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Featured Article

Prevalence and Risk Factors of De Novo Widespread Post-COVID Pain in Nonhospitalized COVID-19 Survivors: A Nationwide Exploratory Population-Based Survey

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Abstract: **This survey investigated the prevalence of de novo widespread musculoskeletal post-COVID pain and risk factors for its development in nonhospitalized COVID-19 survivors. A nationwide exploratory cross-sectional study was conducted, including a cohort of 593,741 Danish residents who had suffered from a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from March 2020 to December 2021. A questionnaire was distributed to the Danish population via the digital mail system (e-Boks). Self-reported demographic data, previous medical comorbidities (diagnosed), socioeconomic data, time of infection, prior chronic pain conditions (diagnosed), development of de novo widespread pain after infection, pain medication, and pain intensity information were collected. Responders consisted of 130,443 nonhospitalized participants (58.2% women; mean age: 50.2 years). At a mean of 14.4 (standard deviation 6.0) months after infection, 6,875 (5.3%) patients reported the presence of de novo widespread musculoskeletal post-COVID pain. Almost 75% of the patients reported a moderate to severe intensity of the pain. In conclusion, de novo widespread post-COVID pain was present in 5.3% of nonhospitalized COVID-19 survivors 1 year after infection (14.4 ± 6.0 months). Older age, female sex, higher BMI, and history of migraine, whiplash, stress, type-2 diabetes, neurological disorders, and lower socioeconomic status were risk factors associated with the development of de novo widespread post-COVID pain in nonhospitalized patients. As de novo widespread pain is considered a sign of sensitization, this group will require specialized pain management attention.**

Perspective: ***This article presents de novo widespread post-COVID pain prevalence in a cohort of 130,443 citizens infected with COVID-19. The study identifies potential risk factors associated with the development of these new pain symptoms. The results may increase focus on this patient group and potentially help identify predictors for postinfection pain development.***

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Key Words: *COVID-19, nonhospitalization, post-COVID, risk factors, de novo widespread pain*

Pain is a symptom experienced during both the acute phase[1] and the post-acute phase[2,3] of the coronavirus, 2019 disease (COVID-19). A meta-analysis focusing on musculoskeletal post-COVID pain reported a pooled prevalence ranging from 4.6% to 23.6% during the first 6 months after infection.[4] Most studies included in this meta-analysis investigated overall post-COVID symptoms and did not focus on pain.[4] When pain is specifically investigated, its prevalence rises to 60%[5-8] depending on when the symptoms are assessed after the infection, and the trajectory is currently not fully clarified.

In a recent Delphi study, pain was the second outcome (after fatigue) included in a core outcome set for generalized patients with post-COVID symptoms.[9] In fact, current research supports that different clusters of patients with post-COVID symptoms exist, and a study including 1.2 million individuals who had symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection identified 3 clusters according to the most prevalent post-COVID symptoms: fatigue with bodily pain (51% of patients), respiratory symptoms (60.4% of patients), and cognitive problems (35.4% of patients).[10] Peter et al[10] identified a "musculoskeletal pain cluster" in almost 16% of patients with post-COVID symptoms. Some authors proposed the term "pain-syndrome pattern" or "post-COVID pain syndrome" for those subjects where pain is the main post-COVID symptom.[11,12] Accordingly, a better understanding of post-COVID pain symptomatology is further needed.

A large, multicenter study including a sample of 1,969 previously hospitalized COVID-19 survivors observed a prevalence of musculoskeletal post-COVID pain symptoms of 45% 8 months after hospital discharge.[13] This study identified female sex, previous history of musculoskeletal pain, and presence of myalgia as associated-onset symptoms as risk factors associated with the development of musculoskeletal post-COVID pain.[13] A previous nationwide survey in Denmark analyzed the overall presence of post-COVID symptomatology and reported a prevalence of 5.3% for muscle/joint pain and 6% for headache.[14] Nevertheless, a remarkable finding of former evidence on post-COVID pain is that population-based epidemiological studies focusing specifically on post-COVID pain and its description are lacking,[15] such as how many developed de novo widespread pain. In fact, post-COVID pain data in nonhospitalized patients remain scarce, as it is generally easier to recruit previously hospitalized COVID-19 survivors for surveys.[4]

It is also important to note that most studies have focused on post-COVID pain in general terms and not on specific pain characteristics.[4] It has been reported that almost 20% of individuals developing post-COVID pain will exhibit widespread symptomatology after hospitalization.[13] The presence of widespread pain is suggested as a clinical proxy of sensitization mechanisms and could lead to the hypothesis that individuals developing widespread post-COVID pain will exhibit a nociplastic phenotype with pain sensitization and, accordingly, will need particular attention.[16] No published study has focused only on the development of de novo widespread post-COVID pain and its associated risk factors in the general population.

Accordingly, the aims of the current population-based, national survey were 1) to investigate the development of de novo widespread post-COVID pain in nonhospitalized COVID-19 survivors and 2) to investigate risk factors associated with the development of de novo widespread post-COVID pain in nonhospitalized COVID-19 survivors.

Methods

Study Design

This nationwide exploratory cross-sectional survey included a cohort of residents from Denmark who suffered from a SARS-CoV-2 infection from March 2020 to December 2021. In Denmark, mass testing via reverse transcription polymerase chain reaction (RT-PCR) as testing was widely available during the COVID-19 pandemic. Data are handled by the COVID-19 surveillance system at Statens Serum Institut, and via registers, these data provide a unique insight into how the COVID-19 pandemic has developed over time in Denmark.[17] The study is registered and approved by the Danish Data Protection Agency in compliance with the Danish Health Data Act (2022-056227) and has been granted access to sensitive data of the residents from the Danish Health Data Agency, Statens Serum Institut, and Statistics Denmark. Participation was voluntary, and informed consent was obtained from all participants at the beginning of the questionnaire. The consequences of participation and the rights of the participants were explained in an initial information letter distributed along with the questionnaire.

