delta variants, but not the Omicron variant[61].

Data Collection Procedure

An online questionnaire constructed for data collection was distributed to the participants in September 2022 via e-Boks. Data collection lasted five weeks with a reminder distributed after two weeks. The study focused on *de novo, multi-type,* post-COVID pain defined as pain compatible with the diagnosis of chronic primary musculoskeletal pain according to the International Association for the Study of Pain

(IASP)[47] with a duration longer than six months that had started after SARS-CoV-2 infection. The *de novo* post-COVID pain was acknowledged if the participants' pre-SARS-CoV-2 infection had no pain at all or developed specific new painful symptoms more than six months post-infection. Multi-type post-COVID pain could reflect a nociplastic phenotype suggesting an involvement of pain sensitization mechanisms[21] similar to patients with fibromyalgia[53,54]. The manifestation of multi-type pain symptomatology involved participants reporting two or more types of pain.

The questionnaire, found in the supplementary materials, collected the following self-reported data: (1) demographic data (gender, age, height, weight) as categorical and continuous variables; (2) previous medical comorbidities diagnosed by a medical doctor (categorical); (3) preexisting long-term pain conditions (categorical); (4) development of *de novo, multi-type,* pain after hospitalization by SARS-CoV-2 infection (ordinal and analyzed as continuous in the regression model); (5) medication use for previous pain management (binary and categorical); and (6) intensities of pain in general and for *de novo, multi-type,* pain (4-point Likert scale) (categorical). All variables have been analyzed according to their data variable type. Medical comorbidities were based on the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) platform that provides a framework of clinically relevant comorbidities concerning infectious diseases including COVID-19[29].

Participants were stratified into four pain groups: (Group 1) No pain pre- or post-COVID, (Group 2) pre-COVID pain but no post-COVID pain, (Group 3) no pre-COVID pain but post-COVID pain, and (Group 4) both pre- and post-COVID pain. For a full overview of this group characterization, please refer to **Supplementary Figure 1**. Participants were asked if they had a pre-COVID diagnosis (from a medical doctor) of long-term pain. If not, they would fall into either group 1 or 3, and if yes group 2 or 4.

Groups 2 and 4 were asked about 16 types of long-term pain conditions as well as a free-text option, and other previous diseases that included 17 pre-defined diseases and a free-text option. To further stratify the groups, the participants were asked if they had developed post-COVID pain. Participants with pre-COVID pain were asked if they had developed any *new* pain symptoms. Groups 3 and 4 were asked about the new post-COVID pain types development. These participants were stratified into either 'no multi-type pain' when reporting one pain type or 'multi-type pain' when reporting more than one new pain type.

Experts across Denmark, Spain, Italy, the UK, and Switzerland reviewed the questionnaire. In this way, it was ensured that the relevant comorbidities were included to ensure post-COVID pain-related validity. To avoid misinterpretation, the questionnaire was tested in selected target populations before the distribution of the actual questionnaire. The phenotyping was not identified; thus, we presume that *de novo, multi-type,* pain would be of musculoskeletal origin; but neuropathic components cannot be excluded.

Data about RT-PCR tests were acquired from Statens Serum Institut, and data about hospital admissions were acquired from the Danish Health Data Agency. Hospitalization time was defined as the first hospital admission added to any other hospital admission not separated by more than two calendar days from the first hospital admission because of COVID-19. Time from hospital was defined as the first day of the first hospital admission to questionnaire data collection time.

Registered socio-economic data was included from Statistics Denmark. Three main socio-economic influential factors were included in the present study: 1) personal income as an average of total income three years before data collection, 2) International

Standard Classification of Education (ISCED)[30] defined educational level, and 3) the current living status of each participant.

Statistical Analysis

All data were stored and merged in a secure Research Electronic Data Capture (REDCap) server at Statistics Denmark before initiating the statistical analysis. All are presented as means (standard deviations, SD), percentages as appropriate, and as count for figures. Proportions and means between patients with/without *de novo* post-COVID pain were compared with McNemar's chi-squared test and paired Student t-test, respectively. Multivariate logistic regressions, including all the variables, were performed to identify those associated with *de novo, multi-type*, post-COVID pain development. Muscle pain was the only variable not included as participants not having muscle pain was the primary condition, thus muscle pain was the outcome factor and dependent variable in the multivariate model. To account for individual covariate contributions, each covariate was analyzed independently. A priori, the level of significance was set to 0.05. To avoid potential bias from multicollinearity effects in the multivariate regression model, we calculated the global conditioning number (4.272) for the regression model variables. Further, the variance inflation factor (VIF) for individual predictors was between 1.07 and 1.80. Both the global condition number and the VIF were considered well beneath the limits for inducing potential multicollinearity effects in the multivariate regression analysis[5].

Results

The final sample consisted of 4,712 previously hospitalized COVID-19 survivors (48.6% women, mean ± SD age: 60.1 ± 15.6 years). The response rate was 23.9%, which is in alignment with similar nationwide health-related studies ranging from 20% to 30%[33].

The mean height in the post-COVID pain group and the non-pain group was 1.71 m (SD: 0.09 m) and 1.73 meters (SD: 0.10 m), respectively. Mean weight was 87.4 kg (SD: 21.2 kg) and 85.9 kg (SD: 19.6 kg), respectively. Finally, the mean post-COVID pain-group BMI was 26.2 kg/m^2 (SD: 10.9 kg/m^2) and the non-pain group BMI was 25.3 kg/m^2 (SD: 9.8 kg/m^2).

Prevalence of Multi-type Post-COVID Pain in Hospitalized COVID-19 Survivors

Participants were assessed at least one year after (mean: 21.0, SD: 6.0 months) hospital admission. Overall pain prevalence was reported by 38.6% (1,819). At the time of the survey, 19.3% (907) reported *de novo* post-COVID pain. Of those, 18.0% (847) reported the *de novo* pain to be of multi-type character. Of the participants reporting *de novo* post-COVID pain, 93.4% reported more than one pain type (**Table 1**). Further, 76.8% reported 3 or more types of pain. *De novo, multi-type,* post-COVID pain was described as moderate in intensity by 49.4% of participants, whereas 26.1% of participants reported that pain was severe and 4.9% described the pain as very severe. The present study showed that in participants reporting *de novo, multi-type,* post-COVID pain, 17% of the cases additionally reported other long-term pain conditions (e.g., joint pain) prior to the infection. Also, 31.2% of the participants were taking analgesics to control their post-COVID pain (**Table 2**).

Table 2 depicts demographic and clinical data in hospitalized COVID-19 survivors developing *de novo* post-COVID pain (19.3%) and in those who did not develop *de novo* post-COVID pain (80.7%). Participants developing *de novo* post-COVID pain were younger ($P<0.001$) and had a higher BMI ($P<0.017$) than those who did not. A significant proportion of participants with *de novo* post-COVID pain were females ($P<0.001$). Additionally, 27.5% of the participants developing *de novo* post-COVID pain were admitted to the intensive care unit (ICU) in contrast to the 21.1% of individuals who did

not develop post-COVID pain (P<0.001). There was no difference (P=0.46) in the length of hospitalization between participants who developed *de novo* post-COVID pain (2.14 days, IQR0.25-6.86) and those who did not (2.24 days, IQR0.32-6.17). The time from hospital admission to the survey response did not differ between the *de novo* and the non-*de novo* group (21.0 months versus 21.08 months, respectively, P=0.25).

The group developing *de novo* post-COVID pain reported a higher presence of some specific previous long-term pain conditions including headache (4.1% vs. 2.0%, P=0.001), sore throat (2.5% vs. 1.2%, P=0.004), back pain (8.2% vs. 6.0%, P=0.019), abdominal pain (3.0% vs. 1.4%, P=0.002), neck/shoulder pain (6.8% vs 3.6%, P<0.001), chest pain (3.1% vs 1.4%, P=0.002), whiplash (1.9% vs 0.7%, P=0.003), joint pain (5.8 vs 3.7%, P=0.005), and muscle pain (7.2% vs 3.9%, P<0.001) compared to the group who did not develop *de novo* post-COVID pain. However, the overall percentage of individuals with previous pain conditions was not significantly different between participants developing *de novo* post-COVID pain and those who did not (17.0% vs. 16.1%, P=0.515, **Table 2**). Medication intake for those reporting one or more previous long-term pain conditions was higher in the cohort developing *de novo* post-COVID pain than in the cohort that did not develop *de novo* post-COVID pain (53.9% vs 24.3%, P<0.001).

Overall, the presence of previous medical comorbidities was comparable between hospitalized COVID-19 survivors who developed *de novo* post-COVID pain and those who did not. Pre-infection depression (P=0.006), anxiety (P<0.001), and stress (P<0.001) were more prevalent in the cohort who developed *de novo* post-COVID pain (**Table 2**).

The quality of life information was collected for all responders with pain (Table 2) by the question: ”Even if the pain has now resolved, did your pain affect your daily life before it disappeared?”. The responses showed that 88.9% of the COVID-19

survivors with current muscle pain had reduced quality of life compared to those without muscle pain (p<0.001) while 73.9% of individuals with previous pain, but with post-COVID muscle pain resolved, reported reduced quality of life (**Table 2**).

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Table 1 near here

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Table 2 near here

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Risk Factors Associated with Multi-type Post-COVID Pain in Hospitalized Participants

The multivariate analysis revealed that, after adjusting for all variables, younger age (OR 0.982, 95%CI 0.976-0.987, P<0.01), female gender (OR 1.711, 95%CI 1.444-2.023, P<0.001), body mass index (OR 1.032, 95%CI 1.019-1.045, P<0.001), ICU admission (OR 1.597, 95%CI 1.324-1.926, P<0.001), and previous history of whiplash (OR 2.471, 95%CI 1.004-6.081, P<0.05) and anxiety (OR 3.626, 95%CI 1.355-9.708, P<0.05) were factors associated with an increased risk of developing *de novo, multi-type,* post-COVID pain in our cohort of previously hospitalized COVID-19 survivors (**Table 3**). Conversely, the presence of previous cardiac disease (OR 0.226, 95%CI 0.059-0.863, P<0.05) and chronic obstructive pulmonary disease (OR 0.166, 95%CI 0.033-0.835, P<0.05) were protective factors for the development of *de novo, multi-type,* post-COVID pain (**Table 3**). Additionally, the analysis of socio-economic variables showed that medium (OR 0.784, 95%CI 0.638-0.964, P<0.05) and high (OR 0.744, 95%CI 0.609-

0.984, P<0.05) educational levels were also protective factors, as well as high income (OR 0.635, 95%CI 0.494-0.817, P<0.001).

