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Functional Neurological Disorder Following COVID-19: Results From a Large International Electronic Health Record Database

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ABSTRACT

Background: Following COVID-19, an increased risk of neurological and psychiatric sequelae has been reported. Viral illnesses commonly trigger functional neurological disorder (FND). However, mechanisms beyond immediate biological effects may contribute to FND after COVID-19. While FND cases have been observed after COVID-19, the overall risk and contributing factors remain unclear. In this retrospective cohort study, we compared the rates of FND post-COVID-19 to other respiratory tract infections (RTIs), assessed the influence of disease severity, and the characteristics of newly diagnosed patients.

Methods: We used TriNetX, a global electronic health record network. In total, 2,740,094 COVID-19 cases and 1846 post-COVID-19 FND cases were analysed. We compared FND incidence between 2 weeks and 6 months after COVID-19 to other RTIs and across cohorts of varying COVID-19 severity. Characteristics of individuals with new diagnoses of FND and migraine following COVID-19 were compared.

Results: The incidence of FND was higher in COVID-19 patients with records of hospitalisation (OR 2.165; 95% CI 1.691–2.773) and emergency department visits (OR 1.412; 95% CI 1.069–1.864). Incidence was higher following COVID-19 compared to other RTIs, both in the first 2 years of the pandemic (0.033 vs. 0.021%, OR 1.555, 95% CI 1.271–1.902) and subsequently (0.038 vs. 0.027%, OR 1.394, 95% CI 1.173–1.657). Medical, neurological, and psychiatric comorbidities were more common in newly diagnosed post-COVID-19 FND compared to migraine.

Conclusions: New-onset FND appears more likely after COVID-19 than other RTIs. Both the severity of the triggering illness and pre-existing individual vulnerability may contribute to the development of FND.

1 | Introduction

Many patients with functional neurological disorder (FND) report a physical precipitant in close temporal association with symptom onset, including physical injuries, medical procedures, and infections [1, 2]. Various viral infections have been documented shortly before FND onset, including COVID-19 [3–7]. The physiological and sensory changes associated with

illness, combined with predisposing factors such as past illness experiences, cognitive and affective biases and personal health beliefs, may contribute to the formation of maladaptive predictions about bodily function. Additionally, the distress, arousal, and altered internal milieu, including inflammatory and interoceptive changes that often accompany illness may increase the salience of bodily sensations, reinforcing symptom perception and potentially triggering FND [1, 8]. Further, when considering the COVID-19 pandemic specifically, many potentially relevant triggering factors were at play beyond the direct biological impact of SARS-CoV-2 infection. These include psychosocial factors such as health-related anxiety, uncertainty surrounding prognosis, personal circumstances, as well as the imposition of unfamiliar public health measures and other societal changes, which could all have contributed to a higher FND risk than other infections, particularly in individuals more vulnerable to these effects [9, 10].

COVID-19 has been associated with an increased risk of various neurological and psychiatric sequelae [11–17]. However, the overall risk of developing FND after COVID-19 remains uncertain. Moreover, the key factors influencing its development, whether related to the illness course, pre-existing vulnerabilities such as prior neurological, psychiatric or other medical conditions, or the psychosocial context of the pandemic, are not well understood.

In this retrospective cohort study using electronic health records (EHR), we aimed to identify patient characteristics associated with FND following COVID-19 and to determine whether a COVID-19 diagnosis was linked to a higher incidence of FND compared to other respiratory tract infections (RTIs). Specifically, we sought to: (i) assess the impact of COVID-19 severity on FND risk; (ii) assess the risk of developing FND following COVID-19 compared to other RTIs across distinct time cohorts, reflecting shifts in disease severity, population immunity, and societal factors; (iii) examine how the risk of FND after an infection evolved over the course of the pandemic; and (iv) characterise individuals with newly diagnosed FND following COVID-19, compared to those with another new neurological diagnosis. We chose migraine as a comparator due to similarities in demographics, shared risk factors with FND, and potential mechanistic parallels between the two conditions [18]. Moreover, COVID-19 has been associated with migraine exacerbation [19].

2 | Methods

2.1 | Data and Study Design

We used TriNetX, a global federated health research network aggregating de-identified EHR data from over 164 million patients. The database includes structured data on demographics, diagnoses (coded using ICD-10), medical procedures, and laboratory test results. Contributing healthcare organisations, including hospitals, specialist providers and primary care facilities, continuously update their data. To ensure anonymity and comply with legal regulations, the identities of organisations and their specific contributions remain confidential. Using the TriNetX interface, cohorts are created by applying inclusion and exclusion criteria, matched for confounding variables, and compared for outcomes over defined time periods (Supplementary Methods provide additional details) [20]. Like other TriNetX studies, this retrospective study is exempt from informed consent, and institutional ethical approval was not sought. The analysed data are secondary, involve no interaction with human subjects, and are de-identified under HIPAA Privacy Rule requirements (http://trinetx.com). The RECORD reporting guidelines were followed (Table S1) [21].

