

Title: A Case-Crossover Phenome-wide Association Study (PheWAS) for Understanding Post-COVID-19 Diagnosis Patterns

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Key Points

Question: What patterns of clinical diagnosis tend to occur more frequently after a COVID-19 infection and how do they vary by COVID-19 severity and vaccination status?

Findings: In a cohort of 36,856 COVID-19-positive patients, using a case-crossover phenome-wide association analysis that controls for within-subject confounders, we found symptoms such as anxiety disorder, cardiac dysrhythmias, and respiratory failure to be significantly associated with the “post-COVID-19 period.” Patients with severe COVID-19 were more likely to receive diagnoses related to respiratory conditions in their “post-COVID-19 period” compared to those with mild/moderate COVID-19. The landscape of phenome-wide association signals for the vaccinated group featured common chronic conditions when compared to the signals in the unvaccinated group.

Meaning: Symptoms across multiple organ systems, especially in the mental, circulatory, and respiratory domains, were associated with the “post-COVID-19 period.” Characterization of post-COVID-19 diagnosis patterns is crucial to understand the long term and future healthcare burden of COVID-19.

Abstract

Importance: Post COVID-19 condition (PCC) is known to affect a large proportion of COVID-19 survivors. Robust study design and methods are needed to understand post-COVID-19 diagnosis patterns in all COVID-19 survivors, not just the ones clinically diagnosed with PCC.

Objective: To assess which diagnoses appear more frequently after a COVID-19 infection and how they differ by COVID-19 severity and vaccination status.

Design: We applied a case-crossover phenome-wide association study (PheWAS) in a retrospective cohort of COVID-19 survivors, comparing the occurrences of 1,649 diagnosis-based phenotype codes (PheCodes) pre- and post-COVID-19 infection periods in the same individual using a conditional logistic regression.

Setting: Patients tested for or diagnosed with COVID-19 at Michigan Medicine from March 10, 2020 through May 1, 2022.

Participants: 36,856 SARS-CoV-2-positive patients and 141,615 age- and sex-matched SARS-CoV-2-negative patients as a comparison group for sensitivity analysis.

Exposure: SARS-CoV-2 virus infection as determined by RT-PCR testing and/or clinical evaluation.

Main Outcomes and Measures: We compared the rate of occurrence of 1,649 disease classification codes in “pre-” and “post-COVID-19 periods”. We studied how this pattern varied by COVID-19 severity and vaccination status at the time of infection.

Results: Using a case-crossover PheWAS framework, we found mental, circulatory, and respiratory disorders to be strongly associated with the “post-COVID-19 period” for the overall COVID-19-positive cohort. A total of 325 PheCodes reached phenome-wide significance ($p < 3e-05$), and top hits included cardiac dysrhythmias (OR=1.7 [95%CI: 1.6-1.9]), respiratory failure, insufficiency, arrest (OR=3.1 [95%CI: 2.7-3.5]) and anxiety disorder (OR=1.7 [95%CI: 1.6-1.8]). In the patients with severe disease, we found stronger associations with many respiratory and circulatory disorders, such as pneumonia ($p=2.1e-18$) and acute pulmonary heart disease ($p=2.4e-8$), and the “post-COVID-19 period,” compared to those with mild/moderate disease. Test negative patients exhibited a somewhat similar association pattern to those fully vaccinated, with mental health and chronic circulatory diseases rising to the top of the association list in these groups.

Conclusions and Relevance: Our results confirm that patients experience myriad symptoms more than 28 days after SARS-CoV-2 infection, but especially mental, circulatory, and respiratory disorders. Our case-crossover PheWAS approach controls for within-person confounders that are time-invariant. Comparison to test negatives with a similar design helped identify enrichment specific to COVID-19. As we look into the future, we must be aware of COVID-19 survivors’ healthcare needs in the period after infection.

Introduction

Though most patients with Coronavirus Disease 2019 (COVID-19) recover¹, many survivors report symptoms long after disease onset, a condition commonly referred to as “long COVID” or “post COVID-19 condition” (hereinafter abbreviated as PCC).^{2–4} While initially the names and definitions of PCC were highly heterogeneous, the consensus clinical case definition³ proposed by the WHO in October 2021 represented a significant step towards reaching global consistency. A recent meta-analysis estimated that 43% (95%CI: 39%-46%) of COVID-19 survivors experience at least one lingering condition post-COVID-19.⁵ This, paired with estimates for global COVID-19 reported case counts⁶, the estimated prevalence of PCC among initially asymptomatic cases⁷, and the fraction of unreported COVID-19 infections^{8,9}, forms the basis that hundreds of millions of people may have or have had post-COVID-19-related health complications.

Female sex, older age, severe COVID-19, and comorbidities such as asthma are claimed to be associated with PCC.⁵ Common symptoms include fatigue, brain fog/memory issues, headache, heart conditions, respiratory conditions, sleep disorders, and mental health conditions,⁴ but PCC symptomatology still remains heterogeneous. Recent research has shown that COVID-19 may increase risk for cardiovascular events, kidney-related outcomes, and diabetes sometimes long after infection^{10–12} and that PCC can persist for months after infection^{13,14}. Regardless of a formal diagnosis, several surveys indicated that post-COVID-19-related disabilities have affected a large proportion of the population^{15–17}.

However, there are also skepticisms and contradictions in the literature. One recent study suggested that not every new or persistent symptom post-infection can be attributed to a confirmed COVID-19 diagnosis.¹⁸ Another important question is whether vaccination or later SARS-CoV-2 variants reduces PCC development. To date, results have been inconsistent, with some studies finding vaccination to confer a protective effect, but others finding the contrary.^{19–}

While a proper population-based survivorship cohort with adequate follow-up time is the ideal study design to understand post-COVID-19 clinical outcomes, electronic health records (EHRs) offer snapshots of patients' health status and thus allow comparisons of the medical phenotype of COVID-19-positive patients before and after COVID-19 diagnosis. EHRs are easily accessible and enabled many studies on post COVID-19 complications.^{10–12,14,23,24} Phenome-Wide Association Studies (PheWAS) are an increasingly common EHR-based method to agnostically find associations between hundreds of phenotypes and some other health-related factor (typically a genetic variant).²⁵ Recently, PheWAS have been used to understand the relationship between pre-existing conditions, baseline characteristics and COVID-19 outcomes.²⁶ Such studies can be error-prone due to lack of a suitable control group or confounding due to differences in other patient characteristics determining who is getting tested and diagnosed for COVID-19 as well as who is seeking post-COVID-19 care. Researchers may consider matching, weighting or regression adjustment as potential remedies to this problem, but these methods are only able to adjust for a limited set of *measured* confounders.^{27,28}