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De novo, multi-type, Post-COVID Pain Stratified on Time and SARS-CoV-2 Variant

In **Table 4** the cohort of 4,489 COVID-19 survivors was stratified in time intervals. Because of missing time delay data 223 participants were excluded from this analysis. For each stratified segment, the parenthesis depicts the percentage of individuals reporting a development of *de novo* post-COVID pain. Here, 146 of 974 (15%) participants reported *de novo* pain 8-11 months following hospital admission for COVID-19, 121 of 647 (18.8%) after 12-17 months, while 413 of 2,017 (20.5%), and 161 of 867 (18.7%) participants reported *de novo* pain after 18-23 and 24-32 months, respectively. SARS-CoV-2-variant stratification showed that 592 of 2,971 (20%) participants reported *de novo* pain after recovering from the historical strain, 79 of 450 (17.6%) from the Alpha variant, and 170 of 1,084 (15.7%) from the Delta variant. **Figure 2** depicts the number of first hospitalizations from March 2020 to December 2021 with peaks for each SARS-CoV-2 strain during the winter periods. The median length of hospitalizations shows a trend of correlation to the number of hospital admissions with a slight timewise delay from the peaks of hospital admissions. The number of hospitalizations is recorded upon admission date while the median duration of hospitalizations is recorded on the date of hospital discharge, which might explain the time delay.

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Discussion

This study investigated the prevalence of *de novo,* multi-type, post-COVID pain in previously hospitalized COVID-19 survivors in Denmark. Prevalence of pain was 38.6% 21 months after hospital admission. A total of 18.0% reported *de novo,* multi-type, post-COVID pain and almost 80% of those *de novo, multi-type,* classified their pain as moderate or severe and 17% of the cases reported a painful condition prior to hospitalization. Younger age, female gender, higher body mass index (BMI), ICU admission, history of whiplash, and history of anxiety were factors associated with the development of *de novo,* multi-type, post-COVID pain.

Multi-type, Post-COVID Pain in Previously Hospitalized COVID-19 Survivors

The possibility that *de novo,* multi-type, post-COVID pain can develop as one of several symptoms characterizing long-COVID agrees with previous studies[3,9,18,34,55]. The current study focused on the development of *de novo, multi-type,* post-COVID pain, to differentiate it from most previous studies focusing on regional pain conditions[3,9,18,34,55]. The multi-type post-COVID pain resembled in some cases individuals with e.g., fibromyalgia [7,25,53] with pain in different locations, which requires tailored treatment[21] suggesting the pain might be of widespread nature.

Risk Factors Associated with Multi-type Post-COVID Pain

Age and gender.

Associations of age with overall post-COVID-19 symptoms are not evident from previous studies[10,32]. Pooled data from over 800,000 COVID-19 survivors in different meta-analyses evaluating prognostic risk factors for post-COVID-19 symptoms did not confirm any age associations[41,45]. Different pain symptoms have been associated with both older and younger age[31,64]. Older age is considered a risk factor for both widespread pain and musculoskeletal chronic pain in general[67], widespread post-COVID pain[51], and for the severity of COVID-19[68]. The present study may indicate that for the more severely affected previously hospitalized participants, younger age, and female gender could be a risk factor[4,34,65].

Female gender is associated with a higher risk of developing overall post-COVID-19 symptoms after hospitalization[41,45]. Savin et al. found an incidence of a new diagnosis of fibromyalgia syndrome in 15% of COVID-19 survivors, and female gender was a risk factor (OR 3.65, 95%CI 1.41-8.9)[54]. Females reporting a higher prevalence of widespread post-COVID pain is in accordance with the fact that chronic widespread pain is overall more prevalent in females than in males[56]. Biological, psychological, and sociocultural gender differences may contribute to this overall female predominance in COVID-19-related pain[23,26].

Body Mass Index

Higher BMI was associated with the development of *de novo, multi-type,* post-COVID pain contrary to Karaarslan et al. who, in a smaller sample, found no association between higher BMI and higher risk of post-COVID arthralgia and myalgia[35]. Higher

BMI has been associated with the overall development of post-COVID-19 symptoms[45] and associated with more severely affected individuals[1]. In general, obesity has been associated with the development/presence of widespread pain symptoms[12].

Intensive Care Unit Admission.

Intensive Care Unit (ICU) admission was another factor related to the presence of *de novo, multi-type,* post-COVID pain in our study. Leite et al. likewise observed that patients admitted to the ICU reported a higher prevalence of persistent pain (33.9%) than those in hospital wards (27.1%)[38]. It is well known that ICU admission can generate Post-Intensive Care Syndrome (PICS) in up to 60.8% of patients[27,51], where 28% to 77% also report post-ICU pain[42]. Up to 70% of ICU survivors suffer from at least one PICS-related impairment (e.g., pain), which can persist 5–15 years after hospital discharge[13]. For the COVID-19 participants referred to ICU, the relative contributions and importance of COVID-19 infection and ICU hospitalization for the development of post-COVID pain cannot be estimated.

Pre-existing Comorbidities

Pre-existing cardiac disease or chronic obstructive pulmonary diseases did not prime for the development of *de novo, multi-type,* post-COVID pain although leading to more severe COVID-19 and higher mortality[49]. Evidence also supports that subjects suffering from previous respiratory diseases do not represent a risk factor for COVID-19 susceptibility nor cause a more severe disease[24]. We have previously shown that having myalgia during hospitalization is a risk factor for long-COVID pain[18], which could be a proxy for the severity of the infection as cytokines are prominent drivers of musculoskeletal pain[28] and the current data showed that 17% of the cases had pre-COVID

pain conditions. The difference in the use of medication (53.9 vs. 24.3%) between the multi-type and non-multi-type pain groups is not obvious. A recent study by Ebbesen et al. showed an additional medicinal intake in a long-term widespread pain non-hospitalization population was 25.4%[15]. The present study did not allow for further analysis of this topic.

Previous Injury-Related Pain

Previous history of whiplash injury was the only long-term pain condition found to be associated with the development of *de novo, multi-type,* pain. In general, whiplash-associated pain exhibits a widespread pain pattern and, hence, could share common underlying mechanisms, such as sensitization[6]. Non-recovered whiplash patients exhibit a high degree of pain sensitization and hence are prone to develop widespread pain[10,11,63].

Effect of Timing after Initiation of the Pandemic

Virus transmissions traditionally peak during colder periods[37,40] including SARS-CoV-2[43,58]. This is supported by the present findings and data and data from Danish registers[62]. Unfortunately, the current survey does not allow us to assign this effect to the SARS-CoV-2 which is known to be important for the development of post-COVID pain[17].

Our data showed that the risk of developing *de novo, multi-type,* post-COVID pain increases over time, possibly due to an accumulation of cases. Relative to the lowest quartile, the risk increases until two years after a SARS-CoV-2 infection, with the risk being significantly increased until 32 months post-infection. Previous data have shown that persistent infection-related symptoms such as fatigue, dyspnea, and anxiety, and in general physical, neurological, and psychological sequelae tend to decrease over time

although many symptoms persist two years after the infection[50], suggesting that additional analysis is required.

Socioeconomic Influence

It is widely recognized that effects of socioeconomics on chronic pain outcome are substantial[46,52,59]. This study found that lower socioeconomic status was associated with the development of *de novo, multi-type,* post-COVID pain symptoms. A recent study from our group found similar results in a Danish cohort of previously non-hospitalized COVID-19 survivors[15]. When looking independently at income level, high income was a protective factor in both studies with a tendency to be more protective for previously hospitalized COVID-19 survivors. For the low- and medium-income levels, no differences were found, supporting existing literature stating that income was not of importance concerning risk factors for the development of chronic pain in general[16].

Limitations

Due to the nature of the study, an online self-report survey was used for collecting data. Although supported by existing literature, the observed decrease in prevalence rates beyond 23 months from a SARS-CoV-2 infection could be affected by recall bias when relying on the memory of the pain experience. However, it should be noted that epidemiological studies investigating post-COVID pain have used similar survey designs[20]. When the questionnaire was sent out to participants asking about the new pain development, it was at least 8 months (on average 21.0 months) after the initial COVID infection and hence it can be termed at least long-term. However, if participants had a pre-COVID pain condition, there could be a possibility that the pain was reported as a new pain simply due to a worsening of existing pain. It is known that in up to 50% of

post-COVID patients, a worsening of pre-COVID existing muscle pain has been reported[17]. As it has been anticipated that all answered the questions to their best abilities, misunderstandings could occur when asked about new pain caused by the COVID-19 infection. Newer painful events (back pain, knee pain, or neck pain) occurring after the infection (e.g. by accidents) could directly or indirectly influence the responses.

Current prevalence rates focus on *de novo, multi-type,* post-COVID pain data that may be influenced by overall post-COVID pain prevalence in this current cohort, in which participants reporting a single pain syndrome, such as osteoarthritis or fibromyalgia, could elicit multi-type post-COVID pain.

The cross-sectional design does not allow evolution of *de novo, multi-type,* post-COVID pain evaluation during the follow-up period, making it difficult to exclusively attribute the presence of pain to the SARS-CoV-2 infection. The survey could be slightly biased towards the less severe long-term pain participants, as those with a more disabling pre-COVID pain condition or potentially worse outcomes could be less likely to respond and mortality rates were not investigated. Finally, information about race and ethnicity was not available for the current study, hence generalizability is limited to the variables discussed in this article.

Conclusion

This is to our knowledge the largest nationwide cohort study focusing on the impact of COVID-19 on the development of long-term, *de novo,* multi-type post-COVID pain after hospitalization.

The development of *de novo, multi-type,* post-COVID pain may affect quality of life. In a cohort of 4,712 previously hospitalized COVID-19 survivors 38.6% experienced post-COVID pain and 18.0% suffered from *de novo,* multi-type, post-COVID pain on average

21 months after hospitalization. Younger age, female gender, higher body mass index, ICU admission, previous history of whiplash, and previous history of anxiety were risk factors associated with the development of *de novo, multi-type,* pain. The pain phenotype may in some cases resemble the pain patterns of nociplastic pain conditions like fibromyalgia, characterized by widespread pain. These patients may therefore need specialized medical attention.

Disclosures

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Data availability statement

The anonymized questionnaire dataset is available upon request to the corresponding author. Due to the legal limitations applied by the Danish Health Act, § 42, subsection 1, supporting registered data is not available.

Figure legends

Figure 1: Flow diagram of the exclusion of participants from the final hospitalized cohort.

Figure 2: Number of hospitalizations over time from the first COVID-19-related hospital admission in March 2020 to 31st December 2021. The red line depicts the median length of the first hospital admission related to the individual hospital admissions over time.

