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Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection

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Postural orthostatic tachycardia syndrome (POTS) was previously described after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; however, limited data are available on the relation of POTS with Coronavirus Disease 2019 (COVID-19) vaccination. Here we show, in a cohort of 284,592 COVID-19-vaccinated individuals, using a sequence–symmetry analysis, that the odds of POTS are higher 90 days after vaccine exposure than 90 days before exposure; we also show that the odds for POTS are higher than referent conventional primary care diagnoses but lower than the odds of new POTS diagnosis after SARS-CoV-2 infection. Our results identify a possible association between COVID-19 vaccination and incidence of POTS. Notwithstanding the probable low incidence of POTS after COVID-19 vaccination, particularly when compared to SARS-Cov-2 post-infection odds, our results suggest that further studies are needed to investigate the incidence and etiology of POTS occurring after COVID-19 vaccination.

Coronavirus Disease 2019 (COVID-19) vaccination has been shown to be safe and effective in multiple trials[1–4]. Vaccine pharmacovigilance has revealed diverse rare side effects in the setting of population-wide administration[5,6], including off-target cardiovascular effects, with the most well-characterized being myocarditis[7,8]. Reports have emerged regarding cases of postural orthostatic tachycardic syndrome (POTS) after vaccination[9]. Recognized as a clinical syndrome that manifests with orthostatic intolerance and postural tachycardia, POTS is diagnosed based on clinical features, such as orthostatic dizziness, palpitations and pre-syncope, and a 10-minute stand test or a tilt table test that demonstrate a heart rate elevation of at least 30 beats per minute from supine to standing position[10–12]. Given that POTS may be associated with small fiber or autonomic neuropathy, further diagnostic evaluation with autonomic function tests and/or a skin biopsy for the assessment of small fiber neuropathy may be performed. POTS is now known as one of many possible features of post-acute COVID-19 syndromes that can develop after SARS-CoV-2 infection[13–16]. Given that COVID-19 vaccination elicits an immunological response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, there is biological plausibility for a similar, even if attenuated, systemic response to vaccine when compared to that seen from viral exposure. Therefore, in this study,

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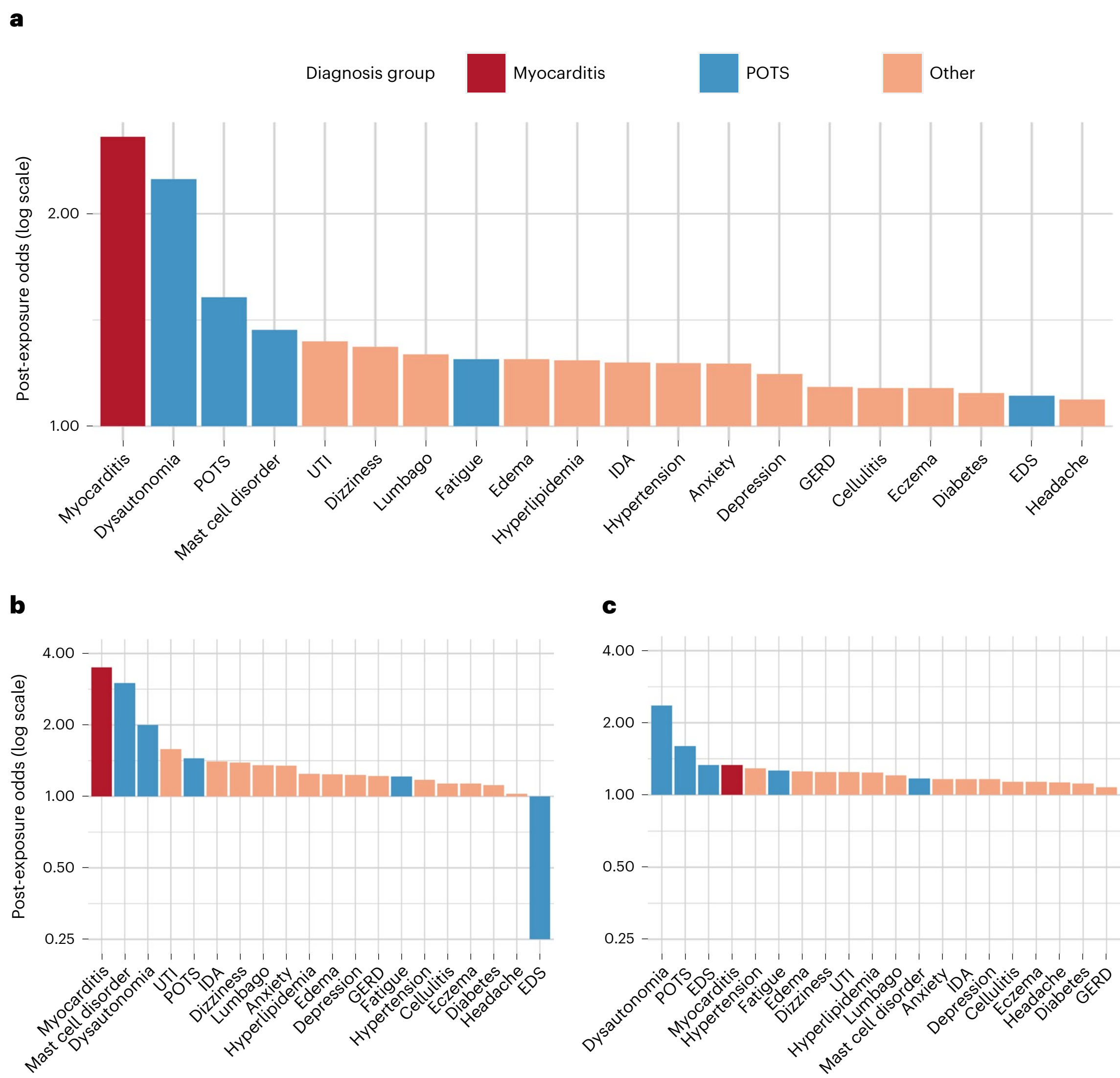