2.2 | The Influence of Illness Severity

Given the wide range of COVID-19 severity, we hypothesised that greater illness severity increases the risk of subsequent FND. We therefore compared FND risk in COVID-19 patients admitted to a hospital from 1 week before to 2 weeks after the diagnosis (as a proxy for illness severity) to those not hospitalised. We also compared outpatients who did or did not visit an emergency department from 1 day before to 2 weeks after the COVID-19 diagnosis.

Patients were included if a diagnosis of 'COVID-19, virus identified' (U07.1), was recorded in their EHR between 16 January 2020 (the date of the first reported case among countries contributing to TriNetX) [22], and 30 June 2022, a date corresponding to a period when COVID-19 had transitioned to a more endemic phase, with many regions experiencing reduced severity as immunity increased through vaccinations and prior infections [23, 24]. All individuals were aged between 13 and 80 years at the time of the diagnosis, had at least one follow-up (indicated as any ICD-10 diagnosis recorded in EHR) and were alive 6 months after COVID-19, and had no previous diagnosis within the dissociative and conversion disorders category (Supplementary Methods specify criteria and codes used). The pairs of cohorts compared were matched for confounding variables using propensity score matching (see Section 2.5 below).

The diagnosis of FND was defined as any of the following: Conversion disorder with motor symptom of deficit (F44.4), Conversion disorder with seizures or convulsions (F44.5), Conversion disorder with sensory symptom or deficit (F44.6), Conversion disorder with mixed symptom presentation (F44.7), Dissociative amnesia (F44.0), Other dissociative and conversion disorders (F44.89), Dissociative and conversion disorder, unspecified (F44.9). These ICD-10 categories are most commonly used for the typical FND phenotypes: functional motor disorder, functional/dissociative seizures, functional sensory disorder, FND with mixed symptoms, cases of functional cognitive disorder, other type of FND, and unspecified FND, respectively. Other diagnoses within the F44 category, such as dissociative fugue, stupor, and identity disorder, were excluded from the FND definition in this study, as these presentations are not typically considered manifestations of FND. The outcome was any newly diagnosed FND between 14 days and 6 months after COVID-19. Excluding the first 14 days after the diagnosis limited possible examples of late recordings of previous diagnoses and excluded the period of acute illness and recommended self-isolation [25]. The observation window was limited to 6 months to increase the likelihood of a causal association between the infection and the outcome.

Using measures of association, we calculated the odds ratios (ORs) for a diagnosis of FND after hospital admission or emergency department visit for the two cohort outcome comparisons. Statistical significance was set at $p < 0.025$ (applying Bonferroni correction for two outcome analyses).

2.3 | Incidence of Newly Diagnosed FND After COVID-19 and Other RTIs

Next, we assessed the incidence of a newly diagnosed FND following COVID-19, using contemporaneous cohorts of patients with other RTIs as comparators due to their prevalence, broad age distribution and clinical similarity, consistent with previous studies using the same database to evaluate mental health outcomes after COVID-19 [11–13]. Two cohorts were created: (i) a 2020–2021 cohort (diagnosed between 16 January 2020 and 31 December 2021), representing a period of more severe disease, greater novelty and uncertainty relating to the infection itself and the pandemic, and the time of most restrictions present in society; and (ii) a 2022–2023 cohort (diagnosed between 1 January 2022 and 31 December 2023), marking a transition to a more endemic phase, with milder illness for most and the lifting of most societal restrictions [24].

The COVID-19 cohorts included patients aged 13–80 years who received a COVID-19 diagnosis (U07.1) within the specified time periods. These patients had no diagnosis of a non-SARS-CoV-2 RTI within 6 months before or after COVID-19. The control cohorts included patients aged 13–80 years with any other RTI (J00-06, J09-18 excluding SARS-CoV-2-associated pneumonia, J20-22), without a diagnosis of COVID-19 or a positive SARS-CoV-2 RNA test within 6 months before or after another RTI. Eligible patients from both cohorts had no prior diagnosis of a conversion or dissociative disorder, had at least one follow-up, and were alive 6 months post-infection. To limit the risk of differences in outcomes caused by varying disease severities, we repeated the analyses by excluding patients who were admitted to a hospital from 1 week before to 2 weeks after COVID-19 or another RTI (Supplementary Methods specify criteria and codes used).