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Figure 1_flow chart

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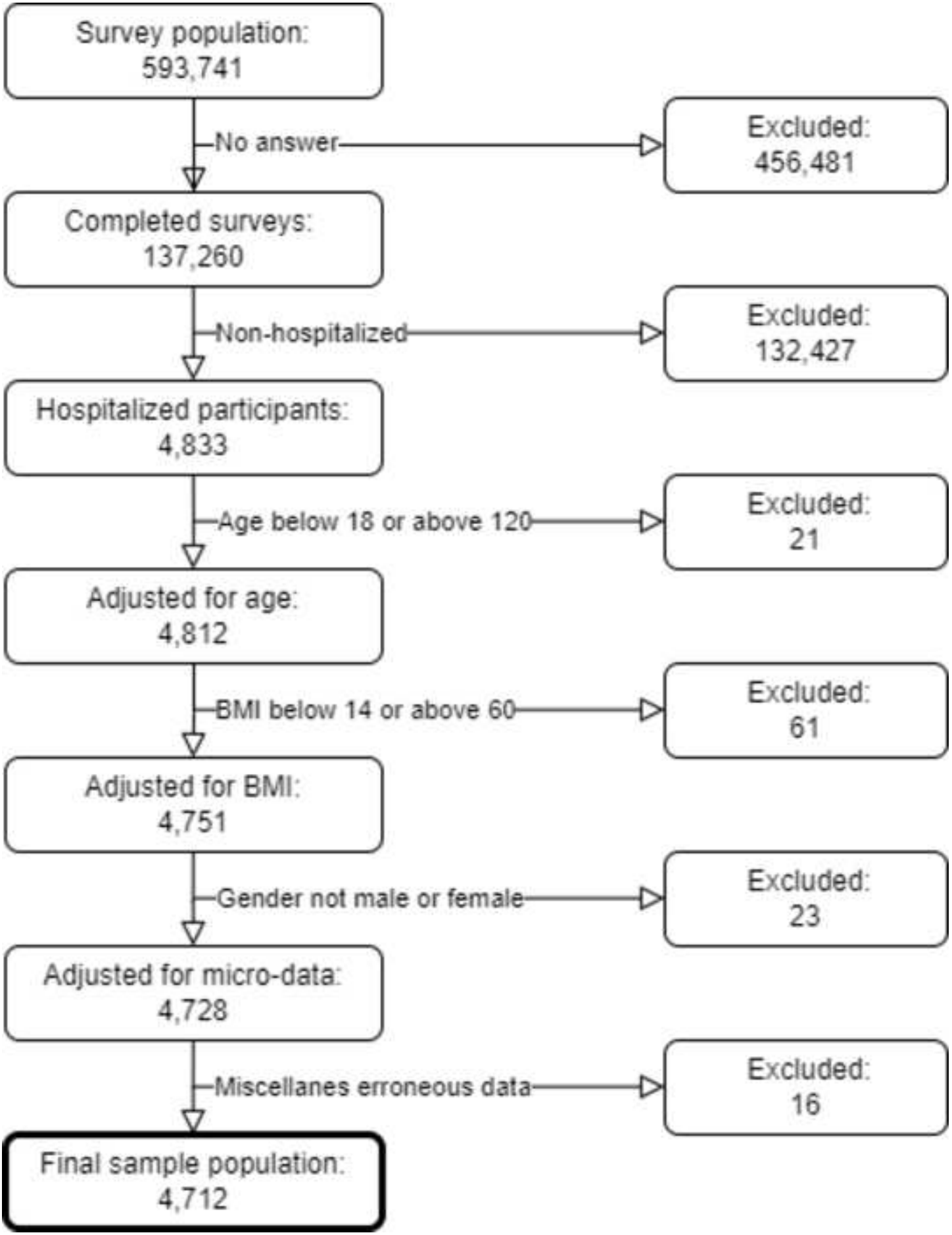


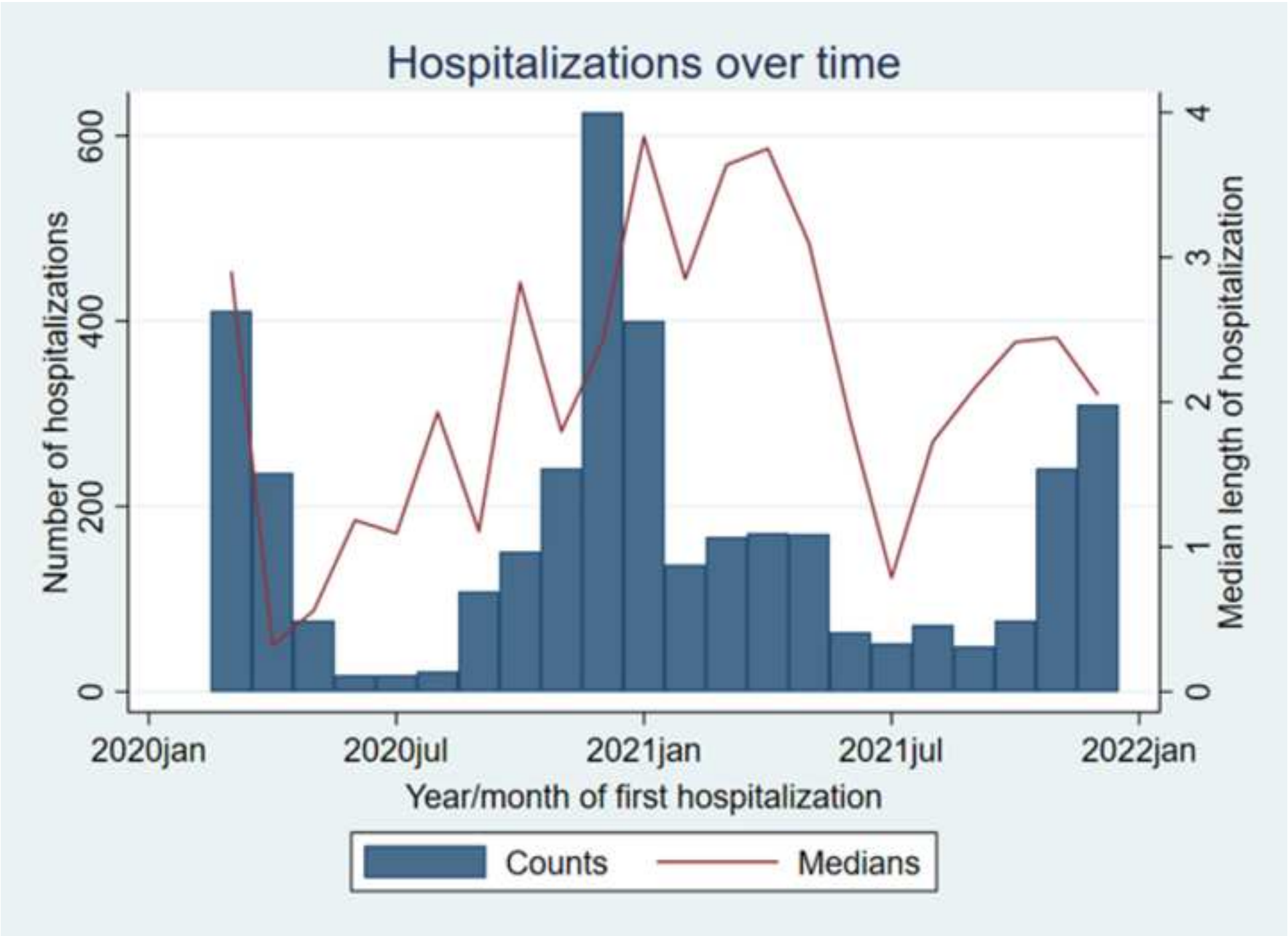


Table 1: Demographic data of the de novo post-COVID pain reportings of participants reporting one or more pain types.

Number of post-COVID pain types	With Post-COVID Muscle Pain (n=907)
0	-
1	60 (6.6%)
2	151 (16.6%)
3	198 (21.8%)
4	180 (19.8%)
5	114 (12.6%)
6	81 (8.9%)
7	50 (5.5%)
8	36 (4.0%)
9	20 (2.2%)
10	8 (0.9%)
11+	9 (1.0%)
Total	907 (100%)

n: number

Table 2: Demographic and clinical data of de novo post-COVID pain in 4,712 previously hospitalized COVID-19 survivors stratified by whether they reported de novo post-COVID pain or not.

	With Post-COVID Pain (n=907)	**Without Post-COVID Pain (n=3,805)**	**P-Value**
Age, mean (SD), years	56.1 (15.1)	61.0 (15.6)	<0.001
Female gender, n (%)	543 (59.9)	1,747 (45.9)	<0.001
Body Mass Index, mean (SD), kg/m^2	26.2 (10.9)	25.3 (9.8)	0.017
Weight, mean (SD), kg	87.4 (21.2)	85.9 (19.6)	<0.001
Height, mean (SD), m	1.71 (0.09)	1.73 (0.10)	0.038
Admitted ICU, n (%)	250 (27.5)	801 (21.1)	<0.001
Time at hospital, days, median	2.14 (0.25-6.86)	2.24 (0.32-6.17)	0.46
Time from hospital admission, months, median	21.08 (17.20-23.47)	21.00 (16.33-23.57)	0.25
Previous pain conditions, n (%)	154 (17.0)	611 (16.1)	0.515
Migraine, n (%)	22 (2.4)	66 (1.7)	0.172
Any other type of headache, n (%)	37 (4.1)	76 (2.0)	0.001
Sore throat, n (%)	23 (2.5)	44 (1.2)	0.004
Breathing pain, n (%)	29 (3.2)	92 (2.4)	0.198
Arthritis, n (%)	33 (3.6)	92 (2.4)	0.049
Osteoarthritis, n (%)	43 (4.7)	152 (4.0)	0.308
Back pain, n (%)	74 (8.2)	228 (6.0)	0.019
Abdominal pain, n (%)	27 (3.0)	53 (1.4)	0.002
Neck or shoulder pain, n (%)	62 (6.8)	136 (3.6)	<0.001
Chest pain, n (%)	28 (3.1)	55 (1.4)	0.002
Whiplash, n (%)	17 (1.9)	27 (0.7)	0.003
Nerve damage, n (%)	22 (2.4)	59 (1.6)	0.086
Other nerve disease, n (%)	6 (0.7)	17 (0.4)	0.425
Post-operative pain, n (%)	12 (1.3)	34 (0.9)	0.258
Joint pain, n (%)	53 (5.8)	140 (3.7)	0.005
Muscle pain, n (%)	65 (7.2)	149 (3.9)	<0.001
Others, n (%)	28 (3.1)	135 (3.5)	0.545
Medication intake			
For previous pain conditions, n (%)	83 (53.9)	149 (24.3)	<0.001
For multi-type post-COVID pain, n (%)	283 (31.2)	Not Applicable	
History of medical conditions, n (%)	154 (17.0)	610 (16.0)	0.485
Depression, n (%)	30 (3.3)	69 (1.8))	0.006
Stress, n (%)	31 (3.4)	55 (1.4)	<0.001
Anxiety, n (%)	31 (3.4)	41 (1.1)	<0.001
Type-1 Diabetes Mellitus, n (%)	1 (0.1)	13 (0.3)	0.493
Type-2 Diabetes Mellitus, n (%)	23 (2.5)	93 (2.4)	0.905
Asthma, n (%)	33 (3.6)	196 (5.2)	0.189
Dementia, n (%)	1 (0.1)	3 (0.1)	0.575
Chronic Cardiac Disease, n (%)	19 (2.1)	81 (2.1)	1.000
Hypertension, n (%)	57 (6.3)	196 (5.2)	0.189
Chronic Obstructive Pulmonary Disease, n (%)	10 (1.1)	60 (1.6)	0.359
Chronic Kidney Disease, n (%)	7 (0.8)	16 (0.4)	0.184
Liver Disease, n (%)	5 (0.6)	7 (0.2)	0.090
Malignant tumours, n (%)	9 (1.0)	16 (0.4)	0.042
Chronic neurological disorders, n (%)	21 (2.3)	59 (1.6)	0.116
Others, n (%)	42 (4.6)	173 (4.5)	0.929
Pain Intensity			
Mild, n (%)	136 (15.0)	Not Applicable	
Moderate, n (%)	448 (49.4)		