The case-crossover design is an elegant design-based solution which reduces potential confounding by using events observed for the same person during suitably defined case and control periods.^{29,30} What results is, effectively, a matched case-control design that controls for both observed and unobserved person-level confounders that are invariant over the case and control windows. Case-crossover designs have been used to study early COVID-19 detection and post-COVID-19-vaccination cerebral venous thrombosis.^{31,32} One particular study by Murk et al. used claims data to estimate the association between patient diagnoses and the time period after COVID-19 infection.³³

Though in October 2021 a new diagnosis code specifically for PCC was introduced³⁴, thus facilitating the clear identification of PCC patients, in this study we took an agnostic look across hundreds of diagnoses to understand which ones are more commonly seen post-COVID-19

using a case-crossover design with more than two years of follow-up data. We conduct analyses stratified by COVID-19 severity and vaccination status. We compare these results to the results of the same analysis applied to test negative controls to discern unique contributions of COVID-19. Using this approach, we aim to improve our understanding of post-COVID-19 diagnosis patterns and consequently to advance healthcare and societal support for all COVID-19 survivors.

Methods

COVID-19-positive Cohort

Data were extracted retrospectively from EHRs for patients in the Michigan Medicine (MM) health system. Ethical review and approval were waived for this study due to its qualification for a federal exemption as secondary research for which consent is not required. Determination for exemption was made by the University of Michigan Medical School Institutional Review Board (study ID: HUM00180294). Individual-level data included de-identified information regarding reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2, patient demographics, diagnoses, vaccinations, hospitalizations, ICU admission, and death. We included all adult individuals with either 1) positive RT-PCR test result or 2) diagnosis of COVID-19 infection based on International Classification of Disease (ICD)-10-CM codes U07.1 or U07.2 between March 10, 2020, to May 1, 2022. We defined the date of the first positive test or diagnosis as the index test date for each patient. For patients with multiple positive tests, we considered their first positive test as the index test date. Patients with missing test dates were excluded from this analysis.

Test Negative Controls

We also measured test negative controls - patients tested, but who never received a positive RT-PCR result nor a COVID-19 diagnosis. We matched negative to positive patients at a 4:1 ratio on age and gender. The index test date for negative patients who were tested multiple times was defined as the date of their first COVID-19 test to ensure sufficient follow-up post-test.

Study Design

We used a case-crossover design where each COVID-19-positive case served as its own control. We defined three time periods relative to the index test date (time zero): “pre-COVID-19

period” (-2 years to -14 days), “acute and short COVID-19 period” (-14 days to +28 days), and “post-COVID-19 period” (+28 days to +1 year; **Figure 1**). Thus, the “post-COVID-19 period” did not include the acute phase of COVID-19. We included 14 days prior to the index test date in the “acute and short COVID-19 period” to account for individuals who may have had COVID-19 and related symptoms before testing positive. Patients were included in the study if they had at least one EHR encounter with a diagnosis in both the “pre-” and “post-COVID-19 period.”

We implemented two matching schemes to be used in the case-crossover design-based PheWAS. Primarily, we used a L:M matched design in which we randomly sampled (without replacement) up to L case windows (“cases”) and up to M control windows (“controls”), each S days in length, from each study participant’s “post-COVID-19 period” and “pre-COVID-19 period”, respectively (termed L:M matched S-day analysis). We also used a fixed window design where we selected 1 case and 1 control window (of length S days) from the date most proximal to the index test (termed fixed S-day analysis).

Demographic and Clinical Variables

Age, gender, race, and Body Mass Index (BMI) were reported from patients’ EHRs. Patients aged ≥ 90 years were coded as being exactly 90 years old for confidentiality reasons. A patient was considered a MM primary care patient if they received primary care at MM in the last two years. Comorbidity score was calculated as described in Gu et al³⁵.

COVID-19 Severity

COVID-19-related hospital and ICU admission were defined for COVID-19 positive patients as having each respective outcome within 30 days following the index test date. COVID-19-related death was defined as death within 60 days following the index test date. These outcomes describe 30-day all-cause-hospitalization and 60-day all-cause-mortality following a COVID positive test.

We define the composite outcome “severe COVID-19” if a COVID-19 patient experienced a COVID-19-related hospitalization, ICU admission, or death as defined above. A patient is considered “mild/moderate COVID-19” otherwise.

COVID-19 Vaccination

The date on which a person was considered fully vaccinated was after either 1) two doses of Moderna or Pfizer-BioNTech or 2) one dose of Janssen vaccine, and 21 or more days had elapsed after their last dose.³⁶ Patients were considered unvaccinated if they had exactly zero or an unknown number of doses at index test date. Partially vaccinated patients were not included in the stratified analysis but were included in the overall analysis.

Diagnosis Code Mapping

ICD diagnosis codes were extracted for each patient and mapped to their corresponding PheCodes according to the PheWAS catalog ICD maps.³⁷ Standard PheCode exclusions were applied, and one observed PheCode during a corresponding time window was considered the presence of a diagnosis. The totality of observed PheCodes for an individual was termed their “phenome.” We grouped PheCodes into symptom groups as defined in the PheWAS catalog³⁸.

Descriptive Analysis of Diagnosis Patterns

We tabulated presence of any new PheCodes (and *PCC-related* PheCodes as defined in **eTable 1**)⁴ as well as the number of new PheCodes received during the “post-COVID-19 period.” A PheCode was considered new if it was present in the “post-COVID-19 period” but not present during the “pre-COVID-19 period.” Additionally, we counted visits per month and follow-up time (in weeks) during both the “pre-“ and “post-COVID-19 periods”. A visit was defined as any unique day on which at least one diagnosis was recorded, and follow-up time was computed by taking the difference between the date most proximal to the index test date for a period (-14 days for

“pre-COVID-19 period”, +28 days for “post-COVID-19 period”) and the most distal date on which they received a diagnosis in their “pre-“ and “post-COVID-19 periods” (up to -2 years for “pre-COVID-19 period”, up to +1 year for “post-COVID-19 period”).