The outcome (new FND diagnosis 14 days to 6 months after COVID-19 or another RTI) was compared in matched cohorts, and the ORs were calculated. Statistical significance was set at $p < 0.025$, applying Bonferroni correction for the two analyses in each time interval (all and non-hospitalised cases).

2.4 | Evolving Risk of Newly Diagnosed FND After an Infection

The risk of new FND diagnoses may have varied during the pandemic due to changes in COVID-19 severity, evolving contextual factors, or shifts in the health profiles of those diagnosed as testing became increasingly limited to those with severe illness or significant comorbidities. To investigate these influences, we conducted further analyses of new FND outcomes: (i) to evaluate changes in the risk profile associated with COVID-19, comparing patients diagnosed with COVID-19 in 2022–2023 to those diagnosed in 2020–2021, with cohorts matched for demographics and comorbidities, where increased odds of newly diagnosed FND would suggest a greater impact of the infection in that cohort; (ii) to identify if patient-specific factors are responsible for any changes in the incidence of post-COVID-19 FND, the same comparison in unmatched cohorts, where a significant difference would emphasise the role of individual patient factors (such as those related to a more severe course of COVID-19 or a predisposition to developing FND) rather than virus-specific or societal factors; and (iii) to assess the influence of broader societal influences associated with the pandemic, a comparison between patients with another RTI in 2022–2023 compared to 2020–2021 (with cases of COVID-19 excluded), where a decreased risk in the more recent cohort would suggest that any previous findings might not be specific to COVID-19 and that other health events would have increased the risk of subsequent FND in the period between 16 January 2020 and 31 December 2021 (see Supplementary Methods for cohort definition criteria).

2.5 | Propensity Score Matching

In each analysis, cohort pairs were matched for demographic and clinical variables using a propensity score matching algorithm integrated into the TriNetX platform. The algorithm employs logistic regression to calculate propensity scores based on user-specified covariates. It then applies a greedy nearest-neighbour matching algorithm with a 1:1 ratio to pair cases and controls. We matched the cohorts for demographic variables, risk factors for COVID-19 severity, and potential risks for developing FND, applying a similar approach to previous studies exploring mental health outcomes after COVID-19 using the same EHR database [11–13]. The selected covariates included medical conditions as COVID-19 risk factors, selected psychiatric and neurological diagnoses (Supplementary Methods) [13, 26, 27]. Baseline characteristics were adequately balanced, with standardised mean differences below 0.1 for all variables of interest (Tables S2–S9) [28].

2.6 | Comparison of Patients With Newly Diagnosed FND and Migraine

We compared demographic features and pre-existing conditions between groups of patients with newly diagnosed FND and migraine following COVID-19. Patients were included if a diagnosis of COVID-19, virus identified (U07.1), or a positive RNA test for SARS-CoV-2 was recorded in their EHR between 16 January 2020 and 26 September 2024 6 months prior to the date of the main analysis, and if they received a new FND diagnosis (recorded in the EHR between 14 days and 6 months after COVID-19 or a positive SARS-CoV-2 RNA test). We examined patients newly diagnosed with migraine in the same timeframe as a comparison group.

We assessed baseline characteristics of each group, focusing on risk factors associated with COVID-19 outcomes, including demographic variables and medical comorbidities [13, 26, 27]. We also investigated potential risk factors for developing FND, including a history of neurological disorders, psychiatric disease, joint hypermobility and Ehlers-Danlos syndrome that may be associated with altered interoception, and the presence

of psychosocial and socioeconomic stressors (Supplementary Methods provide details on variables and coding) [29–33]. Within the TriNetX platform, baseline characteristics were compared using Student's t-tests for continuous and z-tests for categorical variables, with odds ratios with 95% confidence intervals calculated in R (v4.5.0). Statistical significance was set at $p < 0.00111$ (applying Bonferroni correction for 45 comparisons).

3 | Results

3.1 | New Diagnosis of FND as an Outcome After the Infection

Between 16 January 2020 and 30 June 2022, 157,204 COVID-19 cases were hospitalised, compared to 1,552,583 outpatients. Hospital treatment was associated with increased odds of subsequent FND (Figure 1). Among outpatients, an emergency department visit was similarly associated with increased odds of subsequent FND.

In 2020–2021 and 2022–2023 cohorts, new FND diagnoses were more likely following COVID-19 (0.033% and 0.038%, respectively) than other RTIs (0.021% and 0.027%, respectively), both in all and non-hospitalised patients, with ORs ranging from 1.30 to 1.55 across all cohort comparisons (Figure 1).