Fig. 1 | Post-vaccination odds by diagnosis. a, All patients, post-vaccination. **b**, Male patients only, post-vaccination. **c**, Female patients only, post-vaccination. GERD, gastroesophageal reflux disease; IDA, iron deficiency anemia.

we evaluated the relation between COVID-19 vaccination and new POTS-related diagnoses by assessing the odds of diagnosis in the baseline 90 days before first vaccine exposure versus the subsequent 90 days after vaccine exposure in a sequence–symmetry analysis[17]. We first compared new POTS-related diagnosis odds to those for myocarditis and for common primary care (CPC) diagnoses to provide benchmarks accounting for potential confounding from changes in patient engagement with the healthcare system during the pandemic as well as detection bias from the provider standpoint. We then compared risks of new POTS diagnoses arising after vaccination compared to new POTS diagnoses arising after natural infection, to provide a broader context for interpreting results.

Results

For the post-vaccination analysis, we studied 284,592 patients (age 52 ± 20 years; 57% female; 63% White, 10% Asian, 8.9% African American and 12% Hispanic ethnicity). The types of vaccinations received included: 62% Pfizer-BioNTech (BNT162b2); 31% Moderna (mRNA-1273); 6.9% Johnson & Johnson/Janssen (Ad26.COV2.S); and <0.1% other vaccines, including AstraZeneca (ChAdOx1-S), Novavax (NVX-CoV2373) and Sinovac (CoronaVac).

For new diagnoses made after vaccination, we found that the five conditions with the highest post-vaccination odds of new diagnoses were myocarditis, dysautonomia, POTS, mast cell activation syndrome and urinary tract infection (UTI). Two POTS-associated conditions had lower odds, with fatigue demonstrating a moderate ratio and Ehlers–Danlos syndrome (EDS) having the second from the lowest ratio (Fig. 1a and Table 1). Overall, the post-vaccination odds of new POTS-associated diagnoses (n = 4,526, odds = 1.33 (1.25–1.41), $P < 0.001$) was higher than for CPC diagnoses (n = 33,590, odds = 1.21 (1.18–1.23), $P < 0.001$) but lower than for myocarditis (n = 25, odds = 2.57 (1.02–6.77), $P = 0.046$). When we repeated analyses around receipt of second (rather than the first) vaccination dose, we observed overall similar findings (Supplementary Table 1). The odds ratio (OR) of post-vaccine diagnoses of POTS-associated versus CPC conditions was 1.10 (1.03–1.17), $P = 0.003$, with similar results observed from analyses conducted using clustered bootstrapping (OR = 1.10 (1.02–1.17)). Patients with POTS-associated diagnoses (n = 1,924) after vaccination had similar demographics and vaccine types compared to the overall population (age 56 ± 20 years; 59% female; 67% White, 9% Asian and 11% African American and 12% Hispanic ethnicity; 59% Pfizer-BioNTech, 35% Moderna and 6.0% Johnson & Johnson/Janssen). We conducted sex-stratified analyses and found similar

Table 1 | Diagnoses within 90 days of exposure for study sample with documented COVID-19 vaccination (*n* = 284,592)