Statistical Analysis for PheWAS

We used a PheWAS approach with a case-crossover design. To account for the within-subject matched analysis, conditional logistic regression was used to model the association between case and control windows and patients’ phenomes. Let us consider a 1:M matched case-crossover design with N patients analyzing K PheCodes. Let $i = 1, 2, \dots, N$ index patients, $j = 1, 2, \dots, M + 1$ index case and control windows of a patient, and $k = 1, 2, \dots, K$ index Phecodes. Patient i ’s case window ($j = 1$) is matched to multiple control windows ($j = 2, \dots, M + 1$). For each PheCode k , we fit the following model:

$$\text{logit}[\text{Prob}(\text{Window}_{ij} = \text{case} \mid \text{PheCode}_{ij}^k)] = \beta_{0i}^k + \beta_1^k \text{PheCode}_{ij}^k$$

where PheCode_{ij}^k is an indicator for whether PheCode k is present in window j of patient i and Window_{ij} denotes the case/control window for patient i . The conditional logistic regression conditions on the matched design or the fact that Window_{i1} is a case window and $\text{Window}_{i2}, \dots, \text{Window}_{iM+1}$ are control windows for the same individual i , such that the patient-specific intercept β_{0i}^k is eliminated and the conditional likelihood only retains β_1^k , the coefficient of PheCode k shared by all patients. The resulting conditional likelihood for PheCode k takes the following form:

$$L^k_{CLR} = \prod_{i=1}^N \left[\frac{\exp(\beta_1^k \text{Phecode}_{i1}^k)}{\sum_{j=1}^{M+1} \exp(\beta_1^k \text{Phecode}_{ij}^k)} \right]$$

For a model to be run, we specified that at least 10 subjects (5 for cohorts with <5,000 subjects) in the analytic dataset should have a given PheCode in their case (control) periods. We used

Manhattan plots to visualize the p-values corresponding to the null hypotheses $H_{0k}: \beta_1^k = 0, k = 1, \dots, K$ and the directions of the association.

For each sampling scheme, a PheWAS was run on the entire COVID-19-positive cohort (termed “overall” cohort) and several subgroups – severe, mild/moderate, fully vaccinated, and unvaccinated patients. 1:4 matched 90-day sampling was used in the primary analysis. Sensitivity analyses included fixed 90-day, 1:2 matched 180-day, 2:4 matched 90-day, 1:4 matched 90-day on test negative controls, and 1:4 matched 90-day looking only at cohorts defined by year of infection (2020 vs. 2021+). For test negative controls, we performed PheWAS on controls matched to the overall cohort and to the severe cohort. We formally compared cohorts by testing for a difference in effect sizes (**eMethods 1**).

All analyses were performed in R (version 4.1.2)³⁹, and the PheWAS package was used.⁴⁰ Summary statistics are reported as median (interquartile range [IQR]) for continuous variables or n (%) for categorical variables. Odds Ratios (ORs) with Wald-type 95% Confidence Intervals (CIs) and p-values are reported from each conditional logistic regression model. Phenome-wide significance was determined by the Bonferroni-corrected p-value threshold (0.05/d, where d = number of PheCodes evaluated). PheCodes with p-values below the Bonferroni threshold are referred to as significant “hits.”

Results

Cohort Description

Between March 10, 2020 and May 1, 2022, 332,579 patients were tested or diagnosed for COVID-19 at MM. 36,856 COVID-19-positive patients were included in our study, to which 141,615 test negative controls were matched (see **eFigure 1** for a flow diagram defining the analytic cohort). Median (IQR) age was 47 (30-62), and 60% of the cohort was female (**Table 1**). Of the positive patients, 2,288 (6.2%) patients experienced severe COVID-19, and 34,568 (94%) had mild/moderate COVID-19. 10,834 (29%) patients were fully vaccinated and 24,280 (66%) were unvaccinated at their index test date.

Descriptive Diagnosis Patterns

Both COVID-19-positive (**Table 2**) and COVID-19-negative patients (**eTable 2**) received a similar number and rate of diagnoses in the “post-COVID-19 period”, and we saw a similar trend even when looking only at PCC-related diagnoses (**eTable 1**). Increasing COVID-19 severity led to increased numbers and rates of diagnosis (i.e., 89% of severe vs. 77% of mild/moderate with 1+ new diagnosis). Positives and negatives both most commonly received circulatory, mental, and digestive disorders in the “post-COVID-19 period” as well (**eTables 3 and 4**).

Overall Case-Crossover PheWAS Analysis

1,649 PheCodes were evaluated in the primary analysis for the overall cohort (**Figure 2A**), and a total of 325 PheCodes reached phenome-wide significance ($p < 3e-05$). We saw the highest proportion of phenome-wide significant hits in circulatory (56 hits/total of 171 circulatory codes; 33%), mental disorders (23/76; 30%), and respiratory (24/85; 28%; **Table 3**). The top hits in each of these groups were cardiac dysrhythmias ($p = 1.9e-78$, OR=1.7 [95%CI: 1.6-1.9]), respiratory failure, insufficiency, arrest ($p = 1.8e-70$, OR=3.1 [95%CI: 2.7-3.5]) and anxiety disorder ($p = 1.3e-91$, OR=1.7 [95%CI: 1.6-1.8]).

Stratified Analyses

By Severity: Top groups for the mild/moderate cohort (**Figure 2B**) were pregnancy complications (11/46; 24%), circulatory system (41/171; 24%), and neoplasms (33/141; 23%). Infectious and parasitic complications affecting pregnancy ($p=9.9e-61$, OR=8.6 [95%CI: 6.7-11.2]), hypertension ($p=2.2e-58$, OR=1.5 [95%CI: 1.4-1.6]), and skin cancer ($p=3.9e-24$, OR=1.8 [95%CI: 1.6-2.0]) were top hits in these groups. For the severe cohort, we saw a different pattern of hits (**Figure 2C**), with respiratory conditions being a top category (21/85; 25%). Other top groups include circulatory system (29/171; 17%) and hematopoietic conditions (10/62; 16%), and the top hit from these groups were respiratory failure, insufficiency, arrest ($p=1.6e-56$, OR=6.2 [95%CI: 4.9-7.7]), cardiac dysrhythmias ($p=1.1e-24$, OR=2.4 [95%CI: 2.0-2.8]), and other anemias ($p=1.4e-16$, OR=2.0 [95%CI: 1.7-2.4]).