Severe, n (%) Very severe, n (%) Lost values, n (%)	237 (26.1) 44 (4.9) 42 (4.6)		
Quality of life			
With current pain	765 (88.9%)	918 (77.1%)	<0.001
When the pain was already resolved	34 (73.9%)	96 (75.6%)	<0.001

n: number; SD: Standard Deviation

Table 3: Multivariate regression analysis adjusted odds ratio (95% confidence interval) of 907 previously hospitalized COVID-19 survivors. The COVID-19 survivors had no previous pain conditions and/or one or more medical comorbidities. The multivariate analysis was conditioned by participants not having muscle pain, investigating the predictive value of all covariates concerning the risk of developing de novo multi-type post-COVID pain.

	Univariate Analysis	**Multivariate Analysis**
Age	0.981 (0.976; 0.986) #	0.982 (0.976; 0.987) #
Female Gender	1.790 (1.536; 2.085) #	1.711 (1.444; 2.023) #
BMI	1.037 (1.025; 1.050) #	1.032 (1.019; 1.045) #
Admitted to ICU	1.422 (1.198; 1.689) #	1.597 (1.324; 1.926) #
Previous pain conditions		
Migraine	1.275 (0.667; 2.436)	0.722 (0.329; 1.586)
Headache	1.393 (0.775; 2.503)	1.475 (0.694; 3.136)
Sore throat	0.685 (0.202; 2.319)	0.487 (0.093; 2.536)
Breathing pain	0.628 (0.298; 1.324)	0.920 (0.368; 2.296)
Arthritis	1.415 (0.645; 2.033)	1.520 (0.742; 3.112)
Osteoarthritis	0.655 (0.385; 1.115)	0.581 (0.302; 1.119)
Back pain	0.935 (0.644; 1.359)	1.256 (0.748; 2.110)
Abdominal pain	1.295 (0.658; 2.589)	1.573 (0.702; 3.535)
Neck or shoulder pain	1.248 (0.788; 1.976)	1.248 (0.670; 2.324)
Chest pain	0.509 (0.180; 1.437)	0.640 (0.186; 2.208)
Whiplash	2.185 (1.019; 4.686) *	2.471 (1.004; 6.081) *
Nerve damage	1.807 (0.541; 2.182)	1.255 (0.532; 2.959)
Other nerve diseases	0.434 (0.055; 3.392)	0.689 (0.075; 6.360)
Post-operative pain	0.834 (0.319; 2.179)	0.928 (0.306; 2.808)
Joint pain	0.964 (0.538; 1.729)	0.696 (0.325; 1.494)
Others	0.735 (0.460; 1.174)	0.794 (0.446; 1.413)
History of medical comorbidities		
Depression	1.087 (0.575; 2.055)	0.451 (0.183; 1.114)
Stress	1.915 (1.017; 3.605) *	1.129 (0.439; 2.907)
Anxiety	2.814 (1.496; 5.294) *	3.626 (1.355; 9.708) *
Type-2 diabetes mellitus	0.825 (0.443; 1,536)	0.732 (0.323; 1.660)
Asthma	0.998 (0.586; 1.699)	0.784 (0.404; 1.522)
Chronic cardiac disease	0.313 (0.113; 0.865) *	0.226 (0.059; 0.863) *
Hypertension	0.921 (0.617; 1.376)	1.224 (0.699; 2.143)
Chronic obstructive pulmonary disease	0.195 (0.047; 0.808) *	0.166 (0.033; 0.835) *
Chronic kidney disease	1.002 (0.285; 3.524)	1.619 (0.402; 6.515)
Liver disease	2.899 (0.484; 17.380)	1.973 (0.143; 27.224)
Malignant tumors	2.180 (0.816; 5.824)	2.701 (0.867; 8.416)
Chronic neurological disorders	0.887 (0.431; 1.824)	0.633 (0.255; 1.571)
Others	0.881 (0.594; 1.306)	0.805 (0.464; 1.396)
Socio-economic influence		
Income ¤		
Medium-low income	0.961 (0.783; 1.181)	0.981 (0.789; 1.220)
Medium-high income	0.955 (0.779; 1.171)	0.995 (0.797; 1.241)
High income	0.532 (0.424; 0.667) #	0.635 (0.494; 0.817) #
Educational level ¤		
Medium educational level	0.778 (0.640; 0.945) *	0.784 (0.638; 0.964) *
High educational level	0.739 (0.596; 0.916) *	0.774 (0.609; 0.984) *
Living alone	1.132 (0.972; 1.318)	0.944 (0.802; 1.111)

Time since infection ¤		
12-17 months	1.310 (1.004; 1.704) *	1.219 (0.924; 1.609)
18-23 months	1.465 (1.192; 1.801) #	1.681 (1.351; 2.092) #
24-32 months	1.303 (1.019; 1.665) *	1.548 (1.195; 2.005) #

* Statistically significance at P <0.05

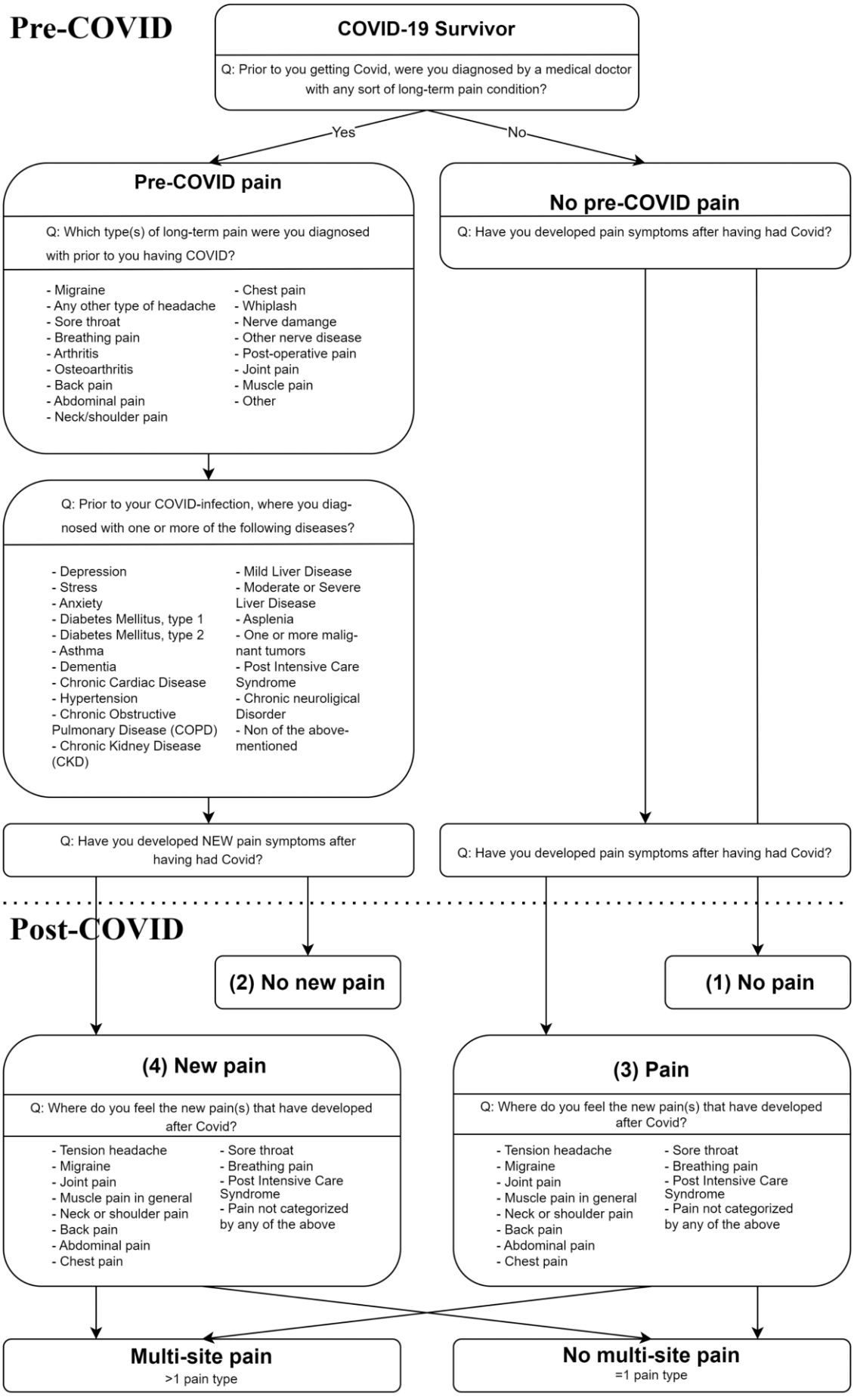
Statistically significance at P <0.001

¤ 'Income' and 'Educational level' have been calculated with 'Low income' as the reference group, and 'Time since infection' has been calculated with the interval 8-11 months as the reference group.

Table 4: Depiction of de novo multi-type post-COVID pain prevalence. Stratification on time from SARS-CoV-2 infection highlights segmented pain prevalence. The COVID strain relative to time is based on sequencing data from Statens Serum Institut.