Among propensity score-matched 2022–2023 and 2020–2021 cohorts, the incidence of new FND diagnoses following COVID-19 did not differ. However, without matching (including all 2,740,094 cases of COVID-19), the incidence was higher in the 2022–2023 cohort. On average, patients diagnosed with COVID-19 later during the pandemic were older and had more psychiatric, neurological, and other medical comorbidities (Table S8). No difference in FND incidence was observed between matched 2022–2023 and 2020–2021 cohorts of other RTIs (Figure 1).

3.2 | Newly Diagnosed FND and Migraine Following COVID-19

A total of 1846 patients were newly diagnosed with FND and 26,464 with migraine between 2 weeks and 6 months after COVID-19. A pre-existing diagnosis of migraine was present in 36% of patients with new FND, while 2% of those newly diagnosed with migraine had a prior FND diagnosis. Seizures were the most common presentation, followed by motor symptoms (Table 1). The Black racial group was more represented among FND cases. Individuals with FND had higher rates of all evaluated neurological and psychiatric conditions and various medical comorbidities.

4 | Discussion

Using a large EHR network, we found that a COVID-19 diagnosis was associated with an increased risk of subsequent FND compared to other RTIs. This association was strongest in cohorts that included all cases, but persisted in subgroups with milder disease not requiring hospital admission. Illness severity, proxied by hospital or emergency department admission, was linked to a higher likelihood of post-COVID-19 FND. Individuals newly diagnosed with FND after COVID-19 had increased rates of pre-existing neurological, psychiatric, and medical conditions, compared to those with new migraine diagnoses.

Even though the overall risk of a new FND diagnosis within 6 months post-COVID-19 is low (0.127% for severe and 0.059% for mild cases), these rates likely reflect the short follow-up.

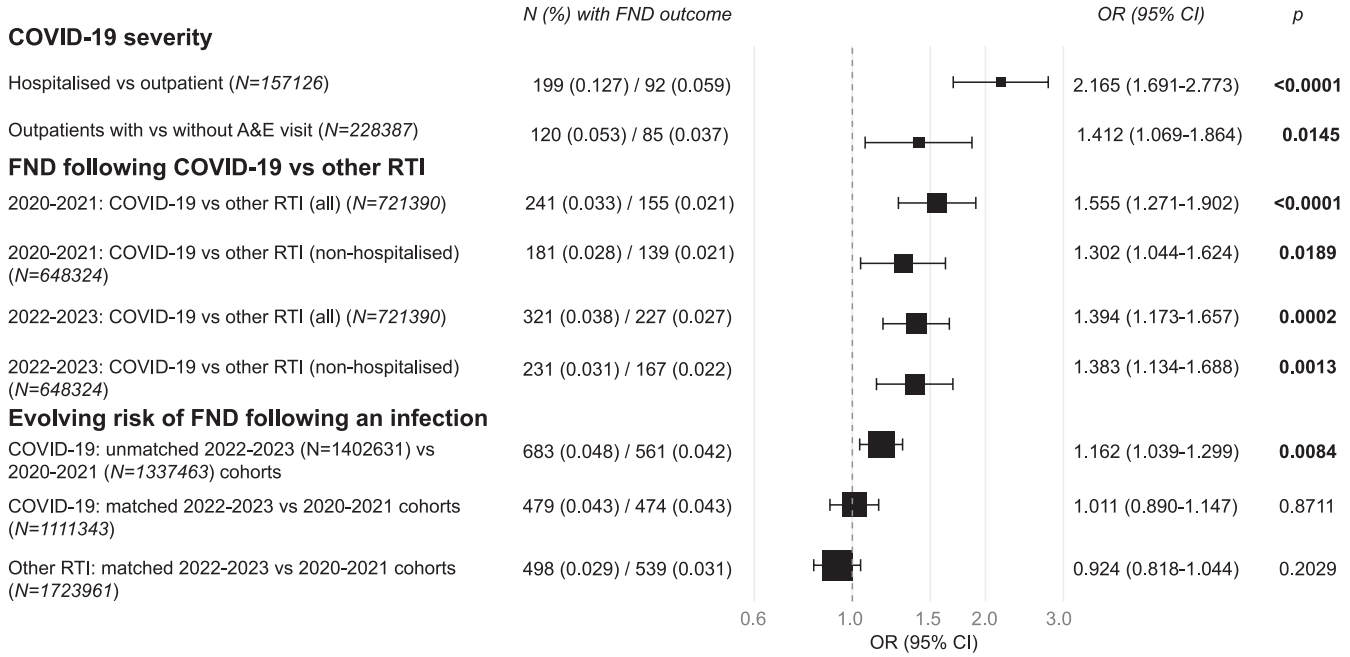

FIGURE 1 | Odds ratios (OR) with 95% confidence intervals (CI) for new diagnoses of functional neurological disorder (FND), comparing patients with varying COVID-19 severity, COVID-19 compared to other respiratory tract infections (RTI), and across different time periods. The number of individuals in each cohort, along with the count (and percentage) of FND outcomes, and *p* values (with significant values in bold) is provided.