Participants

A cohort of 593,741 adult residents registered by the COVID-19 surveillance system at Statens Serum Institut because of a positive RT-PCR test (RT-PCR+) between March 1, 2020 and December 31, 2021 was encompassed. Participants were included in the invitation list if they were ≥18 years old, had a confirmed SARS-CoV-2 infection (RT-PCR+) at least 6 months prior to the study, consented to participate in the study, were residents in Denmark with a valid social security number, and if they had access to the official, secure, national mailing system (e-Boks), used in Denmark, at the time of data collection.[18] Participants were excluded if they did not complete the questionnaire or if their reported demographic information was considered an outlier. Nonhospitalization was established by self-reporting whether the participants had been hospitalized due to COVID or not.

Data Collection Procedure

Data collection consisted of a questionnaire (addendum) distributed to the included participants via the secured national e-mailing system (e-Boks). The questionnaire was open for 5 weeks after distribution, with a reminder after 2 weeks. The current study focused specifically on "de novo" widespread post-COVID pain. The operationalization of the pain symptomatology of widespread pain was defined by participants experiencing pain at least at 2 sites of the body; 1 site on the upper part of the body and 1 site on the lower part of the body. In addition, de novo post-COVID pain was defined as participants experiencing pain symptoms either 1) when there was no pain at all prior to the SARS-CoV-2 infection or 2) when specific new pain symptoms developed in regions where pain symptoms were not present prior to the SARS-CoV-2 infection. Finally, we focused on pain symptoms compatible with the diagnosis of chronic primary musculoskeletal pain according to the International Association for the Study of Pain,[19] with a duration longer than 6 months.

The questionnaire, which can be found in the addendum, collected in addition the following self-reported info: 1) demographic data (gender, age, height in centimeters, weight in kilos); 2) previous medical comorbidities; 3) prior chronic pain conditions; 4) development of de novo widespread pain symptoms after SARS-CoV-2 infection; 5) medication used for pain management; and 6) intensity of widespread pain (4-point Likert scale). Possible comorbidities were based on the International Severe Acute Respiratory and emerging Infection Consortium platform, which provides a collaborative platform with a particular focus on COVID-19.[20]

To ensure the relevance of comorbidities included and that the questionnaire reflected actual medical challenges associated with post-COVID pain, the questionnaire was peer-reviewed before approval by experts and medical doctors in collaborating COVID-19 research teams across Denmark, Spain, Italy, the UK, and Switzerland. Before distribution, the questionnaire was tested on a group of participants similar to the target population to avoid potential misunderstandings and implied formulations. The purpose of this study was to show the prevalence of de novo widespread post-COVID pain and potential risk factors. Hence, the potential causal effects of individual data variables collected via the questionnaire and registered data were not discussed.

Socioeconomic data was collected from Statistics Denmark's database after approval of the application. Registered data included 1) income calculated as an average total income of the last 3 years from data collection time point, 2) educational level, as defined by the International Standard Classification of Education,[21] and whether the participants were living alone or with others.

Statistical Analysis

All data were stored and merged in a secure Research Electronic Data Capture server at Statistics Denmark before starting the analysis to ensure full security of personal data. Data are presented as means (standard deviation [SD]), percentages, quartiles, odds ratios, or ranges as appropriate. McNemar's Chi-squared test and paired Student t-tests were used to compare proportions and means between patients with and without musculoskeletal post-COVID pain. Univariate and multivariate logistic regressions were conducted to identify potential associations of widespread musculoskeletal post-COVID pain development with demographic variables, pre-existing medical comorbidities, and prior pain conditions. In the regression analysis, results are conditioned by the participants not having muscle pain. Adjusted odds ratio (OR) and confidence intervals (95% CI) were calculated. Each covariate was analyzed individually for the contribution of each covariate. Income and educational level were calculated in quartiles to understand the difference between low and high socioeconomic influence.

A priori, the level of significance was set at .01. To ensure that the results from the multivariate regression analysis were not due to multicollinearity effects, the global condition number (4.264) for parameters included in the regression model was analyzed. A condition number larger than 10 is usually a measure of instability.[22] The variance inflation factor for each individual predictor was also considered and calculated. The analysis found no cause for concern regarding multicollinearity as none of the variables used as input in the regression model was correlated with one another.

Results

From a population of 593,741 adult Danish residents registered by the COVID-19 surveillance system at Statens Serum Institut due to a positive RT-PCR test (last date December 31, 2021), a total of 137,261 participants completed the survey (response rate of 23.2%); however, 6,979 were excluded due to erroneous data entries (ie, negative or unrealistic values for demographic data). According to Rambøll, a company in Denmark conducting nationwide surveys, the response rate aligned with similar national health-related studies ranging between 20% and 30%.[23] Genders reported as nonbinary were excluded due to the extremely low number of participants (n = 2). Accordingly, the final sample consisted of 130,443 nonhospitalized (RT-PCR+) participants (58.2% women, mean ± SD age: 50.2 ± 15.8 years).

Prevalence of Widespread Post-COVID Pain in Nonhospitalized Patients

Participants were assessed 1 year (mean: 14.4, SD 6.0 months) after the SARS-CoV-2 infection. At the time of the survey completion, 6,875 (5.3%) individuals reported de novo widespread musculoskeletal post-COVID pain.

Table 1 compares demographic and clinical data between COVID-19 survivors who developed de novo widespread post-COVID pain and those who did not. Overall, patients developing de novo widespread post-COVID pain were older and with higher body mass

Table 1. Demographic and Clinical Data of 1,30,443 Nonhospitalized COVID-19 Survivors According to the Presence or Absence of De Novo Widespread Post-COVID Pain