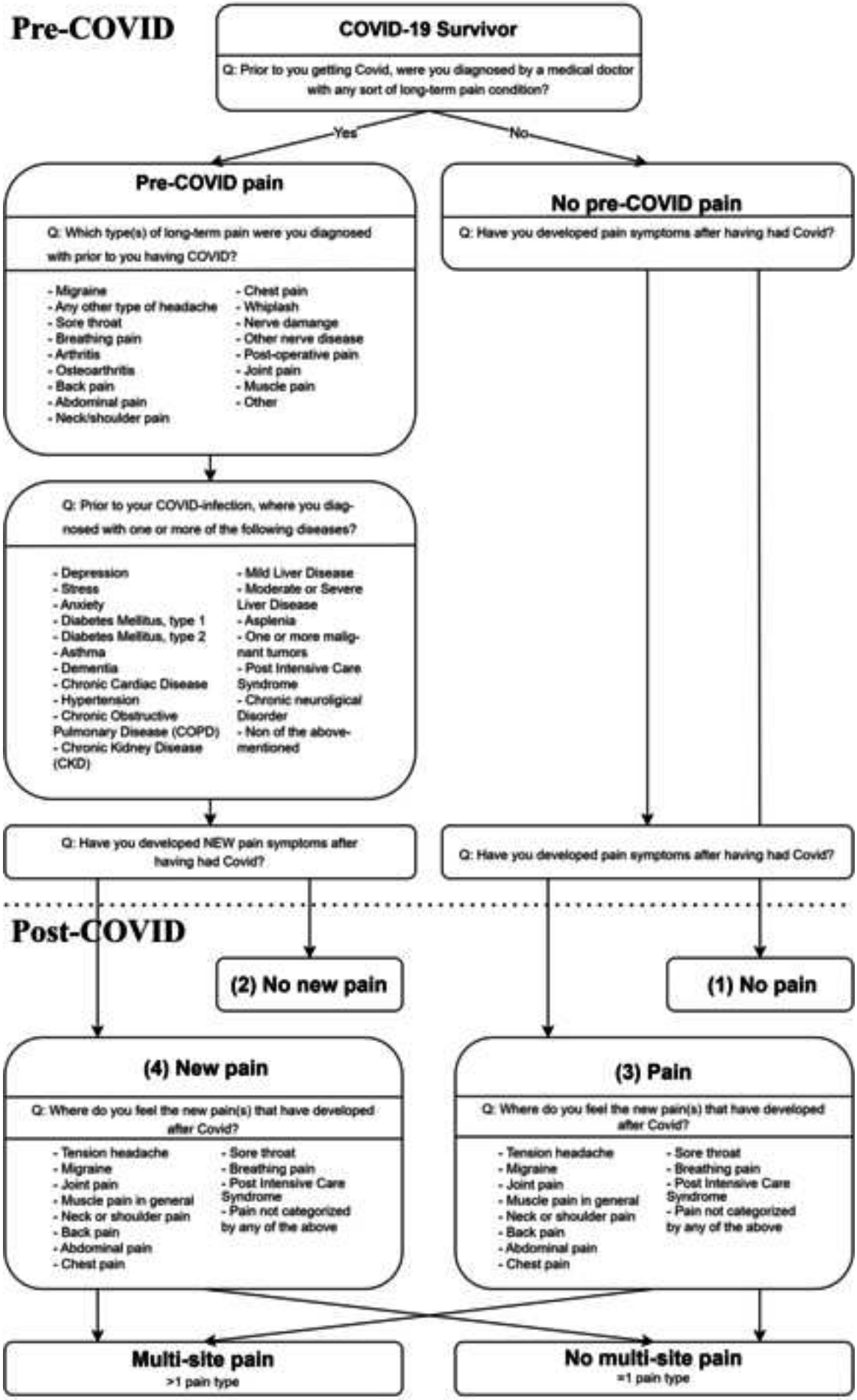
	Prevalence
Time from Infection, Months	
8-11	146 (15 %)
12-17	121 (18.8 %)
18-23	413 (20.5 %)
24-32	161 (18.7 %)
Dominant COVID-19 Strain	
Wuhan (March 2020 to September 2020)	592 (20 %)
Alpha (October 2020 to June 2021)	79 (17.6 %)
Delta (July 2021 to December 2021)	170 (15.7 %)

Supplementary Figure 1: Coding overview of how participants were stratified into pain and non-pain groups according to how the questions in the diagram relevant to the stratification were answered.


Pre-COVID
COVID-19 Survivor
Q: Prior to you getting Covid, were you diagnosed by a medical doctor with any sort of long-term pain condition?
Yes
No
Pre-COVID pain
Q: Which type(s) of long-term pain were you diagnosed with prior to you having COVID?
- Migraine
- Any other type of headache
- Sore throat
- Breathing pain
- Arthritis
- Osteoarthritis
- Back pain
- Abdominal pain
- Neck/shoulder pain
- Chest pain
- Whiplash
- Nerve damange
- Other nerve disease
- Post-operative pain
- Joint pain
- Muscle pain
- Other
No pre-COVID pain
Q: Have you developed pain symptoms after having had Covid?
Q: Prior to your COVID-infection, where you diagnosed with one or more of the following diseases?
- Depression
- Stress
- Anxiety
- Diabetes Mellitus, type 1
- Diabetes Mellitus, type 2
- Asthma
- Dementia
- Chronic Cardiac Disease
- Hypertension
- Chronic Obstructive Pulmonary Disease (COPD)
- Chronic Kidney Disease (CKD)
- Mild Liver Disease
- Moderate or Severe Liver Disease
- Asplenia
- One or more malignant tumors
- Post Intensive Care Syndrome
- Chronic neuroligical Disorder
- Non of the above-mentioned
Q: Have you developed NEW pain symptoms after having had Covid?
Q: Have you developed pain symptoms after having had Covid?
Post-COVID
(2) No new pain
(1) No pain
(4) New pain
Q: Where do you feel the new pain(s) that have developed after Covid?
- Tension headache
- Migraine
- Joint pain
- Muscle pain in general
- Neck or shoulder pain
- Back pain
- Abdominal pain
- Chest pain
- Sore throat
- Breathing pain
- Post Intensive Care Syndrome
- Pain not categorized by any of the above
(3) Pain
Q: Where do you feel the new pain(s) that have developed after Covid?
- Tension headache
- Migraine
- Joint pain
- Muscle pain in general
- Neck or shoulder pain
- Back pain
- Abdominal pain
- Chest pain
- Sore throat
- Breathing pain
- Post Intensive Care Syndrome
- Pain not categorized by any of the above
Multi-site pain
>1 pain type
No multi-site pain
=1 pain type

Multi-type pain stratification diagram

Click here to access/download;Supplemental Files;Figure 3_multi-type pain diagram.png



Addendum: Survey questions

Dear participant,

We would like to thank you for participating in this project by filling out the questionnaire. Your participation is extremely valuable, without your engagement we would be unable to complete this project.

This project focuses on the development of pain after a Covid infection. In the questionnaire we ask a number of questions about your experience of pain before and/or after Covid infection.

The questionnaire should take no longer than 10 minutes to complete. Thank you for your time and for helping us understand pain and Covid.

On behalf of

Aalborg University Hospital: Professor Bodil Steen Rasmussen and Professor Henrik Nielsen

Aarhus University Hospital: Professor Berit Schiøttz-Christensen

Bispebjerg University Hospital: Chief Physician Pernille Lykke Petersen and Professor Christian Sylvest Meyhoff

Aalborg University: Professor Lars Arendt-Nielsen and Ph D Stipend Brian Duborg Ebbesen

Information about the project is described in detail in the information letter in which the link for this questionnaire appears.

Your data will be confidential and will only be used in relation to your reply to this questionnaire. The general conditions to our storage and application of data, anonymization and subsequently deletion of data, as well as your rights to withdraw your consent or reply to this questionnaire are described in the information letter in your e-Boks in which the link for this investigation is present.

By consenting to the following question, you are informed that You can always withdraw your consent to use your personal data. You are informed that if You want to withdraw your consent You must contact:

The North Denmark Region by mail at COVID@RN.dk

This means that if You withdraw your consent, any further use of your personal data will not happen for the purpose described in this consent agreement and in the information letter. This means that information that has already been used for this research project prior to the withdrawal of consent, can still be applied to the results.

Consent for the use of personal information in the research project 'Pain in relation to Corona':

By choosing yes you consent to participate in this questionnaire

(1) Yes

(2) No

Initially we would like you to fill in some basic demographic data about yourself:

Gender

(1) Female

(2) Male

(3) Non-binary _____

(99) I do not wish to answer

Age

_____

Height in centimeters (e.g., 165)

_____

Weight in kilos (e.g., 63)

_____

The next questions will concern possible pain that you have experienced before and/or after you had Covid and when you recovered from Covid.

Were you admitted to a hospital with Covid?

(1) Yes

(2) No

Were you admitted to intensive care?

(1) Yes

(2) No

Why were you admitted to a hospital?

(1) I was admitted to the hospital specifically for the treatment of a Covid infection

(2) I was admitted to the hospital because of another disease but contracted Covid at the same time

(3) I was already in the hospital but got infected with Covid during my admission

Prior to you getting Covid, were you diagnosed by a medical doctor with any sort of long-term pain condition?

(1) Yes

(2) No

Which type(s) of long-term pain were you diagnosed with prior to you having Covid? Please tick all that apply.

(1) Migraine

(2) Any other type of headache

(3) Sore throat

(4) When I breathe, I have pain

(5) Arthritis

(6) Osteoarthritis

(7) Back pain

(8) Abdominal pain

(9) Pain in the neck/shoulder

(10) Chest pain

(11) Whiplash

(12) Nerve damage

(13) Other nerve disease

(14) After operation

(15) Joint pain

(16) Muscle pain

(17) Other (If other, please state in the text field) ____

Has the specific pain(s) marked in the previous question, changed after you recovered from Covid?

(1) Yes

(2) No

If so, how has the pain(s) changed?

(1) It/they have become much worse

(2) It/they have become a little worse

(3) It/they have improved a bit/a lot but still remain

(4) It/my pain(s) have now stopped and completely resolved

Do you take any medication for your pain?

(1) Yes

(2) No

If the pain has completely resolved, did you take any medicine for the pain before it improved?

(1) Yes

(2) No

(99) Not applicable

Do you take more pain medication after Covid than you did before getting Covid?

(1) Yes

(2) No

(99) Not applicable

The following questions concern factors that may influence a Covid infection.

Prior to your Covid infection, were you:

Physically active 30 minutes a day on average?

(1) Yes

(2) No

Smoking?

(1) Yes

(2) No

(3) Former smoker

Prior to your Covid infection, were you:

Diagnosed with one or more of the following diseases?

(1) Depression

(2) Stress

(3) Anxiety

(4) Diabetes Mellitus type 1

(5) Diabetes Mellitus type 2

(6) Asthma

(7) Dementia

(8) Chronic Cardiac Disease

(9) Hypertension

(10) Chronic Obstructive Pulmonary Disease (COPD)

(11) Chronic Kidney Disease (CKD)

(12) Mild Liver Disease

(13) Moderate or Severe Liver Disease

(14) Asplenia

(15) One or more malignant tumors

(16) Post Intensive Care Syndrome because of previous admission to intensive care at a hospital

(17) Chronic Neurological Disorder.

(99) No of the above-mentioned

Have you developed pain after having had Covid?