TABLE 1 | Characteristics of patients with a new diagnosis of functional neurological disorder (FND) compared to a new diagnosis of migraine in 2 weeks to 6 months after COVID-19. Case numbers are provided with percentages in parentheses unless specified otherwise. *p* values (highlighted in bold if significant after Bonferroni correction for 45 variables, $p < 0.00111$), odds ratios (OR) with 95% confidence intervals (CI) for categorical variables, and standardised mean differences (SMD) for the group comparison are provided. The number of dissociative and conversion disorder cases in the FND group represents new instances, while in the migraine group they reflect prior diagnoses. Conversely, the number of cases of migraine in the migraine group indicates new diagnoses, while in the FND group they correspond to previously diagnosed migraine.

	FND	Migraine	OR (95% CI)	SMD	*p*
Number	1846	26,464			
Age: mean (SD) (years)	49.5 (18.0)	44.8 (16.2)		0.2687	**< 0.0001**
Gender					
Female	1273 (69)	20,613 (78)	0.63 (0.57–0.70)	0.2032	**< 0.0001**
Male	522 (28)	4706 (18)	1.82 (1.64–2.03)	0.2512	**< 0.0001**
Unknown	51 (3)	1145 (4)	0.63 (0.47–0.84)	0.0847	0.0012
Race					
White	1157 (63)	16,700 (63)	0.98 (0.89–1.08)	0.0847	0.7122
Black or African American	354 (19)	3912 (15)	1.37 (1.21–1.54)	0.1172	**< 0.0001**
Asian	39 (2)	754 (3)	0.74 (0.53–1.02)	0.0474	0.0637
American Indian or Alaska Native	12 (1)	89 (0)	1.94 (1.06–3.55)	0.0448	0.0288
Native Hawaiian or Other Pacific Islander	20 (1)	184 (1)	1.56 (0.98–2.49)	0.0414	0.0566
Other Race	58 (3)	1506 (6)	0.54 (0.41–0.70)	0.1243	**< 0.0001**
Unknown Race	206 (11)	3319 (13)	0.88 (0.75–1.02)	0.0428	0.082
Dissociative and conversion disorders	All	489 (2)			
Dissociative amnesia	20 (1)	10 (0)			
Conversion disorder with motor symptom or deficit	646 (35)	169 (1)			
Conversion disorder with seizures or convulsions	734 (40)	205 (1)			
Conversion disorder with sensory symptom or deficit	282 (15)	94 (0)			
Conversion disorder with mixed symptom presentation	138 (7)	47 (0)			
Other dissociative and conversion disorders	262 (14)	27 (0)			
Dissociative and conversion disorder, unspecified	348 (19)	124 (0)			
Migraine	667 (36)	All			
Overweight and obesity	897 (49)	10,514 (40)	1.43 (1.31–1.58)	0.1792	**< 0.0001**
BMI: mean (SD) (kg/m2)*	30.7 (8.9)	30.9 (8.2)		0.0209	0.4492
Diabetes mellitus type 1	142 (8)	583 (2)	3.70 (3.06–4.47)	0.2552	**< 0.0001**
Diabetes mellitus type 2	538 (29)	3632 (14)	2.59 (2.33–2.88)	0.3826	**< 0.0001**
Hypertensive diseases	1096 (59)	10,488 (40)	2.23 (2.02–2.45)	0.4028	**< 0.0001**
Hypertensive chronic kidney disease	252 (14)	1222 (5)	3.27 (2.83–3.77)	0.3175	**< 0.0001**
Ischaemic heart disease	508 (28)	3133 (12)	2.83 (2.54–3.15)	0.4023	**< 0.0001**
Other forms of heart disease	1059 (57)	8128 (31)	3.04 (2.76–3.34)	0.5574	**< 0.0001**

(Continues)

TABLE 1 | (Continued)