Diagnosis	No. new diagnoses	New diagnosis before exposure	New diagnosis after exposure	Post-exposure risk		Diagnostic group
	n (per 100,000)	*n* (per 100,000)	*n* (per 100,000)	Odds (95% CI)	*P* value	
Myocarditis	25 (8.78)	7 (2.46)	18 (6.32)	2.57 (1.02–6.77)*	0.046	Myocarditis
Dysautonomia	68 (23.89)	21 (7.38)	47 (16.51)	2.24 (1.30–3.87)†	0.002	POTS
POTS	1,264 (444.14)	501 (176.04)	763 (268.10)	1.52 (1.36–1.71)‡	<0.001	POTS
Mast cell disorders	64 (22.49)	27 (9.49)	37 (13.00)	1.37 (0.81–2.32)	0.26	POTS
UTI	2,038 (716.11)	879 (308.86)	1,159 (407.25)	1.32 (1.21–1.44)‡	<0.001	CPC
Dizziness	2,191 (769.87)	954 (335.22)	1,237 (434.66)	1.30 (1.19–1.41)‡	<0.001	CPC
Lumbago	2,845 (999.68)	1,256 (441.33)	1,589 (558.34)	1.27 (1.17–1.36)‡	<0.001	CPC
Fatigue	3,090 (1,085.76)	1,377 (483.85)	1,713 (601.91)	1.24 (1.16–1.34)‡	<0.001	POTS
Edema	1,196 (420.25)	533 (187.29)	663 (232.97)	1.24 (1.11–1.40)‡	<0.001	CPC
Hyperlipidemia	4,373 (1,536.59)	1,952 (685.89)	2,421 (850.69)	1.24 (1.17–1.32)‡	<0.001	CPC
Hypertension	4,639 (1,630.05)	2,080 (730.87)	2,559 (899.18)	1.23 (1.16–1.30)‡	<0.001	CPC
Iron deficiency anemia	1,688 (593.13)	757 (265.99)	931 (327.13)	1.23 (1.12–1.36)‡	<0.001	CPC
Anxiety	2,929 (1,029.19)	1316 (462.42)	1,613 (566.78)	1.23 (1.14–1.32)‡	<0.001	CPC
Depression	1,737 (610.35)	795 (279.35)	942 (331.00)	1.18 (1.08–1.30)‡	<0.001	CPC
GERD	2,795 (982.11)	1,308 (459.61)	1,487 (522.50)	1.14 (1.05–1.23)‡	<0.001	CPC
Cellulitis	1,799 (632.13)	844 (296.56)	955 (335.57)	1.13 (1.03–1.24)*	0.01	CPC
Eczema	1,799 (632.13)	844 (296.56)	955 (335.57)	1.13 (1.03–1.24)*	0.01	CPC
Diabetes mellitus	1,269 (445.90)	600 (210.83)	669 (235.07)	1.12 (1.00–1.25)	0.06	CPC
EDS	40 (14.06)	19 (6.68)	21 (7.38)	1.11 (0.57–2.14)	0.87	POTS
Headache	2,292 (805.36)	1,096 (385.11)	1,196 (420.25)	1.09 (1.00–1.19)*	0.039	CPC

CI, confidence interval; GERD, gastroesophageal reflux disease. Odds of post-exposure diagnosis were estimated using one-sample proportions testing with continuity correction, and two-sided *P* values are shown without correction for multiple testing while noting that a conservative Bonferroni threshold of 0.05/20 = 0.0025 may be considered for aiding interpretation of results. **P* < 0.05, †*P* < 0.01, ‡*P* < 0.001.

between-sex results for POTS-associated diagnoses, although EDS was rarely diagnosed in males (*n* = 5) compared to females (*n* = 35) (Fig. 1b,c).

For new diagnoses made after SARS-CoV-2 infection, we conducted separate analyses in 12,460 patients with documented SARS-CoV-2 infection (age 47 ± 23 years; 50% female; 54% White, 6% Asian and 20% African American and 29% Hispanic ethnicity). Overall, the post-infection odds of new POTS-associated diagnoses (*n* = 1,004, odds = 1.52 (1.33–1.72), *P* < 0.001) was numerically higher than that for CPC diagnoses (*n* = 3,325, odds = 1.4 (1.31–1.50), *P* < 0.001) (Fig. 2 and Table 2); however, the OR was not significantly higher (1.08 (0.93–1.25), *P* = 0.29), potentially related to limited sample size. Similar results were observed when analyses were conducted using clustered bootstrapping (OR = 1.08 (0.94–1.26)). Patients who received POTS-associated diagnoses (*n* = 686) after infection had similar demographics to the overall COVID-19 population but were slightly older (47% female; 59% White, 6.1% Asian and 22% African American and 26% Hispanic ethnicity; mean age 60 ± 20 years). Similar sex-stratified analyses showed similar results, with the slightly higher rate of myocarditis in men being non-significant likely due to the low rate of new outpatient new diagnoses (three in men and two in women) (Fig. 2b,c).

To interpret post-exposure odds of new diagnoses in the context of their overall frequency, we plotted both post-exposure odds and absolute rates of new diagnosis occurrence for all studied conditions (Fig. 3). For the post-vaccination cohort, the odds of new POTS, dysautonomia and myocarditis diagnoses were elevated but with variably low rates of occurrence. For the post-infection cohort, both the odds of new diagnoses and their rate of occurrence tended to be elevated particularly for conditions such as diabetes, POTS and hypertension. For most conditions studied, post-infection rates were higher than post-vaccination rates. For POTS-associated diagnoses, in particular, the risk rate was 5.35 (5.05–5.68 *P* 0.001) times higher in patients who had recent SARS-CoV-2 infection than in patients who had recent COVID vaccination. This difference represents the ratio of crude risks derived from different and mutually exclusive populations, within a study design that precludes the ability to apply conventional multivariable adjustments. Given the populations have different underlying risks of POTS, difference in crude risk should not be causally attributed to an isolated effect of SARS-Cov-2 infection versus COVID vaccination.