	WITH DE NOVO WIDESPREAD POST-COVID PAIN (N = 6,875)	*WITHOUT DE NOVO WIDESPREAD POST-COVID PAIN (N = 123,568)*	*P VALUE*
Age, mean (SD), years	50.9 (13.6)	50.2 (15.9)	< .001
Female sex, n (%)	4,722 (68.7)	71,152 (57.6)	< .001
Body mass index, mean (SD), kg/m^2	27.7 (5.4)	26.3 (5.0)	< .001
Weight, mean (SD), kg	81.4 (18.3)	79.5 (17.4)	< .001
Height, mean (SD), m	1.71 (.09)	1.73 (.09)	< .001
Previous long-term pain conditions, n (%)	946 (13.8)	8,256 (6.7)	< .001
Migraine, n (%)	175 (18.5)	982 (11.9)	< .001
Any other type of headache, n (%)	143 (15.1)	921 (11.2)	< .001
Sore throat, n (%)	60 (6.3)	243 (2.9)	< .001
Breathe pain, n (%)	44 (4.7)	167 (2.0)	< .001
Arthritis, n (%)	163 (17.2)	1,294 (15.7)	< .001
Osteoarthritis, n (%)	291 (30.8)	2,596 (31.4)	< .001
Back pain, n (%)	442 (46.7)	3,393 (41.1)	< .001
Abdominal pain, n (%)	93 (9.8)	483 (5.9)	< .001
Neck or shoulder pain, n (%)	337 (35.6)	2,228 (27.0)	< .001
Chest pain, n (%)	60 (6.3)	206 (2.5)	< .001
Whiplash, n (%)	92 (9.7)	573 (6.9)	< .001
Nerve damage, n (%)	111 (11.7)	916 (11.1)	.001
Other nerve disease, n (%)	35 (3.7)	219 (2.7)	< .001
Postoperative pain, n (%)	48 (5.1)	456 (5.5)	< .001
Joint pain, n (%)	262 (27.6)	1,995 (24.2)	< .001
Muscle pain, n (%)	310 (32.8)	1,691 (20.5)	< .001
Others, n (%)	173 (18.3)	1,463 (17.7)	< .001
Medication intake			
For previous pain conditions, n (%)	541 (57.2)	1,175 (14.2)	< .001
For de novo widespread post-COVID pain, n (%)	1,749 (25.4)	Not applicable	
History of medical conditions, n (%)	946 (13.8)	8,256 (6.7)	< .001
Depression, n (%)	151 (16.0)	792 (9.6)	< .001
Stress, n (%)	166 (17.5)	822 (10.0)	< .001
Anxiety, n (%)	121 (12.8)	675 (8.2)	< .001
Type-1 diabetes mellitus, n (%)	7 (.7)	71 (.9)	.195
Type-2 diabetes mellitus, n (%)	85 (9.0)	502 (6.1)	< .001
Asthma, n (%)	106 (11.2)	832 (10.1)	< .001
Dementia, n (%)	4 (.4)	21 (.3)	.04
Chronic cardiac disease, n (%)	58 (6.1)	483 (5.9)	< .001
Hypertension, n (%)	236 (24.9)	2,016 (24.4)	< .001
Chronic obstructive pulmonary disease, n (%)	28 (3.0)	236 (2.9)	< .001
Chronic kidney disease, n (%)	6 (.6)	48 (.6)	.064
Liver disease, n (%)	15 (1.6)	59 (.7)	< .001
Malignant tumors, n (%)	22 (2.3)	158 (1.9)	< .001
Chronic neurological disorders, n (%)	111 (11.7)	754 (9.1)	< .001
Others, n (%)	360 (38.1)	3,682 (44.6)	< .001
Pain intensity			
Mild, n (%)	1,300 (18.9)	Not applicable	
Moderate, n (%)	3,668 (53.4)		
Severe, n (%)	1,529 (22.2)		
Very severe, n (%)	183 (2.7)		

Abbreviation: n, number.

index (BMI) compared to those without widespread post-COVID pain (P < .001) (Table 1).

Significant clinical background differences between subjects developing de novo widespread post-COVID pain and those without were found. Patients developing de novo widespread post-COVID pain reported significantly greater presence (P > .001) of previous chronic pain conditions (13.8%) as compared to those without de novo widespread post-COVID pain (6.7%) development. Further, the analgesic medication intake was significantly higher (P < .001) in chronic pain patients who developed de novo widespread post-COVID pain (57.2%) in contrast to the subgroup not developing de novo widespread post-COVID pain (14.2%).

Additionally, 25.4% (n = 1,749) of patients who developed de novo widespread post-COVID pain reported taking analgesic medication for this pain (most likely to be considered as additional pain medication). This may be related to the fact that de novo widespread post-COVID pain was described as moderate in intensity by 53.4% of patients, severe in intensity by 22.2%, and very severe in intensity by 2.7% when asked about pain intensity in the survey (Table 1).

Overall, patients developing de novo widespread post-COVID pain reported a higher prevalence ($P < .001$) of previous medical comorbidities (13.8%) when compared to those without de novo widespread post-COVID pain (6.7%). All specific medical comorbidities assessed in this study were more prevalent in the cohort of patients developing widespread musculoskeletal post-COVID pain, except type-1 diabetes, dementia, and chronic kidney disease ($P > .01$) (Table 1).

Risk Factors Associated With the Development of De Novo Widespread Post-COVID Pain

The univariate and multivariate analyses are detailed in Table 2. Table 2 includes 130,282 nonhospitalized (RT-PCR +) participants because of missingness in a small subset of data from registered socioeconomic data (130,282 vs 130,443). After adjusting all variables, the multivariate analysis revealed that female sex (OR 1.594, 95% CI 1.508–1.687, $P < .001$), higher BMI (OR 1.043, 95% CI 1.039–1.048, $P < .001$), older age (OR 1.003, 95% CI 1.001–1.005, $P < .01$), and type-2 diabetes mellitus (OR 1.563, 95% CI 1.133–2.156, $P < .01$), whiplash (OR 1.562, 95% CI 1.175–2.078, $P < .01$), previous history of migraine (OR 1.554, 95% CI 1.235–1.956, $P < .001$), chronic neurological disorders (OR 1.532, 95% CI 1.125–2.086, $P < .01$), and stress (OR 1.470, 95% CI 1.104–1.959, $P < .01$), were ranked risk factors for the development of de novo widespread post-COVID pain. Further, the influence of socioeconomic factors revealed that medium-low income relative to low income (OR 1.203, 95% CI 1.120–1.292, $P < .001$) was a risk factor while high income (OR .782, 95% CI .716–.855, $P < .001$), medium educational level relative to low educational level (OR .801, 95% CI .745–.861, $P < .001$), and high educational level relative to low educational level (OR .603, 95% CI .556–.653, $P < .001$) were protective factors in the development of de novo widespread post-COVID pain. Finally, the time since infection showed that 12 to 17 months since infection relative to 8 to 11 months (OR 1.811, 95% CI 1.671–1.963, $P < .001$), 18 to 23 months (OR 2.179, 95% CI 2.058–2.307, $P < .001$), and 24 to 32 months (OR 2.543, 95% CI 2.298–2.815, $P < .001$) were risk factors for the development of de novo widespread post-COVID pain.