(1) Yes

(2) No

Have you developed new pain symptoms after having had Covid?

(1) Yes

(2) No

Where do you feel the new pain(s) that have developed after Covid?

(1) Tension headache

(2) Migraine

(3) Joint pain

(4) Muscle pain in general

(5) Neck or shoulder pain

(6) Back pain

(7) Abdominal pain

(8) Chest pain

(9) Sore throat

(10) I have pain when I breathe

(11) Post Intensive Care Syndrome because of admission to intensive care at the hospital with Covid

(12) I have pain that cannot be characterized in any of the above categorizations (please describe which in the text field): _____

How would you describe the intensity of your current pain?

(1) Mild

(2) Moderate

(3) Severe

(4) Very severe

Do you take any new medication for your new pain(s)?

(1) Yes

(2) No

How has the new pain(s) developed since you had Covid changed over time?

(1) The pain has not changed

(2) The pain has become stronger

(3) The pain has become less strong

(4) The pain has disappeared

How long did it last for before it got better?

(1) 1 week or less

(2) Between 1 week and 1 month

(3) Between 1 month and 3 months

(4) More than 3 months

How many times have you had Covid?

(1) 1 time

(2) 2 times

(3) 3 times

(4) 4 times or more

If you had a diagnosis of pain before you caught Covid, or if the pain developed after your first infection, did this pain(s) change after you caught Covid a second time?

(1) The pain has not changed

(2) The pain has become stronger

(3) The pain has become less strong

(4) The pain has disappeared

(99) Not applicable

Did the pain change after the THIRD time you had Covid?

(1) The pain has not changed

(2) The pain has become stronger

(3) The pain has become less strong

(4) The pain has disappeared

(99) Not applicable

Did the pain change after the FOURTH time you had Covid?

(1) The pain has not changed

(2) The pain has become stronger

(3) The pain has become less strong

(4) The pain has disappeared

(99) Not applicable

Have you been vaccinated against Covid? (This includes booster injections you may have received)

(1) Yes, one time

(2) Yes, two times

(3) Yes, three times

(4) No

Relative to your vaccination(s) when were you infected with Covid?

(1) I was infected with Covid before my first dose of the vaccine

(2) I got infected with Covid after my first dose of the vaccine

(3) I was infected with Covid after my second dose of the vaccine

(4) I got infected with Covid after my third dose of the vaccine

Have you developed new pain symptoms or a worsening of pain symptoms from your Covid infection after having received your vaccination?

(1) Yes, headache

(2) Yes, joint pain

(3) Yes, muscle pain in general

(4) Yes, neck or shoulder pain

(5) Yes, back pain

(6) Yes, throat pain

(7) I have pain when I breathe

(9) No

(8) I have pain that cannot be characterized in any of the above categorizations (please describe your pain(s) in the text field):

Did the intensity of your pain change after you received a Covid vaccination (If you had Covid-19 after your vaccine shots, just choose 'The pain has not changed')?

(1) The pain has not changed

(2) The pain has become stronger

(3) The pain has become less strong

(4) The pain has disappeared

Does pain affect your everyday life?

(1) Yes

(2) No

Even if the pain has now resolved, did your pain affect your daily life before it disappeared?

(1) Yes

(2) No

Do you feel fully recovered from Covid?

(5) Strongly agree

(4) Agree

(3) Neither agree nor disagree

(2) Disagree

(1) Strongly disagree

If we do further investigations of pain and Covid, can we then contact you again?

(1) Yes

(2) No

You have now finished the questionnaire. We thank you for taking your time to fill in the questionnaire.

To finish the questionnaire press 'Finish' in the bottom of this page. You can print the answers from your questionnaire by pressing the printing icon in the end of this text.

Thank you again for your participation!

Summary

De novo multi-type post-COVID pain is prevalent in 18.0% of the present cohort of previously hospitalized COVID-19 survivors 21 months after a SARS-CoV-2 infection.

Prevalence and Risk Factors of Multi-type Post-COVID Pain in a Cohort of Previously Hospitalized COVID-19 Survivors: A Danish Cross-Sectional Survey

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Abstract

This population-based study investigated the prevalence of *de novo, multi-type,* post-COVID pain and its associated risk factors in previously hospitalized COVID-19 survivors. The nationwide, cross-sectional study included a cohort of Danish residents previously hospitalized due to SARS-CoV-2 infection between March 2020 and December 2021. Demographic data, pre-existing medical comorbidities, previous pain-related symptoms, medication use for pain management, pain intensity (4-point scale), and development of *de novo, multi-type,* post-COVID pain were collected by a self-reported survey distributed via e-Boks (a secured national digital mail system used in Denmark to provide public information to residents). The sample comprised 4,712 previously hospitalized COVID-19 survivors (48.6% women, mean age: 60.1±15.6 years). At the time of the study (21±6 months after hospitalization), 18.0% (847) reported the presence of *de novo, multi-type*, post-COVID pain, and 38.6% of any pain. A multivariate analysis revealed that female sex (OR 1.711, 95%CI 1.444-2.023), higher body mass index (OR 1.032, 95%CI 1.019-1.045), intensive care unit admission (OR 1.597, 95%CI 1.324-1.926), previous history of whiplash (OR 2.471, 95%CI 1.004-6.081), anxiety (OR 3.626, 95%CI 1.335-9.708), and younger age (OR 0.982, 95%CI 0.976-0.987) were factors associated with development of *de novo, multi-type*, post-COVID pain. High income (OR 0.635, 95%CI 0.494-0.817) and high educational level (OR 0.774, 95%CI 0.609-0.984) were protective factors. In conclusion, multi-type pain as a *de novo* post-COVID symptom was present in 18.0% of previously hospitalized

COVID-19 survivors more than one year after hospital discharge and as such can be considered as adding to the global burden of chronic pain.

Perspective

The study investigates the prevalence of de novo, multi-type, post-COVID pain in previously hospitalized COVID-19 survivors. This article presents potential risk factors associated with developing new pain symptoms. The results will contribute to understanding the possibility of predicting post-infectious pain from COVID-19 for future analysis.

Short-running title: Post-COVID Pain after Hospitalization

Keywords: COVID-19, multi-type pain, long-term pain, post-COVID, risk factors, hospitalization.

Introduction

Long-term pain has been reported to be prevalent in individuals who survived the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and, in addition to several other symptoms, is termed post-COVID-19 condition or long-COVID[19,22,39,44]. The reported prevalence of post-COVID pain in previously hospitalized patients by coronavirus disease, 2019 (COVID-19) is highly heterogeneous and depends on the study design, the follow-up period, and the pain definitions used. The prevalence of post-COVID pain during the first six months has been estimated to be between 4.6% and 23.6%[20]. Peter et al. identified a "musculoskeletal pain cluster" in up to 16% of individuals with post-COVID symptoms[48]. However, the prevalence rate of post-COVID

pain can reach 60% in some studies depending on the time of assessment[3,9,34,55]. Hence, the prevalence of post-COVID pain is not fully elucidated and depends e.g. on time of observation after the infection and severity (hospitalized versus non-hospitalized).

Most studies investigating post-COVID pain have included relatively small cohorts of previously hospitalized COVID-19 survivors[3,9,34,55]. A large cohort study including 1,969 previously hospitalized COVID-19 survivors found post-COVID musculoskeletal pain symptoms related to the musculoskeletal system (i.e., post-COVID musculoskeletal pain) in 45% of the patients eight months after hospital discharge[18]. Large-scale population-based epidemiological studies focusing specifically on post-COVID pain are scarce[2]. Two nationwide, large cohort surveys, conducted in Denmark analyzed the overall presence of post-COVID symptoms; however, these were non-hospitalized cohorts[57,66] and based only on data collected during the first year of the pandemic in 2021.

The prevalence of post-COVID pain depends on whether the pain is assessed as a local or widespread problem[3,9,20,34,48,55]. Data suggests that a subgroup of individuals with post-COVID pain develop a multi-type pain pattern like fibromyalgia syndrome[25]. This suggests that some post-COVID pain patients may exhibit a pain-related phenotype characterized by nociplastic features involving pain sensitization[21]. However, no studies have specifically investigated the development of *de novo* (a new pain symptom appearing after the SARS-CoV-2 infection) multi-type post-COVID pain in a large cohort of previously hospitalized COVID-19 survivors. In addition, the possible risk factors for developing this specific disabling pain symptomatology are largely unknown.

The aims of this nationwide, population-based study were 1) to investigate the prevalence of *de novo*, *multi-type*, post-COVID pain (defined as more than one pain type) in a large cohort of previously hospitalized COVID-19 survivors, and 2) to investigate risk factors associated with the development of this specific pain symptomatology.

Methods

Study design

This nationwide, exploratory, cross-sectional, questionnaire-based survey included a cohort of residents from Denmark who were previously hospitalized due to an acute SARS-CoV-2 infection from March 2020 to December 2021. In Denmark, mass testing via reverse transcription-polymerase chain reaction (RT-PCR) was used in the management of the COVID-19 pandemic. Data was handled by the COVID-19 Surveillance System at Statens Serum Institut to control how the COVID-19 pandemic has developed over time in Denmark[60]. The current cohort study was registered and approved by the Danish Data Protection Agency (approval #F2022-004) in compliance with the Danish Health Data Act (approval #2022-056227) and has been granted access to sensitive data of residents from the Danish Health Data Agency and Statens Serum Institut (approval #FSEID-00006572). The extent of participation in the survey and the rights of the participants were explained in a preceding information letter distributed with the questionnaire and, hence, informed consent was obtained from all participants before starting data collection. According to Danish legislation, approval from the Scientific Ethics Committee was not required.

Participants

From a population of 593,741 adult residents registered by the COVID-19 surveillance system received our questionnaire. A total of 137,260 completed the full questionnaire. Of those, a total sample of 4,833 residents had previously been hospitalized. All participants had been previously hospitalized and registered by the COVID-19 Surveillance System at Statens Serum Institut because of a positive RT-PCR test between 1 March 2020 and 31 December 2021. However, 121 participants were

excluded due to erroneous data entries (i.e., negative or unrealistic values for demographic features, or microdata issues) or erroneous administrative hospitalization data. **Figure 1** depicts the final sample size of 4,712.

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Figure 1 near here

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Participants were included in the invitation list if they: (1) were ≥18 years old, (2) had a confirmed SARS-CoV-2 infection (RT-PCR+) and had been hospitalized due to the acute infection, (3) consented to participate in the study, (4) were resident in Denmark with a valid social security number, (5) had access to the official, secure, national, digital mailing system (e-Boks), in use in Denmark, at the time of data collection[14], and (6) received pre-defined clinical COVID-19 codes (International Statistical Classification of Diseases and Related Health Problems; ICD-10) as the main diagnosis during the hospital admission. Survey respondents were excluded if they did not complete the questionnaire or if reported demographic data were considered outliers. The cohort included individuals infected during the period in Denmark with circulating SARS-CoV-2 of the historical Wuhan strain, Alpha, or Delta variants, but not the Omicron variant[61].