Discussion

In our large and diverse population, using a sequence–symmetry analysis, we found apparent evidence of POTS-associated diagnoses occurring more frequently after COVID-19 vaccination than before vaccination. These new POTS diagnoses occurred at a more frequent rate than did new CPC diagnoses after vaccination. The crude risks of new POTS diagnoses made in vaccinated patients was significantly lower than in patients after SARS-CoV-2 infection. This same general trend of proportionately higher risks of new diagnosis in patients after infection compared to patients receiving vaccination was consistently seen for myocarditis, which we considered the benchmark condition, as well as for other more common diagnoses, which we considered the referent conditions. We note that higher post-infection compared to post-vaccination rates reflect observations from separate post-infectious and post-vaccinated cohorts with inherent baseline differences, respectively, which precludes the ability to estimate fully-adjusted comparisons accounting for theoretically shared potential confounders.

POTS occurring after SARS-CoV-2 infection has been described, but reports of POTS or other neuropathies after COVID-19 vaccination have only started to emerge in case reports[9,18]. Historically similar reports of post-vaccination POTS have appeared in the context of

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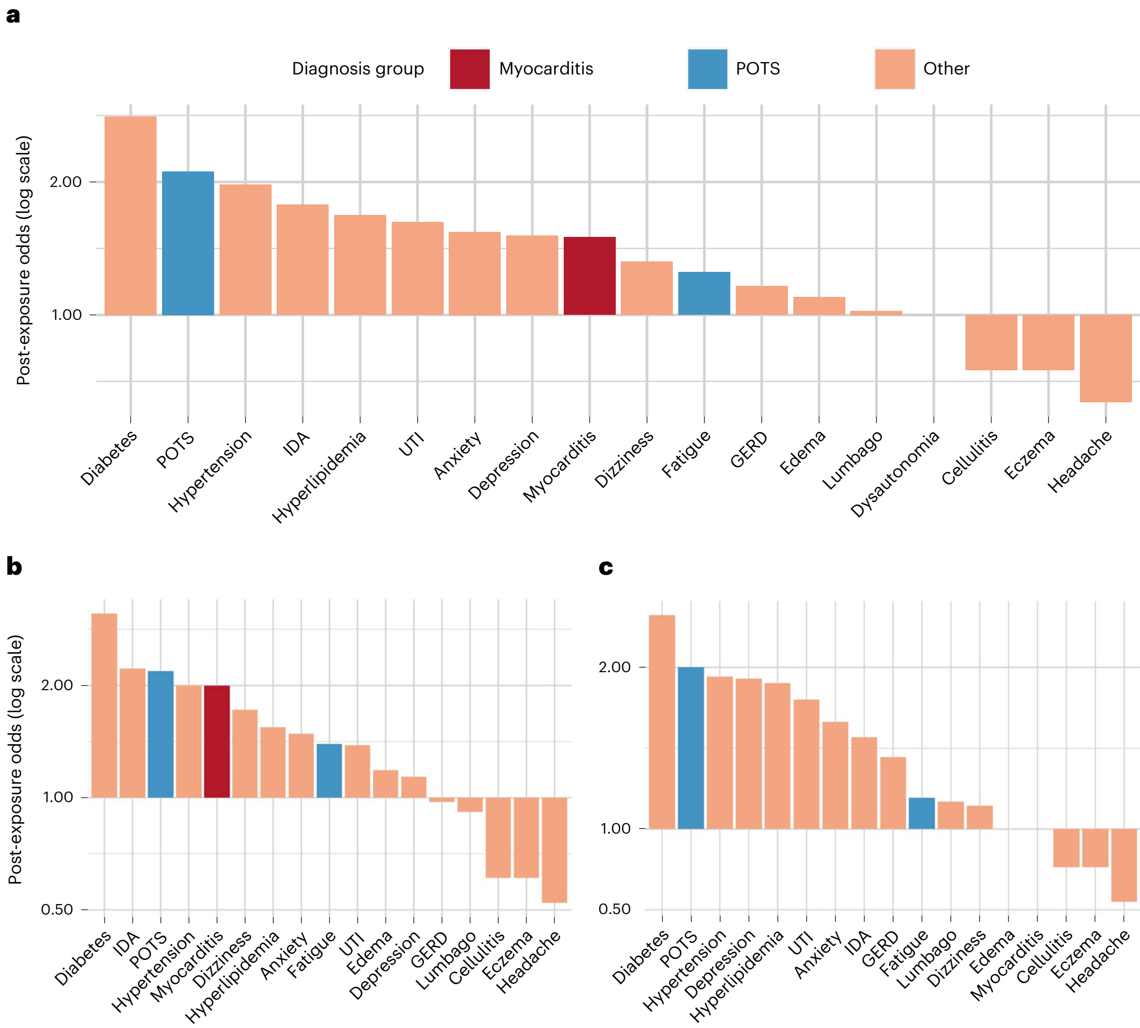