Time and Variant-Related Prevalence of De Novo Widespread Post-COVID Pain

Table 3 depicts the stratified cohort where 2,656 (3.5%) participants reported de novo widespread pain 8 to 11 months postinfection, 886 (6.1%) after 12 to 17 months, 2,624 (7.5%) after 18 to 23 months, and 499 (8.4%) after 24 to 32 months. When stratifying for the SARS-CoV-2 variant, 3,210 (7.6%) participants reported pain after being infected with the Wuhan strain, 628 (5.8%) after the Alpha variant, and 2,736 (3.6%) after the Delta variant. Both stratifications had the same endpoint date equal to the termination of data collection.

Discussion

This is the first large, nationwide, population-based study focusing specifically on the prevalence of self-reported de novo widespread post-COVID pain in nonhospitalized COVID-19 survivors. Overall, the prevalence of de novo widespread post-COVID pain was 5.3%. Almost 75% of the patients reported a moderate to severe intensity of the de novo widespread post-COVID pain. Older age, female sex, higher BMI, and previous history of migraine, whiplash, stress, type-2 diabetes, lower socioeconomic status, and neurological disorders were risk factors associated with the development of the de novo widespread post-COVID pain in nonhospitalized COVID-19 survivors.

Post-COVID De Novo Widespread Pain in Nonhospitalized COVID-19 Survivors

The current results showed a lower prevalence rate of post-COVID pain in general than studies conducted in previously hospitalized COVID-19 survivors.[5-8,13] Several differences, for example, age, sex, pre-existing medical comorbidities, previous chronic pain conditions, and particularly the nature of the cohort referring only to nonhospitalized COVID-19 survivors, might explain this discrepancy. It would be expected that the prevalence of post-COVID pain will be higher in hospitalized COVID-19 survivors. However, Fernández-de-las-Peñas et al[24] found that the prevalence rates of post-COVID pain were 30% in both hospitalized and nonhospitalized patients. Sørensen et al[14] found, in a national, population-based study survey similar prevalence rates of muscle/joint pain (5.3%) and of headache (6%) as in the present study. It is crucial to point out that the current study focused exclusively on the development of de novo widespread post-COVID pain, whereas previous studies investigated the presence of any pain area.[5-8,13,14,24] Another potential difference is that we included individuals infected with either the Wuhan strain, Alpha variant, or Delta variant (no Omicron variant). It has been observed that the prevalence of widespread musculoskeletal post-COVID pain is higher in those individuals infected with the Wuhan strain (20%) than in those infected with Alpha (5%) or Delta (6%) variants.[25] Again, this study only included previously hospitalized patients.

The present study focused on differentiating the pain specifically from previously pre-COVID localized pain conditions. In fact, 13.8% of patients developing widespread pain as a new post-COVID symptom reported previous localized chronic pain, for example, joint pain.

Table 2. Adjusted Odd Ratio (95% Confidence Interval) of the Univariate and Multivariate Regression Analyses of 6,875 Nonhospitalized COVID-19 Survivors Conditioned by Not Having Muscle Pain and Suffering From Previous Long-term Pain Conditions and/or Having a History of One or More Medical Comorbidities

	UNIVARIATE	*MULTIVARIATE*
Female Sex	1.602 (1.519; 1.689)*	1.594 (1.508; 1.687)†
BMI, kg/m^2	1.051 (1.047; 1.055)*	1.043 (1.039; 1.048)†
Age, years	1.002 (1.001; 1.004)*	1.003 (1.001; 1.005)†
Previous long-term pain conditions		
Whiplash	2.988 (2.319; 3.850)*	1.562 (1.175; 2.078)†
Migraine	2.832 (2.320; 3.457)*	1.554 (1.235; 1.956)†
Abdominal pain	2.621 (1.910; 3.596)*	1.421 (1.006; 2.007)
Chest pain	2.681 (1.560; 4.610)*	1.300 (.707; 2.391)
Neck or shoulder pain	2.234 (1.902; 2.623)*	1.185 (.969; 1.450)
Breathing pain	1.976 (1.029; 3.795)*	1.179 (.586; 2.372)
Others	1.920 (1.593; 2.313)*	1.143 (.926; 1.410)
Back pain	2.025 (1.782; 2.301)*	1.118 (.940; 1.329)
Arthritis	1.701 (1.365; 2.118)*	1.087 (.582; 1.386)
Nerve damage	1.934 (1.505; 2.486)*	1.081 (.812; 1.438)
Sore throat	2.324 (1.381; 3.910)*	1.008 (.552; 1.841)
Osteoarthritis	1.627 (1.390; 1.905)*	.870 (.718; 1.054)
Joint pain	1.526 (1.219; 1.912)*	.856 (.667; 1.100)
Headache	1.778 (1.374; 2.301)*	.784 (.586; 1.049)
Postoperative pain	1.178 (.758; 1.833)	.737 (.477; 1.139)
Other nerve diseases	1.514 (.818; 2.800)	.728 (.381; 1.393)
History of medical comorbidities		
Type-2 diabetes mellitus	2.703 (2.018; 3.619)*	1.563 (1.133; 2.156)†
Chronic neurological disorders	2.268 (1.751; 2.938)*	1.532 (1.125; 2.086)†
Stress	2.948 (2.357; 3.687)*	1.470 (1.104; 1.959)†
Anxiety	2.895 (2.264; 3.703)*	1.297 (.949; 1.774)
Depression	2.902 (2.321; 3.628)*	1.294 (.967; 1.733)
Others	1.669 (1.470; 1.894)*	1.258 (1.052; 1.504)
Malignant tumors	1.704 (.891; 3.258)	1.196 (.624; 2.292)
Chronic cardiac disease	1.814 (1.281; 2.569)*	1.173 (.803; 1.714)
Hypertension	1.811 (1.526; 2.149)*	1.020 (.823; 1.264)
Chronic obstructive pulmonary disease	1.775 (1.079; 2.921)*	.990 (.584; 1.667)
Liver disease	1.857 (.664; 5.192)	.971 (.336; 2.810)
Asthma	1.759 (1.354; 2.285)*	.895 (.671; 1.194)
Chronic kidney disease	1.031 (.248; 4.284)	.564 (.131; 2.428)
Socioeconomic influence		
Income‡		
Medium-low income	1.245 (1.166; 1.330)*	1.203 (1.120; 1.292)†
Medium-high income	.981 (.916; 1.052)	1.063 (.985; 1.147)
High income	.601 (.556; .650)*	.782 (.716; .855)†
Educational level‡		
Medium educational level	.784 (.731; .842)*	.801 (.745; .861)†
High educational level	.546 (.507; .588)*	.603 (.556; .653)†
Living alone	1.058 (1.006; 1.112)	1.209 (.974; 1.087)
Time since infection‡		
12 to 17 months	1.772 (1.639; 1.917)*	1.811 (1.671; 1.963)†
18 to 23 months	2.228 (2.107; 2.357)*	2.179 (2.058; 2.307)†
24 to 32 months	2.519 (2.280; 2.783)*	2.543 (2.298; 2.815)†