Data Collection Procedure

An online questionnaire constructed for data collection was distributed to the participants in September 2022 via e-Boks. Data collection lasted five weeks with a reminder distributed after two weeks. The study focused on *de novo, multi-type*, post-COVID pain defined as pain compatible with the diagnosis of chronic primary musculoskeletal pain according to the International Association for the Study of Pain

(IASP)[47] with a duration longer than six months that had started after SARS-CoV-2 infection. The *de novo* post-COVID pain was acknowledged if the participants' pre-SARS-CoV-2 infection had no pain at all or developed specific new painful symptoms more than six months post-infection. Multi-type post-COVID pain could reflect a nociplastic phenotype suggesting an involvement of pain sensitization mechanisms[21] similar to patients with fibromyalgia[53,54]. The manifestation of multi-type pain symptomatology involved participants reporting two or more types of pain.

The questionnaire, found in the supplementary materials, collected the following self-reported data: (1) demographic data (gender, age, height, weight) as categorical and continuous variables; (2) previous medical comorbidities diagnosed by a medical doctor (categorical); (3) preexisting long-term pain conditions (categorical); (4) development of *de novo, multi-type*, pain after hospitalization by SARS-CoV-2 infection (ordinal and analyzed as continuous in the regression model); (5) medication use for previous pain management (binary and categorical); and (6) intensities of pain in general and for *de novo, multi-type*, pain (4-point Likert scale) (categorical). All variables have been analyzed according to their data variable type. Medical comorbidities were based on the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) platform that provides a framework of clinically relevant comorbidities concerning infectious diseases including COVID-19[29].

Participants were stratified into four pain groups: (Group 1) No pain pre- or post-COVID, (Group 2) pre-COVID pain but no post-COVID pain, (Group 3) no pre-COVID pain but post-COVID pain, and (Group 4) both pre- and post-COVID pain. For a full overview of this group characterization, please refer to **Supplementary Figure 1**. Participants were asked if they had a pre-COVID diagnosis (from a medical doctor) of long-term pain. If not, they would fall into either group 1 or 3, and if yes group 2 or 4.

Groups 2 and 4 were asked about 16 types of long-term pain conditions as well as a free-text option, and other previous diseases that included 17 pre-defined diseases and a free-text option. To further stratify the groups, the participants were asked if they had developed post-COVID pain. Participants with pre-COVID pain were asked if they had developed any *new* pain symptoms. Groups 3 and 4 were asked about the new post-COVID pain types development. These participants were stratified into either 'no multi-type pain' when reporting one pain type or 'multi-type pain' when reporting more than one new pain type.

Experts across Denmark, Spain, Italy, the UK, and Switzerland reviewed the questionnaire. In this way, it was ensured that the relevant comorbidities were included to ensure post-COVID pain-related validity. To avoid misinterpretation, the questionnaire was tested in selected target populations before the distribution of the actual questionnaire. The phenotyping was not identified; thus, we presume that *de novo, multi-type,* pain would be of musculoskeletal origin; but neuropathic components cannot be excluded.

Data about RT-PCR tests were acquired from Statens Serum Institut, and data about hospital admissions were acquired from the Danish Health Data Agency. Hospitalization time was defined as the first hospital admission added to any other hospital admission not separated by more than two calendar days from the first hospital admission because of COVID-19. Time from hospital was defined as the first day of the first hospital admission to questionnaire data collection time.

Registered socio-economic data was included from Statistics Denmark. Three main socio-economic influential factors were included in the present study: 1) personal income as an average of total income three years before data collection, 2) International

Standard Classification of Education (ISCED)[30] defined educational level, and 3) the current living status of each participant.

Statistical Analysis

All data were stored and merged in a secure Research Electronic Data Capture (REDCap) server at Statistics Denmark before initiating the statistical analysis. All are presented as means (standard deviations, SD), percentages as appropriate, and as count for figures. Proportions and means between patients with/without *de novo* post-COVID pain were compared with McNemar's chi-squared test and paired Student t-test, respectively. Multivariate logistic regressions, including all the variables, were performed to identify those associated with *de novo, multi-type*, post-COVID pain development. Muscle pain was the only variable not included as participants not having muscle pain was the primary condition, thus muscle pain was the outcome factor and dependent variable in the multivariate model. To account for individual covariate contributions, each covariate was analyzed independently. A priori, the level of significance was set to 0.05. To avoid potential bias from multicollinearity effects in the multivariate regression model, we calculated the global conditioning number (4.272) for the regression model variables. Further, the variance inflation factor (VIF) for individual predictors was between 1.07 and 1.80. Both the global condition number and the VIF were considered well beneath the limits for inducing potential multicollinearity effects in the multivariate regression analysis[5].

Results

The final sample consisted of 4,712 previously hospitalized COVID-19 survivors (48.6% women, mean ± SD age: 60.1 ± 15.6 years). The response rate was 23.9%, which is in alignment with similar nationwide health-related studies ranging from 20% to 30%[33].

The mean height in the post-COVID pain group and the non-pain group was 1.71 m (SD: 0.09 m) and 1.73 meters (SD: 0.10 m), respectively. Mean weight was 87.4 kg (SD: 21.2 kg) and 85.9 kg (SD: 19.6 kg), respectively. Finally, the mean post-COVID pain-group BMI was 26.2 kg/m^2 (SD: 10.9 kg/m^2) and the non-pain group BMI was 25.3 kg/m^2 (SD: 9.8 kg/m^2).

Prevalence of Multi-type Post-COVID Pain in Hospitalized COVID-19 Survivors

Participants were assessed at least one year after (mean: 21.0, SD: 6.0 months) hospital admission. Overall pain prevalence was reported by 38.6% (1,819). At the time of the survey, 19.3% (907) reported *de novo* post-COVID pain. Of those, 18.0% (847) reported the *de novo* pain to be of multi-type character. Of the participants reporting *de novo* post-COVID pain, 93.4% reported more than one pain type (**Table 1**). Further, 76.8% reported 3 or more types of pain. *De novo*, *multi-type*, post-COVID pain was described as moderate in intensity by 49.4% of participants, whereas 26.1% of participants reported that pain was severe and 4.9% described the pain as very severe. The present study showed that in participants reporting *de novo*, *multi-type*, post-COVID pain, 17% of the cases additionally reported other long-term pain conditions (e.g., joint pain) prior to the infection. Also, 31.2% of the participants were taking analgesics to control their post-COVID pain (**Table 2**).

Table 2 depicts demographic and clinical data in hospitalized COVID-19 survivors developing *de novo* post-COVID pain (19.3%) and in those who did not develop *de novo* post-COVID pain (80.7%). Participants developing *de novo* post-COVID pain were younger (P<0.001) and had a higher BMI (P<0.017) than those who did not. A significant proportion of participants with *de novo* post-COVID pain were females (P<0.001). Additionally, 27.5% of the participants developing *de novo* post-COVID pain were admitted to the intensive care unit (ICU) in contrast to the 21.1% of individuals who did

not develop post-COVID pain (P<0.001). There was no difference (P=0.46) in the length of hospitalization between participants who developed *de novo* post-COVID pain (2.14 days, IQR0.25-6.86) and those who did not (2.24 days, IQR0.32-6.17). The time from hospital admission to the survey response did not differ between the *de novo* and the non-*de novo* group (21.0 months versus 21.08 months, respectively, P=0.25).

The group developing *de novo* post-COVID pain reported a higher presence of some specific previous long-term pain conditions including headache (4.1% vs. 2.0%, P=0.001), sore throat (2.5% vs. 1.2%, P=0.004), back pain (8.2% vs. 6.0%, P=0.019), abdominal pain (3.0% vs. 1.4%, P=0.002), neck/shoulder pain (6.8% vs 3.6%, P<0.001), chest pain (3.1% vs 1.4%, P=0.002), whiplash (1.9% vs 0.7%, P=0.003), joint pain (5.8 vs 3.7%, P=0.005), and muscle pain (7.2% vs 3.9%, P<0.001) compared to the group who did not develop *de novo* post-COVID pain. However, the overall percentage of individuals with previous pain conditions was not significantly different between participants developing *de novo* post-COVID pain and those who did not (17.0% vs. 16.1%, P=0.515, **Table 2**). Medication intake for those reporting one or more previous long-term pain conditions was higher in the cohort developing *de novo* post-COVID pain than in the cohort that did not develop *de novo* post-COVID pain (53.9% vs 24.3%, P<0.001).

Overall, the presence of previous medical comorbidities was comparable between hospitalized COVID-19 survivors who developed *de novo* post-COVID pain and those who did not. Pre-infection depression (P=0.006), anxiety (P<0.001), and stress (P<0.001) were more prevalent in the cohort who developed *de novo* post-COVID pain (**Table 2**).

The quality of life information was collected for all responders with pain (Table 2) by the question: ”Even if the pain has now resolved, did your pain affect your daily life before it disappeared?”. The responses showed that 88.9% of the COVID-19

survivors with current muscle pain had reduced quality of life compared to those without muscle pain (p<0.001) while 73.9% of individuals with previous pain, but with post-COVID muscle pain resolved, reported reduced quality of life (**Table 2**).

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Risk Factors Associated with Multi-type Post-COVID Pain in Hospitalized Participants

The multivariate analysis revealed that, after adjusting for all variables, younger age (OR 0.982, 95%CI 0.976-0.987, P<0.01), female gender (OR 1.711, 95%CI 1.444-2.023, P<0.001), body mass index (OR 1.032, 95%CI 1.019-1.045, P<0.001), ICU admission (OR 1.597, 95%CI 1.324-1.926, P<0.001), and previous history of whiplash (OR 2.471, 95%CI 1.004-6.081, P<0.05) and anxiety (OR 3.626, 95%CI 1.355-9.708, P<0.05) were factors associated with an increased risk of developing *de novo*, *multi-type*, post-COVID pain in our cohort of previously hospitalized COVID-19 survivors (**Table 3**). Conversely, the presence of previous cardiac disease (OR 0.226, 95%CI 0.059-0.863, P<0.05) and chronic obstructive pulmonary disease (OR 0.166, 95%CI 0.033-0.835, P<0.05) were protective factors for the development of *de novo*, *multi-type*, post-COVID pain (**Table 3**). Additionally, the analysis of socio-economic variables showed that medium (OR 0.784, 95%CI 0.638-0.964, P<0.05) and high (OR 0.744, 95%CI 0.609-

0.984, P<0.05) educational levels were also protective factors, as well as high income (OR 0.635, 95%CI 0.494-0.817, P<0.001).