Fig. 2 | Post-infection odds by diagnosis. a, All patients, post-infection. **b**, Male patients only, post-infection. **c**, Female patients only, post-infection. GERD, gastroesophageal reflux disease; IDA, iron deficiency anemia.

human papillomavirus vaccination[19,20], although without sufficient follow-up or validating data to establish causality[21,22]. Similarly, our results should not be interpreted as definitive for any causal links between COVID-19 vaccination and POTS due to the observational design of the study. However, the concordant observations of elevated, albeit less frequent, risks for the same types of diagnoses made after vaccination when compared to those made after infection are suggestive, with the prototypical example represented by myocarditis that presented in our cohorts at frequencies matching those reported by other studies[7,8,23]. In addition, we observed similar effects in patients receiving primarily, but not exclusively, mRNA vaccines. Because heterogeneity is seen in the beneficial responses to COVID-19 vaccination, as well as in clinical responses to natural viral exposure, it is not surprising that heterogeneity would be seen for off-target effects of vaccination[24].

There is biological plausibility for the association between POTS and COVID-19 vaccination in particular. Before the pandemic, mRNA vaccination had been administered in small trials predominantly involving cancer therapy, demonstrating rare off-target neurological effects such as Bell's palsy, which has also been seen with COVID-19 vaccination[25,26]. In SARS-CoV-2 infection, multiple reports of post-infection POTS invoke the possibility of an immune-mediated mechanism triggered by an antigenic component of the spike protein shared with vaccination[13,24,27]. Given the broad expression of ACE2 preceptors, inflammasome activation by synthetic spike protein could result in multi-systemic effects, including neurocardiogenic targets and potential induction of variable types of autoimmunity[28–30]. Additionally, the lipid nanoparticle coating in mRNA vaccine formulations is known to be highly inflammatory, although effects related to the lipid coating appear less likely contributors than spike-protein-mediated effects[31]. Further research is needed to clarify potential mechanisms related to either vaccine formulation or vaccine target. However, some caution should be taken when comparing the crude risk rate of POTS occurring in vaccinated versus infected patient populations externally, owing to inherent differences between populations that can also vary across locations of care. We have observed that POTS in either scenario may respond to conventional therapies. In our experience, patients are managed according to standard-of-care guidelines[11,12] for treatment of POTS, which involves initially conservative therapies, such as salt tablets and hydration, structured exercise programs and compressive stockings. When clinically indicated, usually for substantial or persistent symptoms, medication therapy, such as beta blockers or ivabradine, were prescribed as tolerated for tachycardic response and midodrine for orthostatic intolerance. In patients with hyperadrenergic variants, clonidine was given or considered. Accordingly, patients studied received clinical care that was reviewed to be consistent with guidelines recommendations, and referral to local experts in managing POTS was often pursued in cases that warranted consideration for more specialized evaluation and therapies[11,12].

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Table 2 | Diagnoses within 90 days of exposure for study sample with documented SARS-CoV-2 infection (*n*=12,460)

Diagnosis	No. new diagnoses	New diagnosis before exposure	New diagnosis after exposure	Post-exposure risk		Diagnostic group
	n (per 100,000)	*n* (per 100,000)	*n* (per 100,000)	Odds (95% CI)	*P* value	
Diabetes mellitus	328 (2,632.42)	86 (690.21)	242 (1,942.22)	2.81 (2.19–3.63)‡	<0.001	CPC
POTS	383 (3,073.84)	123 (987.16)	260 (2,086.68)	2.11 (1.70–2.63)‡	<0.001	POTS
Hypertension	642 (5,152.49)	216 (1,733.55)	426 (3,418.94)	1.97 (1.67–2.33)‡	<0.001	CPC
Iron deficiency anemia	125 (1,003.21)	45 (361.16)	80 (642.05)	1.78 (1.22–2.60)†	0.002	CPC
Hyperlipidemia	244 (1,958.27)	91 (730.34)	153 (1,227.93)	1.68 (1.29–2.20)‡	<0.001	CPC
UTI	438 (3,515.25)	167 (1,340.29)	271 (2,174.96)	1.62 (1.33–1.98)‡	<0.001	CPC
Anxiety	211 (1,693.42)	83 (666.13)	128 (1,027.29)	1.54 (1.16–2.05)†	0.002	CPC
Depression	108 (866.77)	43 (345.10)	65 (521.67)	1.51 (1.01–2.26)*	0.043	CPC
Myocarditis	5 (40.13)	2 (16.05)	3 (24.08)	1.50 (0.21–12.78)	1.00	Myocarditis
Dizziness	167 (1,340.29)	72 (577.85)	95 (762.44)	1.32 (0.96–1.81)	0.09	CPC
Fatigue	619 (4,967.90)	275 (2,207.06)	344 (2,760.83)	1.25 (1.06–1.47)†	0.006	POTS
GERD	160 (1,284.11)	74 (593.90)	86 (690.21)	1.16 (0.84–1.60)	0.39	CPC
Edema	107 (858.75)	51 (409.31)	56 (449.44)	1.10 (0.74–1.63)	0.70	CPC
Lumbago	192 (1,540.93)	95 (762.44)	97 (778.49)	1.02 (0.76–1.37)	0.94	CPC
Dysautonomia	2 (16.05)	1 (8.03)	1 (8.03)	1.00 (0.10–9.58)	1.00	POTS
Cellulitis	98 (786.52)	56 (449.44)	42 (337.08)	0.75 (0.49–1.14)	0.19	CPC
Eczema	98 (786.52)	56 (449.44)	42 (337.08)	0.75 (0.49–1.14)	0.19	CPC
Headache	407 (3,266.45)	249 (1,998.39)	158 (1,268.06)	0.63 (0.52–0.78)‡	<0.001	CPC
EDS	0 (0)	0 (0)	0 (0)	–	–	POTS
Mast cell disorders	0 (0)	0 (0)	0 (0)	–	–	POTS