NOTE. The univariate model analyzes each variable individually in relation to the risk of developing de novo widespread post-COVID pain. The multivariate model depicts the predictive value of covariates on the risk of developing de novo widespread post-COVID pain.
*Statistically significance in the univariate analysis ($P < .001$).
†Statistically significance in the multivariate analysis ($P < .01$).
‡"Income" and "Educational level" have been calculated with "Low" as reference group, and "Time since infection" has been calculated 8 to 11 months as reference group.

The presence of widespread post-COVID pain resembles a pattern similar to the one experienced by people with, for example, fibromyalgia syndrome,[26] and the definitions/terms used in the present survey tried to separate this group from the de novo widespread group. Actually, subjects with post-COVID pain may report similar pain patterns to fibromyalgia and chronic fatigue syndrome but with less severe pain and fatigue.[27]

Table 3. Prevalence of De Novo Widespread Post-COVID Pain Stratified on Time From Infection and the Estimated COVID-19 Strain Based on Sequencing Data from Statens Serum Institute

	PREVALENCE
Time from infection, months	
8 to 11	2,565 (3.5%)
12 to 17	886 (6.1%)
18 to 23	2,624 (7.5%)
24 to 32	499 (8.4%)
Dominant COVID-19 strain	
Wuhan (March 2020 to September 2020)	3,210 (7.6%)
Alpha (October 2020 to June 2021)	628 (5.8%)
Delta (July 2021 to December 2021)	2,736 (3.6%)

NOTE. The COVID strain is based on what strain was dominant.

Widespread pain symptoms have been related to general sensitization,[28] deficient immune regulatory mechanisms,[29] and could indicate a prolonged immune system impact in a population of post-COVID pain sufferers.[30] As it is currently suggested, this group of COVID-19 survivors developing widespread pain symptomatology can exhibit a nociplastic phenotype,[16] and, accordingly, will need particular specialized attention.

Risk Factors Associated With De Novo Widespread Post-COVID Pain in Nonhospitalized COVID-19 Survivors

Identification of individuals at a higher risk of developing widespread post-COVID pain is relevant since this subgroup of patients most likely represents the most difficult to treat. The evidence may later show to be important for outcomes after other infectious diseases. The present study found that older age, female sex, higher BMI, and previous history of migraine, whiplash, stress, type-2 diabetes mellitus, lower socioeconomic status, and neurological disorders were risk factors associated with the development of de novo widespread post-COVID pain.

Female sex has previously been found as a risk factor for the development of long-COVID conditions after hospitalization.[31,32] This population-based study also supports that nonhospitalized females are at a higher risk of developing widespread post-COVID pain when compared with males, in agreement with previous findings in hospitalized COVID-19 survivors.[13] Current results agree with Savin et al,[33] who found an incidence of new diagnosis of fibromyalgia of 15% being female sex a risk factor (OR 3.65, 95% CI 1.41–8.9). A female predominance in post-COVID pain can be expected since musculoskeletal pain is, in general, more prevalent in females than in males.[34] Biological, psychological, or sociocultural gender differences would explain this female sex predominance in chronic pain in general but seems also present in COVID-19-related pain.[35,36]

The association of older age with overall post-COVID symptoms is under debate since single studies and systematic reviews[37] support this association, whereas some meta-analyses did not.[31,32] Although, in this study, we observed a significant association between older age and the development of widespread post-COVID pain, looking at age differences between individuals developing de novo widespread post-COVID pain and those who did not, the association seems to be small. It is possible that other factors more commonly associated with age, for example, previous medical comorbidities, can better explain a higher risk of developing de novo widespread post-COVID pain.

The multivariate analysis revealed that some specific medical comorbidities, for example, type-2 diabetes or neurological disorders, were risk factors associated with the development of widespread post-COVID pain. In addition, higher BMI was also a risk factor and could interact with these comorbidities. Although not directly, higher BMI could be linked to a higher risk of developing obesity, a medical condition that has been also associated with overall long-COVID conditions.[32] Furthermore, obesity is associated with a higher prevalence of type-2 diabetes mellitus. These 2 conditions are associated with a more severe course and progression of acute COVID-19.[38,39] In line with the presented results, obesity[40] and type-2 diabetes[41] have been associated with the presence of widespread pain. Accordingly, these metabolic syndromes should be considered when planning the management of an individual's post-COVID pain.