By Vaccination Status: Among those fully vaccinated at index test date (**Figure 2D**), we saw mental disorders (17/76; 22%), circulatory system (33/171; 19%) and endocrine/metabolic (19/169; 11%). Anxiety disorder ($p=1.6e-55$, OR=2.1 [95%CI: 1.9-2.3]), essential hypertension ($p=1.0e-40$, OR=1.8 [95%CI: 1.7-2.0]), and type 2 diabetes ($p=6.2e-24$, OR=2.1 [95%CI: 1.8-2.5]) were top hits in these groups. The unvaccinated cohort (**Figure 2E**) was largely similar to the overall cohort with circulatory (45/171; 26%), mental disorders (19/76; 25%), and respiratory (20/85; 24%) being the top groups. Top hits in these groups were cardiac dysrhythmias ($p=1.2e-46$, OR=1.7 [95%CI: 1.6-1.8]), anxiety disorders ($p=5.3e-50$, OR=1.6 [95%CI: 1.5-1.7]), and respiratory failure, insufficiency, arrest ($p=5.7e-49$, OR=3.1 [95%CI: 2.7-3.7]).

Subgroup Comparison: A large proportion of circulatory hits was common across all cohorts. The most striking observation is the strength of association for respiratory conditions in the severe cohort. Comparing the top 20 hits from each subgroup revealed septicemia and protein-calorie malnutrition were unique to the severe cohort in addition to several severe respiratory

disorders; shortness of breath was unique to those unvaccinated (**eFigure 2**). Bearing in mind that p-value magnitudes are directly influenced by sample sizes (which are dissimilar across cohorts), we note that the p-value ranks/patterns of the mild/moderate, fully vaccinated, and unvaccinated subgroups appeared similar to the overall cohort, but the unvaccinated group was largely driving the strongest associations.

Comparison to Test Negative Controls

Circulatory (111/171; 65%), mental disorders (49/76; 64%), and endocrine/metabolic (91/169; 54%) were the top groups in the PheWAS analysis for the test negative cohort (**eFigure 3**). Top hits in these groups were hypertension ($p=7.9e-210$, OR=1.5 [95%CI: 1.4-1.5]), other mental disorder ($p=5.3e-208$, OR=2.1 [95%CI: 2.0-2.3]), and immunity deficiency ($p=2.2e-308$, OR=4.9 [95%CI: 4.5-5.3]). Details regarding odds ratios and p-values for this PheWAS as well as the primary analysis are in **eTable 5**.

The top symptom groups in negatives were similar to that seen in the fully vaccinated cohort. Viral pneumonia, disturbances of the sensation of smell and taste, and chronic fatigue syndrome were hits in the positive but not negative cohort (**eFigure 4**).

Sensitivity Analyses

We also conducted several sensitivity analyses to evaluate the effect our design and analytic choices made on the primary analysis. Increasing the number of cases and controls used resulted in higher power (more phenome-wide significant hits; **eFigures 5 and 6**). Using the fixed sampling scheme resulted in lower power and a different pattern of hits, although respiratory and circulatory conditions still gave a strong signal (**eFigure 7**). Those diagnosed in 2021 and beyond closely resembled the fully vaccinated cohort (**eFigure 8**).

Formal Comparison of Effect Sizes

By Severity and Vaccination Status: The severe cohort had larger effect sizes than the mild/moderate cohort for the vast majority of PheCodes (**eFigure 9**). Groups that tended to exhibit very large differences include respiratory (OR:1.40 vs 4.31 for pneumonia; $p=2.1e-18$) and circulatory system (OR:2.41 vs 9.12 for acute pulmonary heart disease; $p=2.4e-8$). When looking at vaccination status, those unvaccinated were more likely to be diagnosed with shortness of breath (OR:1.40 vs 1.93; $p=5.4e-5$) and immunity deficiency (OR:1.88 vs 3.71; $p=2.4e-9$) in the “post-COVID-19 period.”

Positive vs. Negative: The positive cohort had much larger effect sizes for many pregnancy complications (OR:6.56 vs 0.62 for infectious and parasitic complications affecting pregnancy; $p=7.3e-51$), respiratory disorders (OR:8.25 vs 2.18 for respiratory insufficiency; $p=8.8e-10$) and mental disorders (OR:1.68 vs 1.49 for anxiety disorder; $p=2.4e-5$).

Comparing the positive severe cohort to a test negative cohort matched only to the subgroup of severe patients, we found several circulatory and respiratory conditions have much stronger effects in the positive severe cohort (**eFigure 10**), validating the patterns seen in this subgroup. **eTable 6** gives full details of the effect size comparisons.

Discussion

Strengths and Principal Findings

In this study, we present a case-crossover PheWAS approach to characterize changes in diagnosis patterns after a COVID-19 infection. Our results show that the “post-COVID-19 period,” defined as +28 days to +1 year from a positive COVID-19 test or diagnosis, is associated with a wide variety of diagnoses across many organ systems. Though we looked at the data agnostically across the phenome, results are remarkably congruent with existing PCC literature in that we found mental, circulatory, and respiratory disorders to be highly enriched in the “post-COVID-19 period” in COVID-19 positives, with the former two groups also being enriched in COVID-19 negatives. Patients with severe COVID-19 were more likely to receive a wide variety of diagnoses, but particularly respiratory and circulatory diagnoses, in the “post-COVID-19 period,” compared to those with mild/moderate COVID-19. Fully vaccinated patients, whose enrichment patterns resembled the test negatives, were more likely than those unvaccinated to be diagnosed with chronic conditions like hypertension and anxiety in the “post-COVID-19 period.” This MM cohort has been extensively studied in the past^{26,35,41–43}, but the current study provides the longest follow-up time (over 2 years) to date and includes a “post-COVID-19 period.”

Contextualization of Results

Healthcare utilization metrics (**Table 2, eTable 2**) were very similar between COVID-19 positives and negatives. However, positives were getting diagnosed with *different kinds of* diagnoses than negatives. We observed much stronger effect sizes for respiratory and mental diagnoses in positives compared to negatives. Further, as results for the overall cohort are the composition of distinct association patterns of the subgroups therein, we note that strong respiratory signals we observed appear to have been driven by those with severe COVID-19. Severe patients also had stronger effect sizes for respiratory conditions than their matched

controls. The common hits between positives and negatives may be a result of our design's inability to control for time-varying factors, such as pandemic-driven changes in health-related behavior and the effects of aging. These findings highlight the need for strict diagnostic criteria for PCC such that coincidental diagnoses are not attributed to the COVID-19 infection. However, the current lack of understanding about the causal mechanisms of PCC hampers such a clear differentiation.