	FND	Migraine	OR (95% CI)	SMD	*p*
Chronic kidney disease	375 (20)	1975 (7)	3.16 (2.80–3.57)	0.3782	**< 0.0001**
Chronic lower respiratory diseases	944 (51)	10,264 (39)	1.65 (1.50–1.82)	0.2503	**< 0.0001**
Nicotine dependence	527 (29)	4448 (17)	1.98 (1.80–2.20)	0.2832	**< 0.0001**
Liver disease	485 (26)	4173 (16)	1.90 (1.71–2.12)	0.26	**< 0.0001**
Neoplasms	745 (40)	8888 (34)	1.34 (1.22–1.47)	0.1406	**< 0.0001**
Rheumatoid arthritis with rheumatoid factor	24 (1)	281 (1)	1.23 (0.81–1.87)	0.0221	0.3376
Other rheumatoid arthritis	104 (6)	943 (4)	1.62 (1.31–1.99)	0.099	**< 0.0001**
Systemic lupus erythematosus	53 (3)	467 (2)	1.65 (0.95–2.41)	0.0736	0.0006
Other immune disorders	216 (12)	1728 (7)	1.90 (1.66–2.20)	0.1804	**< 0.0001**
Psoriasis	63 (3)	755 (3)	1.20 (0.93–1.56)	0.0321	0.165
Hypermobility syndrome	20 (1)	190 (1)	1.51 (0.95–2.41)	0.0387	0.0768
Ehlers-Danlos syndromes	31 (2)	238 (1)	1.88 (1.29–2.75)	0.0692	**0.0008**
Mood disorders	1282 (69)	12,053 (46)	2.72 (2.45–3.01)	0.4983	**< 0.0001**
Anxiety disorder	1286 (70)	14,105 (53)	2.01 (1.82–2.23)	0.3412	**< 0.0001**
Reaction to severe stress and adjustment disorders	693 (38)	5195 (20)	2.46 (2.23–2.72)	0.4044	**< 0.0001**
Somatoform disorders	243 (13)	755 (3)	5.16 (4.43–6.02)	0.3869	**< 0.0001**
Psychotic disorder	364 (20)	666 (3)	9.51 (8.29–10.92)	0.5689	**< 0.0001**
Specific personality disorder	195 (10)	615 (2)	4.96 (4.19–5.88)	0.3269	**< 0.0001**
Neurodevelopmental disorder	150 (8)	523 (2)	4.39 (3.64–5.30)	0.2836	**< 0.0001**
Epilepsy	603 (33)	1291 (5)	9.46 (8.46–10.58)	0.7614	**< 0.0001**
Convulsions	844 (46)	1789 (7)	11.62 (10.47–12.88)	0.9877	**< 0.0001**
Movement disorder	438 (24)	2207 (8)	3.42 (3.05–3.84)	0.4289	**< 0.0001**
Diseases of muscle and neuromuscular junction	84 (5)	482 (2)	2.57 (2.03–3.26)	0.1559	**< 0.0001**
Polyneuropathies	413 (22)	2657 (10)	2.58 (2.30–2.90)	0.3394	**< 0.0001**
Demyelinating CNS diseases	66 (4)	532 (2)	1.81 (1.39–2.35)	0.0951	**< 0.0001**
Potential socioeconomic and psychosocial hazards	480 (26)	2970 (11)	2.78 (2.49–3.11)	0.3868	**< 0.0001**

Abbreviations: BMI, body mass index; CNS, central nervous system.
*Reported in 69% of FND and 76% of migraine cohort.

Nevertheless, the implications of our findings are significant considering the prevalence of the precipitating event. The 6 month incidence of FND is comparable to that of other neurological outcomes previously reported, such as Guillain-Barré syndrome and encephalitis [13]. Greater COVID-19 severity was associated with increased subsequent FND risk, consistent with a dose–response relationship and with illness severity partially mediating the association between COVID-19 and FND. Compared to other RTIs, we observed an increased risk of a new FND diagnosis following COVID-19. This association persisted even in milder COVID-19 cases, suggesting that factors beyond illness severity play a role. However, FND also occurred after other RTIs. Previous studies have similarly reported other neurological outcomes, including migraine and epilepsy, after both COVID-19 and other RTIs. This suggests that COVID-19 might act similarly to other respiratory viruses such as influenza [34].