CI, confidence interval; GERD, gastroesophageal reflux disease. Odds of post-exposure diagnosis were estimated using one-sample proportions testing with continuity correction, and two-sided *P* values are shown without correction for multiple testing while noting that a conservative Bonferroni threshold of 0.05/20=0.0025 may be considered for aiding interpretation of results. **P*<0.05, †*P*<0.01, ‡*P*<0.001

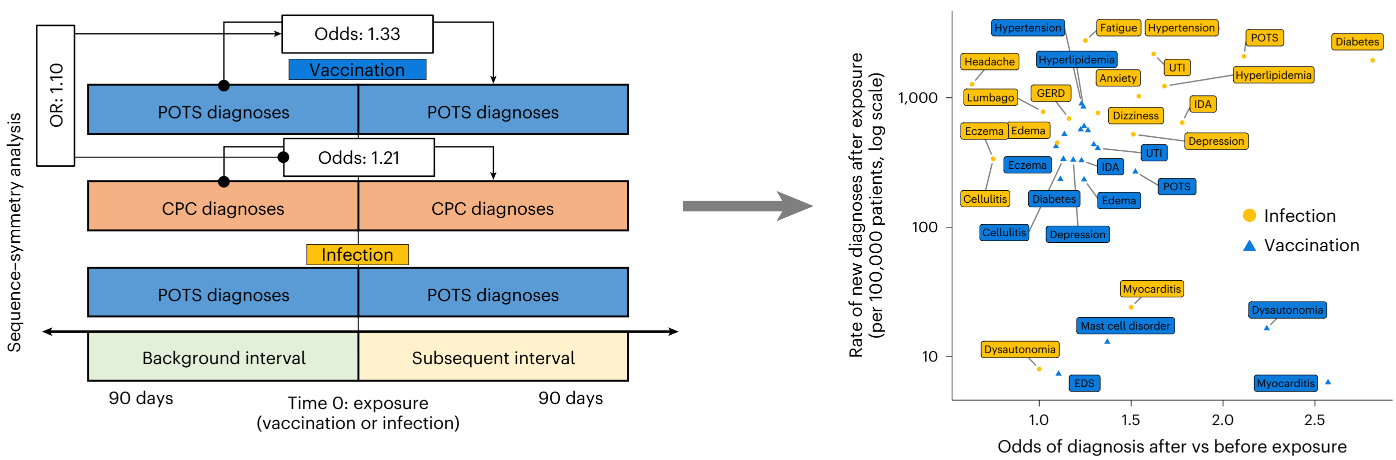

Fig. 3 | Central illustration. Study design (left) and odds of post-exposure diagnosis versus rate per 100,000 for SARS-Cov-2 infection and COVID-19 vaccination (right). For odds and ORs in the left panel, the numerator is designated by the arrow, the denominator by the circle. GERD, gastroesophageal reflux disease; IDA, iron deficiency anemia.

In summary, POTS-related diagnoses appear to be acquired with increased frequency after, compared to before, COVID-19 vaccination, particularly when compared to more commonly diagnosed conditions, Additional research regarding the relation between COVID-19 vaccination and POTS is needed. By further developing the evidence base and augmenting understanding around emerging vaccine side effects, clinical researchers may work to enhance medical trust and improve quality of care as well as communications around vaccines, with the ultimate goal of optimizing vaccine uptake.