Surprisingly, we found fully vaccinated patients with breakthrough infections had similar association patterns to test negative controls. Many phenotypes with large effect sizes for fully vaccinated individuals (hypertension, anxiety disorder) were chronic disorders common across all included patients (**eTables 3 and 4**) and may be more related to willingness to see a physician and healthcare access over time rather than COVID-19 disease. It is worth noting that the COVID-19 virus itself was also different over time. During 2020, the Alpha variant was dominant, while in 2021 and 2022 (when vaccines were widely available in the US) the Delta and Omicron variants were dominant. Temporal variation in symptomatology may be because different variants attack different parts of the body.⁴⁴

It is interesting to note that allergies were strongly associated with the “post-COVID-19 period” in all cohorts including COVID-19-negative patients. Some new evidence suggests PCC responds to treatment with antihistamines.⁴⁵ Our finding that mental health disorders were highly enriched in the “post-COVID-19 period” in positives and negatives is consistent with the notion that the COVID-19 pandemic introduced new mental health challenges, partly due to social changes and partly due to how COVID-19 affects the brain.^{46,47}

Limitations

This study is limited by the implicit assumption in a case-crossover design that there exists no within-person time-varying confounders. However, many aspects of human behavior changed during the COVID-19 pandemic. For example, health-seeking behavior decreased after the pandemic started due to fear of the virus, government restrictions, and lack of healthcare resources.⁴⁸ If anything, the presence of this specific type of time-varying confounding would bias our results *against* seeing an effect because this confounding would result in a relative reduction in diagnoses during the “post-COVID-19 period”. Our analysis stratified by year also gives us confidence that this method is picking up a true signal. An alternative solution could be to add time-varying covariates to the models (i.e. prevalence of cases during the period).

We focused on individuals tested for COVID-19, but there exists a well-documented testing bias which could make our cohort non-representative, especially considering that testing at the beginning of the pandemic was restricted to symptomatic or at-risk individuals.⁴⁹ Additionally, some cases in our cohort presented for COVID-19 symptoms (“for COVID-19”), but others presented for something else and just happened to have COVID-19 (“with incidental COVID-19”), which may help explain the strong effect sizes we observed for pregnancy complications. EHRs are also prone to selection and classification bias.⁵⁰

Our analysis involved choosing the values for several design parameters including the matching ratio, the minimum case/control count, and the window size. It is difficult to know whether the parameters we chose were “correct,” but sensitivity analyses show our matching scheme is robust to the matching ratio and window size. We chose to censor diagnosis records at -2 and +1 years from the index test date, but it is possible that even if an individual has a healthcare visit during the follow-up, the diagnosis codes received during the visit do not comprehensively reflect their health state. Further, diagnosis codes may be poor reflections of the course of

disease. Finally, some spurious associations potentially appeared in our results due to biases we discussed, despite applying the Bonferroni correction.

Conclusions

We present a case-crossover PheWAS framework as a plausible agnostic screen that can be used to identify phenotypes associated with the “post-COVID-19 period.” Future research should investigate the mechanisms by which such sequelae can occur and the myriad factors that might put a patient at risk of new post COVID-19 symptoms.

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Contributions

Conceptualization: XS, LGF, BM

Methodology: SH, XS, LGF, BM

Supervision: XS, LGF, BM

Writing – original draft: SRH, CC, XS, LGF, BM

Writing – review & editing: SRH, CC, XS, LGF, BM

Conflicts of Interest

The authors have no competing interests.

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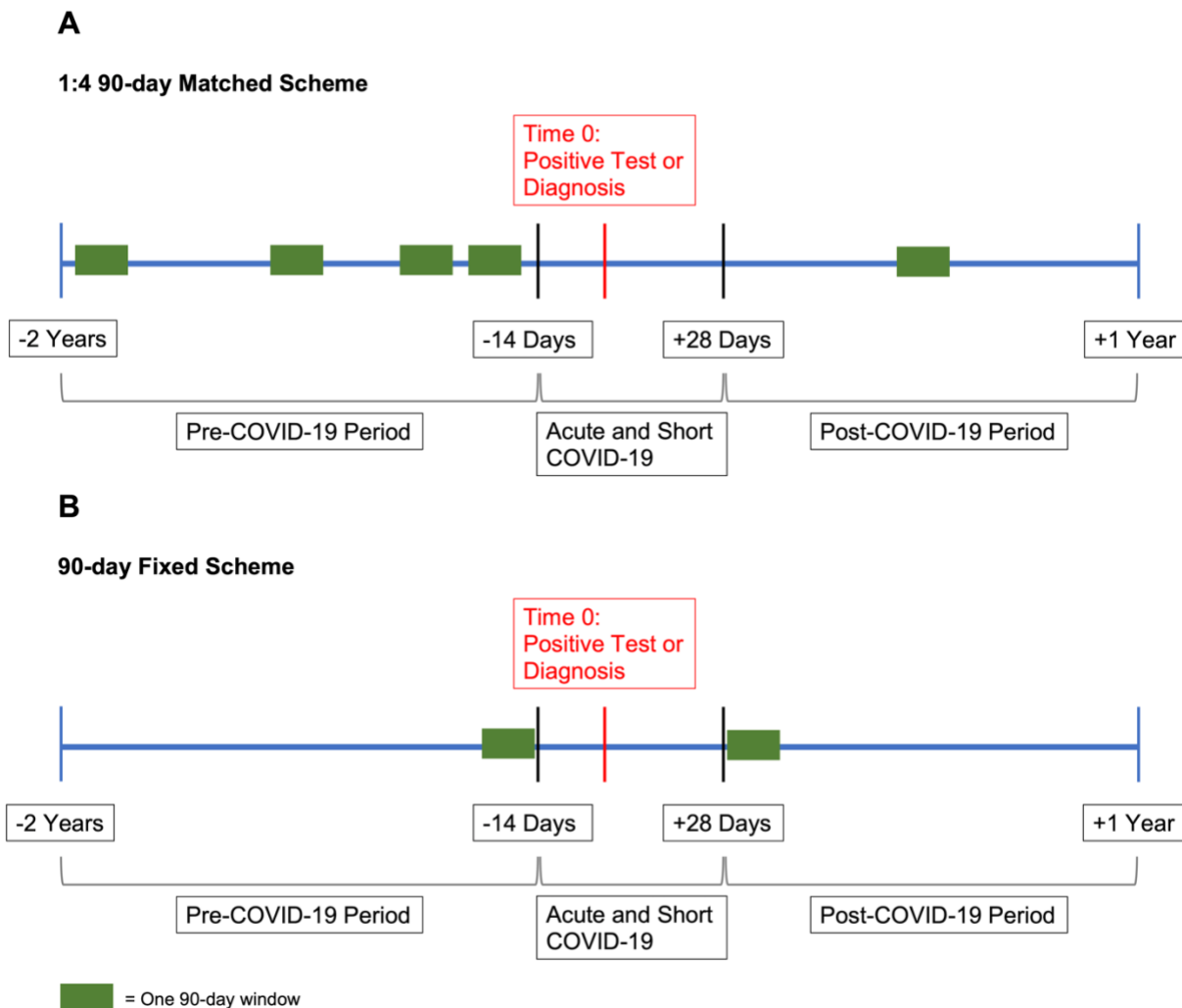