It should be expected that the presence of chronic pain before a SARS-CoV-2 infection could be a risk factor promoting the development of post-COVID pain. Fernández-de-las-Peñas et al[13] found that a prior history of musculoskeletal pain was a risk factor for developing musculoskeletal post-COVID pain in hospitalized patients. The current study found that previous history of migraine and whiplash injury was likewise factors associated with the development of de novo widespread post-COVID pain in nonhospitalized COVID-19 survivors. This association can be explained by the fact that whiplash-associated disorders, migraines, and widespread pain share common underlying mechanisms and often are present with pain sensitization.[42,43]

It is well established that socioeconomic comorbidities play a significant role in relation to chronic pain.[44–47] Especially settings with low income and lower levels of education have been shown to influence the prevalence and severity of perceived pain in chronic pain conditions.[44-46] Among 3 applied socioeconomic factors, the current study found that higher income and educational level were protective factors when compared to low income and low educational level in the population, hence confirming existing literature.[48,49] A possible explanation for the differences seen within educational level could be that higher education provides more resources to cope with chronic pain conditions.[43,46] Low income seems to reflect fewer possibilities to engage in better treatments or coping strategies for chronic pain conditions.[46] The literature,

however, is incongruent, related to income as a socioeconomic driver of chronic pain as other studies have shown only small to no effect of income.[45,46] The findings from the present study highlight that, to a lesser extent, income must be considered when trying to understand the distribution of prevalence of post-COVID pain.

Relative to the lowest quartile, the risk of developing widespread post-COVID pain after a SARS-CoV-2 infection seems to increase significantly over time, which was not expected as normally long-term problems after an infection tend to decrease steadily over time. However, the time from infection could be a proxy measure of string effect as the population was stratified across 3 dominant variants of the SARS-CoV-2 virus: the Wuhan strain (March 2020 to September 2020), and Alpha (October 2020 to June 2021), and Delta variants (July 2021 to December 2021). The stratification of the strains was based on sequencing data from RT-PCR tests conducted by Statens Serum Institut.[50] In a recent systematic review of the literature, Fernández-de-las-Peñas et al[51] concluded that the prevalence of long-COVID symptoms decreased across variants. It varied from the Wuhan strain (40–60% reporting long COVID) over the Alpha variant (36%) to the Delta variant (11%).[51–53] Previous literature has shown that the prevalence is highly dependent on several factors, including hospitalization versus nonhospitalization, follow-up period, and inclusion or exclusion of other nonpain-related symptoms of long COVID and onset symptoms.[2,4,54] Fernández-de-las-Peñas et al[2,4] also showed that the prevalence of post-COVID pain was higher at 90 days postinfection compared to 60 days and, more interestingly, 180 days, supporting existing literature that prevalence seems to rise until 9 months after infection and then fade over time until 180 days postinfection. Data from this study show an increase in the prevalence of de novo widespread post-COVID pain symptoms stratified in time from infection. At the same cutoff time for data collection, data reveal a decrease in the prevalence across the different SARS-CoV-2 variants. With the data available, it is not possible to assign the prevalence to either an effect of time from infection or the SARS-CoV-2 strain/variant; it is not statistically possible to isolate the investigated effect to either time or strain. It would be interesting to look further into this in future studies.

In the cohort with previous chronic pain that reported de novo widespread post-COVID pain, 25.4% of a subsample of 57.2% already taking medication before COVID, reported taking additional medication. This is in range with a recent Nordic survey[55] showing that only 23% of patients took nonsteroidal anti-inflammatory drugs for their pain, like those symptoms reported in the current study. The low rate of additional medication could be a result of the strong focus on precaution with long-term use of analgesics (normally nonsteroidal anti-inflammatory drugs and acetaminophen).[56,57] The current study did not have permission to access the national prescription register to get detailed information related to which drugs were prescribed.

Finally, the role of emotional factors surrounding the COVID-19 outbreak should not be ignored since they can play a relevant role in the development of post-COVID pain.[58] The presence of stress in the evaluated cohort of nonhospitalized COVID-19 survivors was a risk factor for developing de novo widespread post-COVID pain. The role of stress as a general promoting factor for chronic musculoskeletal pain is clearly recognized,[59] with a strong association in individuals with fibromyalgia.[19] The current study increases evidence of the role of perceived stress in the development of widespread post-COVID pain in people suffering from mild to moderate SARS-CoV-2 infection.

Limitations

Although this is the first nationwide study focused specifically on widespread post-COVID pain in nonhospitalized COVID-19 survivors, some limitations are recognized. First, data were collected via an online survey based on self-reports and hence a collection procedure with a potential bias in population-based survey studies. Nevertheless, it should be noted that most studies investigating post-COVID symptoms have used similar data collection procedures,[4] and the large sample size included in this study does not permit to conduct of face-to-face interviews. Second, only data on widespread pain were collected. Accordingly, the prevalence rate observed in our study does not represent the total prevalence of post-COVID pain, just a subgroup of nonhospitalized patients. Third, the phenotype of post-COVID pain was not identified, hence, we presume that widespread pain would be of musculoskeletal origin; however, we cannot exclude a neuropathic component. Fourth, due to the self-reported nature of the data collection procedure, specific biomarkers were not evaluated. Finally, the cross-sectional design does not allow to evaluate the evolution of widespread post-COVID pain during the follow-up period, making it difficult to exclusively attribute SARS-CoV-2 infection to the presence of widespread pain symptoms 1 year after. The survey could be slightly biased toward less severe chronic pain patients. It is reasonable to assume that those with the most disabling pre-COVID chronic pain symptoms could suffer from worse long-term outcomes, thus not having the energy to respond to the survey. Further, the sample included subjects infected with a mixture of the Wuhan strain and also Alpha and Delta variants. Longitudinal studies investigating the evolution of widespread post-COVID pain in nonhospitalized COVID-19 survivors are needed.

Conclusions

This large nationwide, population-based survey found a 5.3% prevalence of de novo widespread post-COVID pain in a cohort of nonhospitalized COVID-19 survivors 1 year after the infection. Of participants suffering from de novo widespread post-COVID pain, 75.6% reported a pain intensity of moderate to severe. Mild pain intensity was

reported by 18.9% and very severe by 2.7%. Older age, female sex, higher BMI, and previous history of migraine, whiplash, stress, type-2 diabetes mellitus, neurological disorders, low income, and low educational level were risk factors associated with the presence of de novo widespread post-COVID pain in nonhospitalized COVID-19 survivors. It is possible that this subgroup of COVID-19 survivors developing widespread post-COVID pain could resemble the pain pattern of pain sensitization more than other pain conditions, such as fibromyalgia, and should attract specific clinical and management attention.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Disclosures

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2023.08.011.