Study limitations

Our study has several limitations. We focused on data collection from outpatient encounters and excluded data from inpatient encounters in a single medical center, which minimizes confounding but limits external validity. Because patients may also receive care outside of our health system, there is a possibility that some unrecorded exposures could have led to misclassification. However, given the time period of the study, during which vaccinations tended to be delayed by 90 days after infection and during which any vaccine history tended to be diligently

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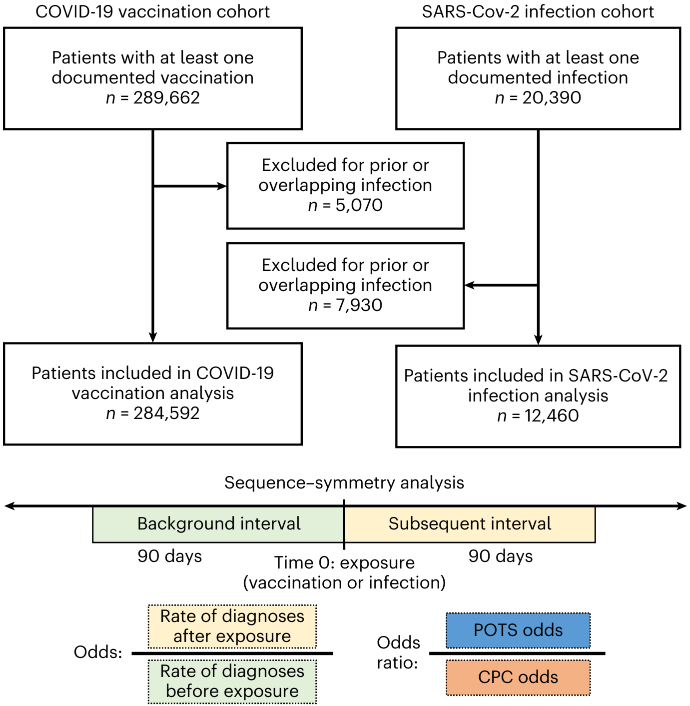

Fig. 4 | Study design. Participant flow and study design.

documented, the effects of any unrecorded exposures are expected to be minimal. Additionally, our separate populations of vaccinated and infected patients were mutually exclusive; recognizing that these populations may have inherent differences, the comparisons between the populations should be interpreted more cautiously than the comparisons within the populations. We did not formally adjudicate all diagnoses due to the large number of events, and an adjudicated subsample did show that a significant degree of non-POTS diagnoses were captured within our International Classification of Diseases (ICD) codes; however, given that this would likely result in non-differential misclassification biasing toward the null, we think that our relative comparisons remain valid. Our analyses, based on medical records data, may have captured vaccinations more effectively than SARS-CoV-2 infections, thus limiting the sample size for the infection-related analyses. Our exclusion criteria limit the generalizability of our results in patients who have had both vaccination and infection, in either order. We did not specifically assess for interactions between infection and vaccination or temporal effects potentially arising from seasonal variation or dynamic factors that evolved over the course of the pandemic (for example, infections caused by Delta versus Omicron variants). Given that POTS is recognized as a condition that is commonly underdiagnosed as well as misdiagnosed[32,33], our records-based search may have underestimated true prevalence. Conversely, the lack of a standard single ICD code for capturing a formal diagnosis of POTS can lead to overlap with other medical conditions and variation in the application of available ICD codes, including in the choice of which POTS-associated codes are used. Thus, prospective studies using more specific methods for identifying POTS and associated conditions are needed to clarify absolute post-exposure diagnosis rates, as opposed to the relative comparisons primarily featured in the current study. Finally, because we focused on data derived from outpatient encounters occurring at a single medical center, additional studies in ideally larger and more diverse external cohorts are needed to assess the generalizability of our findings.

Methods

This study complies with all relevant ethical regulations. The Cedars-Sinai institutional review board approved the study and waived informed consent for this retrospective study. No compensation was given to participants.

Study cohorts

Our study cohorts were derived from the diverse patient population of the Cedars-Sinai Health System in Los Angeles County, California, from 2020 to 2022. Our study design includes two sequence–symmetry analyses[17] within separate retrospective cohorts of patients with COVID-19 vaccination and patients with SARS-CoV-2 infection.

Post-vaccine cohort. In our primary cohort investigating the relation of COVID-19 vaccination with POTS diagnoses, the primary exposure was first COVID-19 vaccination, as documented in the electronic health record (EHR). Of all patients who had at least one COVID-19 vaccination dose documented (n = 289,662), we excluded those with SARS-CoV-2 infection before and within 90 days after the first vaccination dose (n = 5,070). We identified new diagnoses occurring within 90 days of exposure, associated with an outpatient encounter and defined by ICD-9 and ICD-10 codes or grouping by phecode (Supplementary Table 2)[34]. We considered three groups of diagnoses: POTS-associated diagnoses, myocarditis and CPC diagnoses. Given the lack of a single ICD code for POTS, we garnered expert opinion from clinical specialists to define a POTS-associated group of diagnoses that includes dysautonomia, other specified cardiac dysrhythmias (the primary ICD code, herein referred to as POTS), mast cell activation syndrome and related disorders, EDS and fatigue. The CPC diagnoses were prospectively selected from ICD codes frequently documented in primary care[35], excluding diagnoses with strong biological plausibility for being directly related to COVID-19 (for example, upper respiratory infection, cough and fever).