Figure 1. Sampling Schematic for Case-Crossover Design. Panel A depicts the sampling design used in our primary analysis. A patient's index test date is denoted by the red line. The "Acute and Short COVID-19 period" is from -14 days to +28 days, the "post-COVID-19 period" is from +28 days to +1 year, and the "pre-COVID-19 period" is from -14 days to -2 years from the index test date. In this instance, one 90-day case window is randomly selected from the "post-COVID-19 period," and four 90-day control windows are selected from the "pre-COVID-19 period." Panel B depicts the fixed scheme where two fixed 90-day windows are selected from each of the periods.

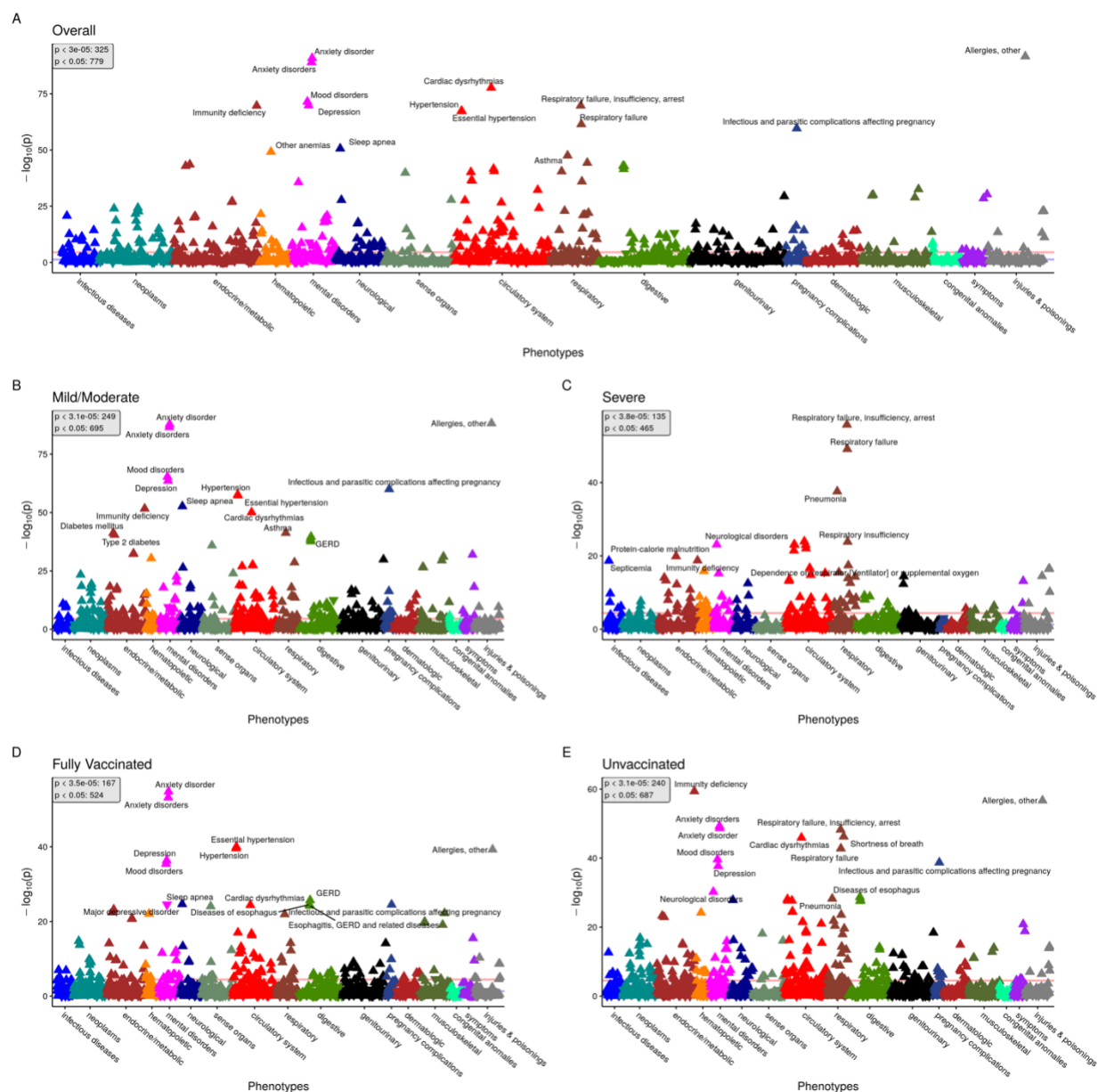


Figure 2. 1:4 Matched 90-day analysis Manhattan plots. Panel of PheWAS Manhattan plots showing overall (panel A) and stratified by COVID-19 severity (panels B and C) and vaccination status (panels D and E). PheCodes (grouped by category) are on the x-axis and the $-\log_{10}(\text{p-value})$ is on the y-axis. Points above the Bonferroni-adjusted p-value threshold line (in red) were considered statistically significant. The nominal p-value threshold (0.05) is also shown in blue. For each panel, the number of hits at the Bonferroni and nominal p-value threshold are provided. Some of the top hits for each plot are annotated. For each hit, an upward pointing triangle represents a positive association ($\text{OR} > 1$), and a downward facing triangle represents a negative association ($\text{OR} < 1$).