While neurological and psychiatric sequelae of COVID-19 are broad, their impact and long-term trajectory vary depending on the diagnosis [11, 12]. Our findings align with previous studies showing an increased risk of some psychiatric diagnoses following COVID-19, particularly in hospitalised patients during the acute phase, but also among non-hospitalised patients [12–14]. Similarly, post-COVID-19 cognitive decline relates to disease severity [35], and severe COVID-19 cases have a higher risk of developing long COVID [36]. The association between greater disease severity and an increased likelihood of a mental health diagnosis is consistent with findings in other viral infections and critical illnesses [16, 37–39]. This pattern may be explained

by shared mechanisms of biological stress, such as neuroinflammatory changes that are not unique to COVID-19 [40, 41], as well as psychological stress arising from the burden of severe illness.

In contrast to the biological factors influencing FND development, our study can provide less insight into the role of psychosocial influences, although these were likely contributors. The early pandemic period was marked by overwhelmed health services, fear of COVID-19, and limited social support. Psychological distress associated with COVID-19 continued to influence mental health outcomes during later stages of the pandemic [42]. Each of these factors could have contributed to the development of FND in individual cases. However, given its design and the data available, our study is ill-equipped to disentangle these influences.

The increased odds of FND following COVID-19, compared to other RTIs, cannot be explained solely by pandemic-related societal factors, as non-COVID-19 outcomes were similar between time periods. Similarly, FND risk after COVID-19 did not differ between the early and later pandemic phases. In fact, in the analysis of unmatched cohorts, the higher FND risk in the 2022–2023 cohort may reflect the characteristics of individuals who were more likely to be tested and diagnosed with COVID-19 later in the pandemic. On average, these patients had more comorbidities, which could themselves constitute risk factors for FND. Different pathogens may predispose to FND through distinct mechanisms, related to inflammatory sequelae, neurotropism or other factors. Evidence from human and animal studies suggests that inflammation itself may induce neural and behavioural plasticity, potentially increasing susceptibility to maladaptive changes underlying FND and related symptoms [43–46]. Individual vulnerability, including that conferred by comorbid conditions, may further modulate this risk.

The comparison of characteristics between patients with newly diagnosed FND and migraine identified several clinical features associated with increased risk of post-COVID-19 FND. Patients with new FND after COVID-19 were, on average, older and more frequently male, even though females still comprised 69% of cases. The Black race was more common in FND cases. This finding is significant, as most FND studies have predominantly included white participants, and racial biases, along with socioeconomic factors such as access to neurologists and mental health providers, may contribute to underreporting in other groups [47]. Other group differences in racial categories likely stem from geographical differences, as racial categories are not coded uniformly across healthcare systems.

Our findings align with previous reports indicating that prior neurological or psychiatric disorders are risk factors for FND [30, 32]. Previous neurological conditions were more common in FND than in migraine following COVID-19, affecting a substantial proportion of patients (epilepsy 33%, movement disorders 24%, and polyneuropathies 22%). Notably, 46% had a history of convulsions, implying that, at least in a subset of patients, COVID-19 may have exacerbated pre-existing symptoms rather than triggered entirely new ones. Mood and anxiety disorders were the most frequent psychiatric comorbidities, consistent with prior studies, though less common conditions like neurodevelopmental disorders were also more prevalent in FND [29–31].

The increased prevalence of other medical diagnoses in FND, compared to migraine, suggests that FND may arise from the context of broader health challenges. Increased rates of cardiovascular, pulmonary, kidney, liver, metabolic disorders and neoplasms diagnoses were observed. Since these conditions are also risk factors for COVID-19 severity, part of the effect could reflect more severe illness. Interestingly, while prior systemic lupus erythematosus or rheumatoid arthritis with rheumatoid factor were not more common in the COVID-19 group, other forms of rheumatoid arthritis were. This may indicate that somatic symptoms in some patients predated the FND diagnosis. Ehlers-Danlos syndrome was also more common in post-COVID-19 FND, supporting the view that altered interoception and repeated physical injuries in this group increase FND risk [33].

Our study's major strength lies in its large sample size, making it the largest investigation to date of precipitating events in FND and the most comprehensive assessment of the association between COVID-19 and FND. Further strengths include extensive clinical data and diverse geographical and clinical settings, though these cannot be traced back to individual healthcare organisations or regions.