References

1. World Health Organization (WHO): Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Published February 24, 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf Accessed February 13, 2023.

2. Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, *et al.* Prevalence of Post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. Eur J Int Med 92:55-70, 2021.

3. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, *et al.* More than 50 Long-term effects of COVID-19: A systematic review and meta-analysis. Sci Rep 11:16144, 2021.

4. Fernández-de-las-Peñas C, Navarro-Santana M, Plaza-Manzano G, Palacios-Ceña, Arendt-Nielsen L: Time course prevalence of Post-COVID pain symptoms of musculoskeletal origin in patients who had survived to SARS-CoV-2 infection: A systematic review and meta-analysis. Pain 163:1220-1231, 2022.

5. Bakılan F, Gökmen iG, Ortanca B, *et al.* Musculoskeletal symptoms and related factors in post-acute COVID-19 patients. Int J Clin Pract 75:14734, 2021.

6. Bileviciute-Ljungar I, Norrefalk JR, Borg K: Pain burden in post-COVID-19 syndrome following mild COVID-19 infection. J Clin Med 11:771, 2022.

7. Karaarslan F, Demircioğlu GF, Kardeş S: Post-discharge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19: Prospective follow-up by phone interviews. Rheumatol Int 41:1263-1271, 2021.

8. Soares FHC, Kubota GT, Fernandes AM, *et al.* Prevalence and characteristics of new-onset pain in COVID-19 survivors, a controlled study. Eur J Pain 25:1342-1354, 2021.

9. Munblit D, Nicholson T, Akrami A, *et al.* A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: An international Delphi consensus study. Lancet Respir Med 10:715-724, 2022.

10. Peter RS, Nieters A, Kräusslich HG, *et al.* Post-acute sequelae of COVID-19 six to 12 months after infection: Population-based study. BMJ 379:071050, 2022.

11. Fiala K, Martens J, Abd-Elsayed A: Post-COVID pain syndromes. Curr Pain Headache Rep 26:379-383, 2022.

12. Yelin D, Margalit I, Nehme M, *et al.* Patterns of long COVID symptoms: A multi-center cross sectional study. J Clin Med 11:898, 2022.

13. Fernández-de-las-Peñas C, de-la-Llave-Rincón AI, Ortega-Santiago R, *et al.* Prevalence and risk factors of musculoskeletal pain symptoms as long-term post-COVID sequelae in hospitalized COVID-19 survivors: A multicenter study. Pain 163:989-996, 2022.

14. Sørensen AIV, Spiliopoulos L, Bager P, *et al.* A nationwide questionnaire study of post-acute symptoms and health problems after SARS-CoV-2 infection in Denmark. Nat Commun 13:4213, 2022.

15. Alonso-Matielo H, da Silva Oliveira VR, de Oliveira VT, Dale CS: Pain in COVID era. Front Physiol 12:624154, 2021.

16. Fernández-de-las-Peñas C, Nijs J, Neblett R, *et al.* Phenotyping post-COVID pain as a nociceptive, neuropathic, or nociplastic pain condition. Biomedicines 10:2562, 2022.

17. Statens Serum Institut: COVID-19. https://covid19.ssi.dk/ Accessed February 13, 2023.

18. Danish Agency for Digitalisation: Danish digital mail. https://digst.dk/it-loesninger/digital-post/ Accessed February 13, 2023.

19. Perrot S, Cohen M, Barke A, Korwisi B, Rief W, Treede RD: IASP Taskforce for the Classification of Chronic Pain: The IASP classification of chronic pain for ICD-11: Chronic secondary musculoskeletal pain. Pain 160:77-82, 2019.

20. International Severe Acute Respiratory and emerging Infection Consortium (ISARIC): COVID-19 Long-term protocol. https://isaric.org/research/covid-19-clinical-research-resources/covid-19-long-term-follow-up-study/ Accessed February 13, 2023.

21. International Standard Classification of Education (ISCED): Eurostat. Last edited June 7, 2023. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=International_Standard_Classification_of_Education_(ISCED)#Implementation_of_ISCED_2011_.28levels_of_education.29 Accessed June 26, 2023.

22. Belsley DA: A guide to using the collinearity diagnostics. Comput Sci Econ Manag 4:1991, 1991.

23. Jarlstrup N: §Røg – en undersøgelse af tobak, adfærd or regler. Published April 12, 2023. tps://www.sdu.dk/da/sif/rapporter/2023/$roeg_tobak_adfaerd_regler Accessed June 29, 2023.

24. Fernández-de-las-Peñas C, Rodríguez-Jiménez J, Cancela-Cilleruelo I, *et al.* Post-COVID-19 symptoms 2 years after SARS-CoV-2 infection among hospitalized vs non-hospitalized patients. JAMA Netw Open 5:2242106, 2022.

25. Fernández-de-las-Peñas C, Cancela-Cilleruelo I, Moro-López-Menchero P, *et al.* Prevalence of musculoskeletal post-COVID pain in hospitalized COVID-19 survivors depending on infection with the historical, Alpha or Delta SARS-CoV-2 variant. Biomedicines 10:1951, 2022.

26. Gavrilova N, Soprun L, Lukashenko M, *et al.* New clinical phenotype of the Post-COVID syndrome: Fibromyalgia and joint hypermobility condition. Pathophysiology 29:24-29, 2022.

27. Haider S, Janowski AJ, Lesnak JB, *et al.* A comparison of pain, fatigue, and function between post-COVID-19 condition, fibromyalgia, and chronic fatigue syndrome: A survey study. Pain 164:385-401, 2023.

28. Arendt-Nielsen L, Graven-Nielsen T: Central sensitization in fibromyalgia and other musculoskeletal disorders. Curr Pain Headache Rep 7:355-361, 2003.