Note: The following two PheCodes were removed from plots for better visualization due to their extreme p-values: “Other infectious and parasitic diseases” ($p = 7.4 \times 10^{-108}$ in overall cohort) and “Other headache syndromes” ($p = 1.3 \times 10^{-131}$ in overall cohort). The former is a PheCode connected to COVID-19 infection and sequelae⁵¹, so its low p-value is unsurprising. The extreme association seen for “Other headache syndromes” is somewhat more surprising because it had a negative association with the “post-COVID-19

period”, perhaps relating to patients being less willing to visit the doctor for a “mild” symptom like headache during a pandemic.

Variable	Overall (n=36,856)	Fully Vaccinated (n=10,834) ^a	Unvaccinated (n=24,280) ^b
Age	47 (30, 62)	50 (33, 65)	45 (28, 61)
Gender			
Female	22,233 (60%)	6,610 (61%)	14,588 (60%)
Male	14,621 (40%)	4,224 (39%)	9,691 (40%)
(Missing)	2 (<0.1%)	0 (0%)	1 (<0.1%)
Race			
African American	4,214 (11%)	967 (8.9%)	3,045 (13%)
Asian	1,383 (3.8%)	565 (5.2%)	733 (3.0%)
Caucasian	28,798 (78%)	8,664 (80%)	18,803 (77%)
Other	1,655 (4.5%)	429 (4.0%)	1,149 (4.7%)
(Missing)	806 (2.2%)	209 (1.9%)	550 (2.3%)
BMI	28 (24, 34)	28 (24, 33)	28 (24, 34)
(Missing)	2388	506	1773
Comorbidity Score	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)
(Missing)	1710	560	1045
Primary Care Patient ^c	19,463 (53%)	6,328 (58%)	12,259 (50%)
COVID-19 Severity ^d			
Mild/Moderate	34,568 (94%)	10,343 (95%)	22,614 (93%)
Severe	2,288 (6.2%)	491 (4.5%)	1,666 (6.9%)

^a 1,742 partially vaccinated patients not represented

^b Includes those with unknown vaccination status

^c Received primary care at MM in last 2 years

^d Severe if experienced COVID-19-related hospitalization, ICU admission or death; mild/moderate otherwise

Table 1. Cohort Summary. Summary statistics for the cohort are presented as median (IQR) for continuous variables and n (%) for categorical variables. The table is stratified by vaccination status at index test date. Missing values are reported for each variable.

Outcome	Cohort	Overall (n=36,856) ^a		Fully Vaccinated (n=10,834) ^a		Unvaccinated (n=24,280) ^{a,b}	
		Pre-COVID-19	Post-COVID-19	Pre-COVID-19	Post-COVID-19	Pre-COVID-19	Post-COVID-19
Follow-up Time (Weeks)	Overall (n=36,856)	90.57 (58.11, 99.71)	22.57 (10.43, 42.14)	94.71 (65.86, 100.57)	10.71 (6.43, 17.14)	88.29 (55.14, 99.14)	34.43 (16.43, 45)
	Mild/Moderate (n=34,568)	90.14 (57.57, 99.57)	22.43 (10.43, 41.86)	94.43 (65.71, 100.43)	10.57 (6.43, 17)	87.57 (54.71, 99)	34.29 (16.57, 44.86)
	Severe (n=2,288)	96.57 (67.71, 101)	26.71 (10.43, 45.57)	98.14 (70.07, 101.29)	11.57 (6.57, 19.93)	95.86 (65.86, 101)	36.71 (13.57, 46.43)
	Hospitalized, No ICU (n=1,703)	96.29 (67.71, 101)	26.29 (10.86, 45.14)	98 (68.5, 101.14)	11.71 (7.36, 19.57)	95.71 (66.36, 100.86)	36.57 (14, 46.29)
	Hospitalized and ICU (n=522)	97.43 (69.82, 101.14)	33.93 (12.57, 46.43)	98.21 (81.61, 101.39)	12.93 (5.18, 22.79)	97.43 (69.14, 101.14)	41.29 (16.86, 46.86)
	Deceased (n=115)	97.71 (65.86, 101.36)	2.29 (0.86, 4.5)	98.71 (69.43, 101.71)	1.86 (1, 3.43)	96.57 (62.5, 101.21)	2.43 (0.86, 5.5)
Visits Per Month	Overall (n=36,856)	0.59 (0.25, 1.4)	0.45 (0.18, 1.17)	0.89 (0.38, 1.87)	0.36 (0.18, 0.81)	0.51 (0.21, 1.15)	0.54 (0.18, 1.26)
	Mild/Moderate (n=34,568)	0.55 (0.21, 1.32)	0.45 (0.18, 1.08)	0.89 (0.38, 1.78)	0.36 (0.18, 0.72)	0.47 (0.17, 1.06)	0.54 (0.18, 1.17)
	Severe (n=2,288)	1.4 (0.59, 2.97)	1.35 (0.45, 3.07)	2 (0.93, 3.7)	1.08 (0.45, 2.17)	1.27 (0.51, 2.55)	1.44 (0.45, 3.34)
	Hospitalized, No ICU (n=1,703)	1.4 (0.59, 2.89)	1.17 (0.45, 2.62)	2 (0.98, 3.67)	0.99 (0.45, 1.99)	1.27 (0.51, 2.46)	1.26 (0.45, 2.8)
	Hospitalized and ICU (n=522)	1.44 (0.59, 3.26)	2.53 (0.99, 5.03)	2.02 (0.86, 3.79)	2.03 (0.77, 3.86)	1.36 (0.55, 3.19)	2.71 (0.99, 5.33)
	Deceased (n=115)	1.36 (0.49, 3.5)	1.9 (0.95, 5.7)	1.91 (1.19, 3.06)	3.8 (0.95, 14.26)	1.19 (0.45, 3.5)	1.9 (0.95, 4.75)
1+ New Diagnosis ^c	Overall (n=36,856)		28,124 (78%)		7,337 (71%)		19,460 (81%)
	Mild/Moderate (n=34,568)		26,089 (77%)		6,935 (70%)		17,947 (81%)
	Severe (n=2,288)		2,035 (89%)		402 (83%)		1,513 (91%)
	Hospitalized, No ICU (n=1,703)		1,491 (88%)		319 (82%)		1,075 (90%)
	Hospitalized and ICU (n=522)		496 (96%)		77 (91%)		401 (97%)
	Deceased (n=115)		89 (79%)		15 (71%)		68 (80%)
1+ New PCC-Related Diagnosis ^c	Overall (n=36,856)		13,024 (59%)		3,198 (48%)		9,131 (63%)
	Mild/Moderate (n=34,568)		11,808 (58%)		2,981 (48%)		8,204 (62%)
	Severe (n=2,288)		1,216 (69%)		217 (58%)		927 (72%)
	Hospitalized, No ICU (n=1,703)		863 (66%)		169 (57%)		638 (69%)
	Hospitalized and ICU (n=522)		344 (78%)		47 (66%)		284 (81%)