Among the limitations, residual confounding could be present, particularly from unmeasured social and psychological factors, and matching for geographic regions is not possible within the TriNetX platform. Further, some medical encounters might occur outside the EHR network. Our COVID-19 cohorts likely contain a disproportionate number of symptomatic cases, as asymptomatic or self-diagnosed infections are less commonly documented in EHR. However, this also applies to the RTIs comparison cohort, impacting incidence estimates more than relative risk calculations and disease severity analyses. A fundamental challenge in clinical practice that is also reflected in our cohort is the difficulty of diagnosing FND. The condition is frequently under-recognised or misattributed, with diagnostic delays averaging between 2 and 9 years [48, 49]. Using a narrower time window strengthened the causal inference between COVID-19 and a subsequent FND diagnosis, though other precipitating events could have occurred. However, many patients whose symptoms began after a SARS-CoV-2 infection may not have received a diagnosis within 6 months. Another limitation, common to all FND research based on ICD-10 coding, is that non-coding for FND is common, leading to underreporting [50], and diagnostic uncertainty may have increased in a post-COVID-19 setting. Some FND cases might also have been misclassified as long COVID [5, 6], suggesting that the rates of FND following COVID-19 might be underestimated in our study. Prospective cohort studies would be valuable to validate our findings.

In conclusion, our findings reveal an increased risk of new-onset FND following COVID-19, particularly among individuals with severe illness. However, the implications extend beyond this specific context, providing broader insights into the pathogenesis of FND. While COVID-19 serves as an example, our results

emphasise the importance of precipitating event severity and individual vulnerability in FND development, and may hold relevance across various clinical contexts. These insights may inform future research and potentially aid in developing targeted prevention strategies for FND.

Author Contributions

R.B. and M.J.E. designed the study, defined cohort inclusion and exclusion criteria, outcome criteria and analytical approaches. R.B. performed data analyses. R.B. and M.J.E., interpreted the data, with contributions from L.A., T.R.N., B.S. and T.A.P. R.B., wrote the original draft. L.A., T.R.N., B.S., T.A.P. and M.J.E., reviewed and edited the manuscript. M.J.E., supervised the project. All authors approved the final version of the manuscript.

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Conflicts of Interest

R.B. has received speaker honoraria from AbbVie and support for attending meetings and travel from Medtronic. L.A. prepares medico-legal patient reports as part of official duties at the Department of Neurology in Essen and is a core group member of the Young Neurology Group of the German Society of Neurology (DGN). T.R.N. does medical expert reporting in personal injury and clinical negligence cases, including in cases of F.N.D. He has received financial support for lectures from the FND Society (FNDS). He receives royalties from CRC Press for The Pocket Prescriber textbook series. He also has received grant funding, including for studies related to FND, from the UK National Institute for Health and Care Research (NIHR) and the Medical Research Council (MRC). He is co-chair of the FNDS patient liaison committee and on the medical advisory boards of the charities FND Hope UK and FND Action and a trustee of FND Action. B.S. does medical expert reporting in personal injury and clinical negligence cases, including in cases with FND. She is on the medical advisory board of FND Hope (UK) and is a trustee of the Association of British Neurologists. T.A.P. does medical expert reporting in personal injury and clinical negligence cases, including in cases of FND. He has received consultancy fees from Arialys Therapeutics. M.J.E. does medical expert reporting in personal injury and clinical negligence cases, including in cases of FND; has shares in Brain & Mind, which provides neuropsychiatric and neurological rehabilitation in the independent medical sector, including in people with FND; has received financial support for lectures from the International Parkinson's and Movement Disorders Society and the FNDS; receives royalties from Oxford University Press for his book The Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorder; has received honoraria for medical advice to Teva Pharmaceuticals; receives grant funding, including for studies related to functional neurological disorder, from the National Institute for Health and Care Research and the Medical Research Council; is deputy editor of the European Journal of Neurology; is on the medical advisory boards of the charities FND Hope UK and Dystonia UK.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** 1. The TriNetX network. 2. Definition of variables for assessing the influence of illness severity. 3. Cohort definition for investigating FND as an outcome following infection. 4. Cohort definition for assessing the evolving risk of newly diagnosed FND. 5. Definition of covariates. 6. Propensity score matching. 7. Cohort definition and variables of interest for patients with FND and migraine after COVID-19. **Table S1:** The RECORD statement. **Table S2:** Characteristics of hospitalised and non-hospitalised COVID-19 cases. **Table S3:** Characteristics of COVID-19 outpatients visiting and not visiting an emergency department. **Table S4:** Characteristics of the COVID-19 and other respiratory tract infection cohorts (2020–2021). **Table S5:** Characteristics of the COVID-19 and other respiratory tract infection outpatient cohorts (2020–2021). **Table S6:** Characteristics of the COVID-19 and other respiratory tract infection cohorts (2022–2023). **Table S7:** Characteristics of the COVID-19 and other respiratory tract infection outpatient cohorts (2022–2023). **Table S8:** Characteristics of the COVID-19 2022–2023 and 2020–2021 cohorts. **Table S9:** Characteristics of other respiratory tract infection 2022–2023 and 2020–2021 cohorts. Supplementary references.