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De novo, multi-type, Post-COVID Pain Stratified on Time and SARS-CoV-2 Variant

In **Table 4** the cohort of 4,489 COVID-19 survivors was stratified in time intervals. Because of missing time delay data 223 participants were excluded from this analysis. For each stratified segment, the parenthesis depicts the percentage of individuals reporting a development of *de novo* post-COVID pain. Here, 146 of 974 (15%) participants reported *de novo* pain 8-11 months following hospital admission for COVID-19, 121 of 647 (18.8%) after 12-17 months, while 413 of 2,017 (20.5%), and 161 of 867 (18.7%) participants reported *de novo* pain after 18-23 and 24-32 months, respectively. SARS-CoV-2-variant stratification showed that 592 of 2,971 (20%) participants reported *de novo* pain after recovering from the historical strain, 79 of 450 (17.6%) from the Alpha variant, and 170 of 1,084 (15.7%) from the Delta variant. **Figure 2** depicts the number of first hospitalizations from March 2020 to December 2021 with peaks for each SARS-CoV-2 strain during the winter periods. The median length of hospitalizations shows a trend of correlation to the number of hospital admissions with a slight timewise delay from the peaks of hospital admissions. The number of hospitalizations is recorded upon admission date while the median duration of hospitalizations is recorded on the date of hospital discharge, which might explain the time delay.

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Discussion

This study investigated the prevalence of *de novo*, multi-type, post-COVID pain in previously hospitalized COVID-19 survivors in Denmark. Prevalence of pain was 38.6% 21 months after hospital admission. A total of 18.0% reported *de novo*, multi-type, post-COVID pain and almost 80% of those *de novo*, *multi-type*, classified their pain as moderate or severe and 17% of the cases reported a painful condition prior to hospitalization. Younger age, female gender, higher body mass index (BMI), ICU admission, history of whiplash, and history of anxiety were factors associated with the development of *de novo*, multi-type, post-COVID pain.

Multi-type, Post-COVID Pain in Previously Hospitalized COVID-19 Survivors

The possibility that *de novo*, multi-type, post-COVID pain can develop as one of several symptoms characterizing long-COVID agrees with previous studies[3,9,18,34,55]. The current study focused on the development of *de novo*, *multi-type*, post-COVID pain, to differentiate it from most previous studies focusing on regional pain conditions[3,9,18,34,55]. The multi-type post-COVID pain resembled in some cases individuals with e.g., fibromyalgia [7,25,53] with pain in different locations, which requires tailored treatment[21] suggesting the pain might be of widespread nature.

Risk Factors Associated with Multi-type Post-COVID Pain

Age and gender.

Associations of age with overall post-COVID-19 symptoms are not evident from previous studies[10,32]. Pooled data from over 800,000 COVID-19 survivors in different meta-analyses evaluating prognostic risk factors for post-COVID-19 symptoms did not confirm any age associations[41,45]. Different pain symptoms have been associated with both older and younger age[31,64]. Older age is considered a risk factor for both widespread pain and musculoskeletal chronic pain in general[67], widespread post-COVID pain[51], and for the severity of COVID-19[68]. The present study may indicate that for the more severely affected previously hospitalized participants, younger age, and female gender could be a risk factor[4,34,65].

Female gender is associated with a higher risk of developing overall post-COVID-19 symptoms after hospitalization[41,45]. Savin et al. found an incidence of a new diagnosis of fibromyalgia syndrome in 15% of COVID-19 survivors, and female gender was a risk factor (OR 3.65, 95%CI 1.41-8.9)[54]. Females reporting a higher prevalence of widespread post-COVID pain is in accordance with the fact that chronic widespread pain is overall more prevalent in females than in males[56]. Biological, psychological, and sociocultural gender differences may contribute to this overall female predominance in COVID-19-related pain[23,26].

Body Mass Index

Higher BMI was associated with the development of *de novo*, *multi-type*, post-COVID pain contrary to Karaarslan et al. who, in a smaller sample, found no association between higher BMI and higher risk of post-COVID arthralgia and myalgia[35]. Higher

BMI has been associated with the overall development of post-COVID-19 symptoms[45] and associated with more severely affected individuals[1]. In general, obesity has been associated with the development/presence of widespread pain symptoms[12].

Intensive Care Unit Admission.

Intensive Care Unit (ICU) admission was another factor related to the presence of *de novo, multi-type,* post-COVID pain in our study. Leite et al. likewise observed that patients admitted to the ICU reported a higher prevalence of persistent pain (33.9%) than those in hospital wards (27.1%)[38]. It is well known that ICU admission can generate Post-Intensive Care Syndrome (PICS) in up to 60.8% of patients[27,51], where 28% to 77% also report post-ICU pain[42]. Up to 70% of ICU survivors suffer from at least one PICS-related impairment (e.g., pain), which can persist 5–15 years after hospital discharge[13]. For the COVID-19 participants referred to ICU, the relative contributions and importance of COVID-19 infection and ICU hospitalization for the development of post-COVID pain cannot be estimated.

Pre-existing Comorbidities

Pre-existing cardiac disease or chronic obstructive pulmonary diseases did not prime for the development of *de novo, multi-type,* post-COVID pain although leading to more severe COVID-19 and higher mortality[49]. Evidence also supports that subjects suffering from previous respiratory diseases do not represent a risk factor for COVID-19 susceptibility nor cause a more severe disease[24]. We have previously shown that having myalgia during hospitalization is a risk factor for long-COVID pain[18], which could be a proxy for the severity of the infection as cytokines are prominent drivers of musculoskeletal pain[28] and the current data showed that 17% of the cases had pre-COVID

pain conditions. The difference in the use of medication (53.9 vs. 24.3%) between the multi-type and non-multi-type pain groups is not obvious. A recent study by Ebbesen et al. showed an additional medicinal intake in a long-term widespread pain non-hospitalization population was 25.4%[15]. The present study did not allow for further analysis of this topic.

Previous Injury-Related Pain

Previous history of whiplash injury was the only long-term pain condition found to be associated with the development of *de novo, multi-type*, pain. In general, whiplash-associated pain exhibits a widespread pain pattern and, hence, could share common underlying mechanisms, such as sensitization[6]. Non-recovered whiplash patients exhibit a high degree of pain sensitization and hence are prone to develop widespread pain[10,11,63].

Effect of Timing after Initiation of the Pandemic

Virus transmissions traditionally peak during colder periods[37,40] including SARS-CoV-2[43,58]. This is supported by the present findings and data and data from Danish registers[62]. Unfortunately, the current survey does not allow us to assign this effect to the SARS-CoV-2 which is known to be important for the development of post-COVID pain[17].

Our data showed that the risk of developing *de novo, multi-type*, post-COVID pain increases over time, possibly due to an accumulation of cases. Relative to the lowest quartile, the risk increases until two years after a SARS-CoV-2 infection, with the risk being significantly increased until 32 months post-infection. Previous data have shown that persistent infection-related symptoms such as fatigue, dyspnea, and anxiety, and in general physical, neurological, and psychological sequelae tend to decrease over time

although many symptoms persist two years after the infection[50], suggesting that additional analysis is required.

Socioeconomic Influence

It is widely recognized that effects of socioeconomics on chronic pain outcome are substantial[46,52,59]. This study found that lower socioeconomic status was associated with the development of *de novo, multi-type*, post-COVID pain symptoms. A recent study from our group found similar results in a Danish cohort of previously non-hospitalized COVID-19 survivors[15]. When looking independently at income level, high income was a protective factor in both studies with a tendency to be more protective for previously hospitalized COVID-19 survivors. For the low- and medium-income levels, no differences were found, supporting existing literature stating that income was not of importance concerning risk factors for the development of chronic pain in general[16].

Limitations

Due to the nature of the study, an online self-report survey was used for collecting data. Although supported by existing literature, the observed decrease in prevalence rates beyond 23 months from a SARS-CoV-2 infection could be affected by recall bias when relying on the memory of the pain experience. However, it should be noted that epidemiological studies investigating post-COVID pain have used similar survey designs[20]. When the questionnaire was sent out to participants asking about the new pain development, it was at least 8 months (on average 21.0 months) after the initial COVID infection and hence it can be termed at least long-term. However, if participants had a pre-COVID pain condition, there could be a possibility that the pain was reported as a new pain simply due to a worsening of existing pain. It is known that in up to 50% of

post-COVID patients, a worsening of pre-COVID existing muscle pain has been reported[17]. As it has been anticipated that all answered the questions to their best abilities, misunderstandings could occur when asked about new pain caused by the COVID-19 infection. Newer painful events (back pain, knee pain, or neck pain) occurring after the infection (e.g. by accidents) could directly or indirectly influence the responses.

Current prevalence rates focus on *de novo, multi-type,* post-COVID pain data that may be influenced by overall post-COVID pain prevalence in this current cohort, in which participants reporting a single pain syndrome, such as osteoarthritis or fibromyalgia, could elicit multi-type post-COVID pain.

The cross-sectional design does not allow evolution of *de novo, multi-type,* post-COVID pain evaluation during the follow-up period, making it difficult to exclusively attribute the presence of pain to the SARS-CoV-2 infection. The survey could be slightly biased towards the less severe long-term pain participants, as those with a more disabling pre-COVID pain condition or potentially worse outcomes could be less likely to respond and mortality rates were not investigated. Finally, information about race and ethnicity was not available for the current study, hence generalizability is limited to the variables discussed in this article.

Conclusion

This is to our knowledge the largest nationwide cohort study focusing on the impact of COVID-19 on the development of long-term, *de novo,* multi-type post-COVID pain after hospitalization.

The development of *de novo, multi-type,* post-COVID pain may affect quality of life. In a cohort of 4,712 previously hospitalized COVID-19 survivors 38.6% experienced post-COVID pain and 18.0% suffered from *de novo,* multi-type, post-COVID pain on average

21 months after hospitalization. Younger age, female gender, higher body mass index, ICU admission, previous history of whiplash, and previous history of anxiety were risk factors associated with the development of *de novo, multi-type,* pain. The pain phenotype may in some cases resemble the pain patterns of nociplastic pain conditions like fibromyalgia, characterized by widespread pain. These patients may therefore need specialized medical attention.

Disclosures

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Data availability statement

The anonymized questionnaire dataset is available upon request to the corresponding author. Due to the legal limitations applied by the Danish Health Act, § 42, subsection 1, supporting registered data is not available.

Figure legends

Figure 1: Flow diagram of the exclusion of participants from the final hospitalized cohort.

Figure 2: Number of hospitalizations over time from the first COVID-19-related hospital admission in March 2020 to 31st December 2021. The red line depicts the median length of the first hospital admission related to the individual hospital admissions over time.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-2	
Objectives	3	State specific objectives, including any prespecified hypotheses	2	
Methods				
Study design	4	Present key elements of study design early in the paper	2-3	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6	
Bias	9	Describe any efforts to address potential sources of bias	15	
Study size	10	Explain how the study size was arrived at	3	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.