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Chronic pain is associated with higher risk of developing and being hospitalized for COVID-19: a Mendelian randomization study

Rheumatology key message

- People with chronic pain are at higher risk of developing COVID-19 and subsequent adverse outcomes.

DEAR EDITOR, Individuals with chronic pain—a characteristic symptom of FM—have increased mortality, including >5-fold higher risk of respiratory disease-related deaths [1]. Whether excess mortality is driven by acute respiratory infections or chronic respiratory diseases has not been examined. This distinction is important, as people with chronic pain may represent a vulnerable population for COVID-19. Traditional observational study designs are limited by confounding and reverse causation, for example, obesity and smoking are both bidirectionally associated with chronic pain and are also strong risk factors for poor outcomes in COVID-19. Mendelian randomization (MR) uses genetic variants as instrumental variables to estimate the causal effect of an exposure on an outcome that is less susceptible to these biases [2]. We aimed to estimate the influence of chronic pain on COVID-19, and vice versa, in univariable and multivariable MR accounting for BMI and smoking.

We used genome-wide association data from 112 612 any-COVID-19 cases (lab-confirmed, physician-diagnosed or self-reported) and 2 474 079 population controls, 24 274 hospitalized COVID-19 cases and 2 061 529 controls, and 8779 very severe COVID-19 cases (respiratory support or death) and 1 001 875 controls [3]. To avoid the limitations of using binary exposures in MR [4], we used a related trait—multisite chronic pain (MSCP)—from 387 649 UK biobank participants [5]. MSCP represents the sum of seven chronic pain sites across the body (head, face, neck/shoulder, back, stomach/abdomen, hip, knee) and is strongly correlated with chronic widespread pain [5]. MSCP was instrumented using 39 independent genome-wide significant ($P < 5 \times 10^{-8}$) variants. A standard and conditional F statistic of >10 was taken to suggest adequate instrument strength in univariable and multivariable MR, respectively. We employed the inverse variance weighted method for the primary analysis and sensitivity methods (e.g. MR-Egger) to explore potential pleiotropy. We applied multivariable MR [6] to additionally account for effects from BMI and smoking. Sensitivity methods were used to account

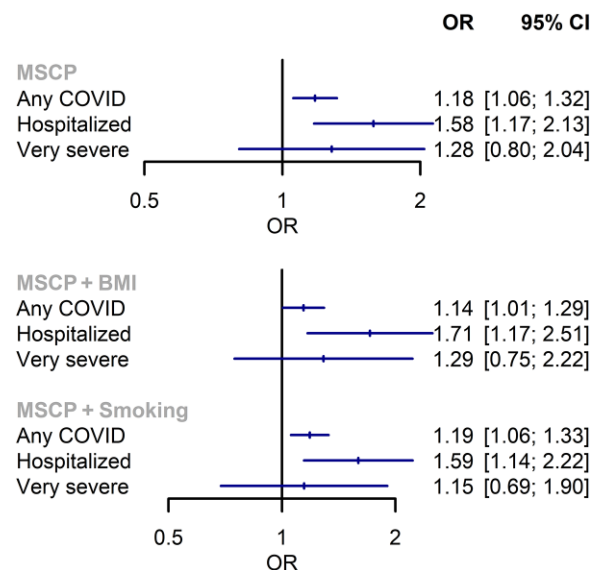
for weak instruments when required [7], which attenuates estimates to the null where populations are non-overlapping, as in this analysis. Finally, ‘reverse’ MR was performed to estimate the effect of COVID-19 on MSCP. Additional methods are presented in the [Supplementary Materials](#), available at *Rheumatology* online.

The F statistic for MSCP was 17. Each additional site of chronic pain increased the risk of any COVID-19 [odds ratio (OR) 1.18; 95% CI 1.06, 1.32; $P = 0.003$] and hospitalization (OR 1.58; 95% CI 1.17, 2.13; $P = 0.003$) (Fig. 1). The results from MR-Egger (any COVID: OR 2.73; 95% CI 1.68, 4.44; $P = 2.49 \times 10^{-4}$; hospitalization: OR 5.57; 95% CI 1.27, 24.43; $P = 0.029$) and other univariable sensitivity analyses were consistent with the primary analysis (shown in the [Supplementary Materials](#), available at *Rheumatology* online).

In multivariable MR, conditional F statistics for MSCP and BMI (9 and 30) and MSCP and smoking (19 and 9) suggested that analyses could be potentially influenced by weak instrument bias. Estimates accounting for BMI or smoking were not meaningfully different from univariable analyses, whether using weak instruments (Fig. 1) or with additional analyses accounting for weak instruments ([Supplementary Materials](#), available at *Rheumatology* online).

Genetic liability to COVID-19 was positively associated with MSCP (any COVID: beta = 0.04, $P = 0.048$; hospitalized: beta = 0.02, $P = 0.02$; severe: beta = 0.01, $P = 0.02$).

Fig. 1 Mendelian randomization estimates of the influence of multisite chronic pain on COVID-19, using univariable (top) and multivariable (bottom) models



MSCP: multisite chronic pain; OR: odds ratio.

Additional results are presented in the [Supplementary Materials](#), available at *Rheumatology* online.

The results of this study support a causal effect of chronic pain on the risk of developing and being hospitalized for COVID-19. These findings are consistent with prior observational data that demonstrate excess any-cause and respiratory-related mortality [1], and indicate that people with chronic pain are a vulnerable 'at-risk' group. We also showed that genetic liability for COVID-19 increases the risk of chronic pain. Recent studies have shown small-fibre pathology and autonomic dysfunction in 'long COVID', suggestive of a possible temporal association between infection and the nervous system [8]. The main limitation of this analysis is the as-yet unclear genetic basis of MSCP, which may pick up the genetic architecture of multiple diseases proximal to MSCP and could lead to mis-specification of the primary phenotype in this analysis. However, the findings were robust to multivariable MR, even when accounting for potentially confounding traits such as smoking and BMI. The results were also supported by multiple pleiotropy robust methods. Further studies are needed to replicate these findings in cohorts with non-European ancestries. In conclusion, genetic analysis supports the hypothesis that chronic pain patient groups are at higher risk of and developing COVID-19 and subsequent adverse outcomes, which could potentially inform public health policy.

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Data availability statement

All data used in this study are publicly available and accessible through relevant citations detailed.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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