	Deceased (n=115)	23 (46%)	5 (36%)	15 (47%)
New	Overall (n=36,856)	0.27 (0.09, 0.81)	0.18 (0, 0.63)	0.36 (0.09, 0.9)
Diagnoses	Mild/Moderate (n=34,568)	0.27 (0.09, 0.72)	0.18 (0, 0.54)	0.27 (0.09, 0.81)
Per Month	Severe (n=2,288)	0.99 (0.27, 2.26)	0.72 (0.18, 1.87)	0.99 (0.27, 2.35)
	Hospitalized, No ICU (n=1,703)	0.72 (0.27, 1.9)	0.54 (0.18, 1.49)	0.81 (0.27, 1.9)
	Hospitalized and ICU (n=522)	1.99 (0.81, 3.97)	1.9 (0.63, 3.07)	2.17 (0.86, 4.06)
	Deceased (n=115)	3.8 (0.95, 13.31)	11.41 (0, 19.96)	1.9 (0.95, 12.36)
New PCC-	Overall (n=36,856)	0.09 (0, 0.18)	0 (0, 0.09)	0.09 (0, 0.18)
Related	Mild/Moderate (n=34,568)	0.09 (0, 0.18)	0 (0, 0.09)	0.09 (0, 0.18)
Diagnoses	Severe (n=2,288)	0.09 (0, 0.27)	0.09 (0, 0.18)	0.09 (0, 0.27)
Per Month	Hospitalized, No ICU (n=1,703)	0.09 (0, 0.27)	0.09 (0, 0.18)	0.09 (0, 0.27)
	Hospitalized and ICU (n=522)	0.18 (0.09, 0.36)	0.18 (0, 0.36)	0.18 (0.09, 0.36)
	Deceased (n=115)	0 (0, 1.66)	0 (0, 2.38)	0 (0, 1.19)

^a Median (IQR) or Frequency (%)

^b Includes those with unknown vaccination status

^c In the ~11 month-long “post-COVID-19 period”

Table 2. Summary of Diagnosis Patterns. This table includes six outcomes: follow-up time in weeks, visits per month, individuals with at least one new diagnosis in the “post-COVID-19 period,” individuals with at least one new PCC-related diagnosis in the “post-COVID-19 period,” the number of new diagnoses per month in the “post-COVID-19 period,” and the number of new PCC-related diagnoses per month in the “post-COVID-19 period.” Each outcome is stratified by both COVID-19 severity, “pre-”/“post-COVID-19 period,” and vaccination status. Statistics are presented as median (IQR) for continuous variables and n (%) for categorical variables, and sample sizes for cohorts are provided.

Symptom Group	Total PheCodes in Group ^b	Phenome-Wide Significant Hits ^a					
		Overall (n=36,856)	Mild/Moderate (n=34,568)	Severe (n=2,288)	Fully Vaccinated (n=10,834)	Unvaccinated (n=24,280)	Negative (n=141,615)
circulatory system	171	56 (33%)	41 (24%)	29 (17%)	33 (19%)	45 (26%)	111 (65%)
congenital anomalies	56	3 (5%)	2 (4%)	-	-	-	4 (7%)
dermatologic	95	16 (17%)	7 (7%)	1 (1%)	5 (5%)	7 (7%)	36 (38%)
digestive	162	24 (15%)	19 (12%)	8 (5%)	11 (7%)	20 (12%)	83 (51%)
endocrine/metabolic	169	40 (24%)	29 (17%)	21 (12%)	19 (11%)	29 (17%)	91 (54%)
genitourinary	173	23 (13%)	17 (10%)	4 (2%)	14 (8%)	15 (9%)	63 (36%)
hematopoietic	62	12 (19%)	6 (10%)	10 (16%)	5 (8%)	7 (11%)	31 (50%)
infectious diseases	69	12 (17%)	6 (9%)	6 (9%)	4 (6%)	7 (10%)	31 (45%)
injuries & poisonings	122	8 (7%)	6 (5%)	7 (6%)	8 (7%)	7 (6%)	41 (34%)
mental disorders	76	23 (30%)	17 (22%)	10 (13%)	17 (22%)	19 (25%)	49 (64%)
musculoskeletal	132	10 (8%)	15 (11%)	6 (5%)	9 (7%)	4 (3%)	52 (39%)
neoplasms	141	27 (19%)	33 (23%)	3 (2%)	13 (9%)	28 (20%)	72 (51%)
neurological	85	19 (22%)	13 (15%)	6 (7%)	5 (6%)	14 (16%)	44 (52%)
pregnancy complications	46	10 (22%)	11 (24%)	-	4 (9%)	6 (13%)	21 (46%)
respiratory	85	24 (28%)	12 (14%)	21 (25%)	9 (11%)	20 (24%)	45 (53%)
sense organs	127	11 (9%)	10 (8%)	-	9 (7%)	7 (6%)	21 (17%)
symptoms	46	7 (15%)	5 (11%)	3 (7%)	2 (4%)	5 (11%)	24 (52%)

^a n (% of total PheCodes in group)

^b Not every available PheCode was evaluated in each PheWAS due to case/control thresholds.

Table 3. PheWAS Hits by Symptom Group. The first and second columns gives PheCode symptom groups as defined by the PheWAS catalog and the total number of PheCodes in each group. The other columns give the number of phenome-wide significant hits and the proportion of hits to the total number of PheCodes in each symptom group for each cohort in the primary analysis.