29. Ryabkova VA, Churilov LP, Shoenfeld Y: Neuroimmunology: What role for autoimmunity, neuroinflammation, and small fiber neuropathy in fibromyalgia, chronic fatigue syndrome, and adverse events after human papillomavirus vaccination? Int J Mol Sci 20:5164, 2019.

30. Khoja O, Silva Passadouro B, Mulvey M, *et al.* Clinical characteristics and mechanisms of musculoskeletal pain in long COVID. J Pain Res 15:1729-1748, 2022.

31. Maglietta G, Diodati F, Puntoni M, *et al.* Prognostic factors for post-COVID-19 syndrome: A systematic review and meta-analysis. J Clin Med 11:1541, 2022.

32. Notarte KI, de Oliveira MHS, Peligro PJ, *et al.* Age, sex and previous comorbidities as risk factors not associated with SARS-CoV-2 infection for long COVID-19: A systematic review and meta-analysis. J Clin Med 11:7314, 2022.

33. Savin E, Rosenn G, Tsur AM, *et al.* The possible onset of fibromyalgia following acute COVID-19 infection. PLoS One 18:0281593, 2023.

34. Mills SEE, Nicolson KP, Smith BH: Chronic pain: A review of its epidemiology and associated factors in population-based studies. Br J Anaesth 123:273-283, 2019.

35. Ganesh R, Grach SL, Ghosh AK, *et al.* The female-predominant persistent immune dysregulation of the post-COVID syndrome. Mayo Clin Proc 97:454-464, 2022.

36. Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A: Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine 36:100899, 2021.

37. Abumweis S, Alrefai W, Alzoughool F: Association of obesity with COVID-19 diseases severity and mortality: A meta-analysis of studies. Obes Med 33:100431, 2022.

38. Chen Z, Peng Y, Wu X, *et al.* Comorbidities and complications of COVID-19 associated with disease severity, progression, and mortality in China with centralized isolation and hospitalization: A systematic review and meta-analysis. Front Public Health 10:923485, 2022.

39. D'Onghia M, Ciaffi J, Lisi L, *et al.* Fibromyalgia and obesity: A comprehensive systematic review and meta-analysis. Semin Arthritis Rheum 51:409-424, 2021.

40. Cox ER, Coombes JS, Keating SE, Burton NW, Coombes BK: Not a painless condition: Rheumatological and musculoskeletal symptoms in type 2 diabetes, and the implications for exercise participation. Curr Diabetes Rev 16:211-219, 2020.

41. Henningsen P, Hausteiner-Wiehle C, Häuser W: Migraine in the context of chronic primary pain, chronic overlapping pain disorders, and functional somatic disorders: A narrative review. Headache 62:1272-1280, 2022.

42. Karsan N, Goadsby PJ: Migraine is more than just headache: Is the link to chronic fatigue and mood disorders simply due to shared biological systems? Front Hum Neurosci 15:646692, 2021.

43. Eriksen J, Jensen MK, Sjøgren P, Ekholm O, Rasmussen NK: Epidemiology of chronic non-malignant pain in Denmark. Pain 106:221-228, 2003.

44. Goode AP, Freburger JK, Carey TS: The influence of rural versus urban residence on utilization and receipt of care for chronic low back pain. J Rural Health 29:205-214, 2013.

45. Newman A, Van Dyke B, Torres C, *et al.* The relationship of sociodemographic and psychological variables with chronic pain variables in a low-income population. Pain 158:1687-1696, 2017.

46. Saastamoinen P, Leino-Arjas P, Laaksonen M, Lahelma E: Socio-economic differences in the prevalence of acute, chronic and disabling chronic pain among ageing employees. Pain 114:364-371, 2005.

47. Bonathan C, Hearn L, Williams ACC: Socioeconomic status and the course and consequences of chronic pain. Pain Manag 3:159-162, 2013.

48. Prego-Domínguez J, Khazaeipour Z, Mallah N, Takkouche B: Socioeconomic status and occurrence of chronic pain: A meta-analysis. Rheumatology 60:1091-1105, 2021.

49. Statens Serum Institut: Evaluation of population immunity against SARS-CoV-2 in Denmark. Published January 26, 2022. https://www.sst.dk/-/media/Udgivelser/2022/Corona/Vurdering-af-befolkningsimmunitet-mod-SARS-CoV-2-i-Danmark.ashx Accessed July 7, 2023.

50. Fernández-de-las-Peñas C, Notarte KI, Peligro PJ, *et al.* Long-COVID symptoms in individuals infected with different SARS-CoV-2 variants of concern: A systematic review of the literature. Viruses 14:2629, 2022.

51. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ: Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. Lancet 399:2263-2264, 2022.

52. Azzolini E, Levi R, Sarti R, *et al.* Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. JAMA 328:676-678, 2022.

53. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B: Global prevalence of post COVID-19 condition or long COVID: A meta-analysis and systematic review. J Infect Dis 226:1593-1607, 2022.

54. Arendt-Nielsen L, Schepman P, Blakeman KH, *et al.* Prescription patterns and predictors of unmet pain relief in patients with difficult-to-treat osteoarthritis in the Nordics: Analyses from the BISCUITS study. Scand J Pain 23:149-160, 2022.

55. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D: Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 10:287-333, 2006.

56. Galluzzo V, Zazzara MB, Ciciarello F, *et al.* Gemelli against COVID-19 Post-Acute Care Team, Use of first-line oral analgesics during and after COVID-19: Results from a survey on a sample of Italian 696 COVID-19 survivors with post-acute symptoms. J Clin Med 12:2992, 2023.

57. Chaturvedi SK: Health anxiety, health-related life events, and somatization during COVID-19 pandemic can increase chronic pain. Pain 161:2652, 2020.

58. Buscemi V, Chang WJ, Liston MB, McAuley JH, Schabrun SM: The role of perceived stress and life stressors in the development of chronic musculoskeletal pain disorders: A systematic review. J Pain 20:1127-1139, 2019.

59. Kaleycheva N, Cullen AE, Evans R, Harris T, Nicholson T, Chalder T: The role of lifetime stressors in adult fibromyalgia: Systematic review and meta-analysis of case-control studies. Psychol Med 51:177-193, 2021.