To assess the validity of our approach to identifying possible POTS diagnoses, we conducted clinical adjudication of 50 sequentially encountered patients identified has having both the I49.8 and G90.9 codes. From this adjudication process, we observed that 40 (80%) were either formally confirmed POTS through comprehensive diagnostic testing or with signs and symptoms consistent with guidelines definitions of POTS but still awaiting full diagnostic testing for confirmation. We used limited but available ICD codes in attempts to identify POTS diagnoses with optimal sensitivity and specificity while recognizing that misclassification can result from both variable ICD coding patterns and the prior absence of a unique ICD code for POTS. Notwithstanding the acceptable results of having clinically adjudicated a subset of our identified cases, we recognize that our analyses of EHR data are intrinsically subject to non-differential misclassification that generally tends to bias results toward the null.

Post-infection cohort. The secondary cohort investigated the relation of SARS-CoV-2 infection with POTS diagnoses for contextual comparison. We included all patients with documented SARS-CoV-2 infection (n = 20,390) and excluded those with vaccination before or within 90 days after infection (n = 7,930). The primary exposure for the secondary cohort was first SARS-CoV-2 infection. We analyzed the same diagnoses and diagnosis groups occurring within 90 days of first SARS-CoV-2 infection. In designing our study, we observed increases in multiple post-COVID-19 CPC diagnosis odds, particularly for diabetes and hypertension (unadjusted for other CPC diagnoses). Increase in diabetes and cardiometabolic risk has been previously reported from separate cohorts[36–40]. Thus, we recognized the importance of including these diagnoses within the CPC group, given that they represent conditions that are commonly diagnosed in primary care settings even if elevated in the post-exposure setting for reasons that are not yet entirely clear. We also recognized that the increased risk ratio for these diagnoses would conservatively bias our primary comparative results toward the null.

Statistical analyses

This study was designed to address multiple potential confounding factors at the outset. Given the medical-records-based data source with certain intrinsic limits to query-able patient-level data, we recognized that a self-controlled design would allow at least some ability to control for time-invariant confounders, such as age and sex, or latent but time-invariant confounders that could reflect differences in healthcare interaction between vaccinated patients and those unvaccinated at time of infection. We also recognized that the exposure itself could influence healthcare behavior—for example, patients may feel more comfortable visiting physicians after vaccination. To this end, we compared the events of new diagnoses of POTS with new diagnoses of myocarditis (the benchmark event) and with new diagnoses of other conditions commonly made during primary care visits (referent events). The comparisons between populations with two distinct but discernible exposures (vaccination and SARS-CoV-2 infection) could permit controlling for detection bias after exposure. Because our source dataset includes patients who may have had SARS-CoV-2 infection or vaccination events occurring outside of our health system, potentially influencing the outcomes of interest, we were careful to restrict our analyses to data collected within a specific and limited timeframe before and after the exposure 'event' (that is, infection or vaccination) given that unrecorded (that is, unmeasured) exposures could otherwise have more opportunity to exert confounding effects. For this reason, we employed a sequence–symmetry analysis along with pre-specified narrow timeframes around documented exposures to help minimize the possibility that unrecorded and potentially confounding or interacting additional exposures could have occurred during the same narrow time period[17]. We note that, because our pre-specified separate populations of vaccinated and infected patients were mutually exclusive, the results of comparison analyses conducted between the populations should be interpreted more cautiously than the results of comparison analyses conducted within the populations.

We expressed new diagnosis events as a rate per 100,000 exposures rather than a rate per number of sequence–symmetry exposure periods (for example, two per exposure), given that the rate per exposure is more readily clinically interpretable. We used these rates to calculate two sets of primary outcomes. The first was the diagnosis-specific odds that the new diagnosis occurred after exposure versus before exposure. The second was the OR of acquiring a post-exposure new POTS group diagnosis versus a new CPC diagnosis. Odds of post-exposure diagnosis were estimated using one-sample proportions testing with continuity correction; ORs were estimated with logistic regression with cluster-robust standard errors to account for possible repeated measures (for example, multiple diagnoses) between patients. With these comparisons, we sought to assess not only the relative odds of developing a new diagnosis after versus before a given exposure but also whether any new POTS-related post-exposure may be disproportionately more common when compared to other newly occurring diagnoses, given potential for the frequency of new diagnoses to temporally vary during the pandemic (Fig. 4). In secondary analyses, we repeated the main analyses after exchanging the first dose of vaccine with the second dose of vaccine as the index exposure. We also repeated primary OR analyses using clustered bootstrapping (2,000 replications with ordinary non-parametric bootstrapping). Additionally, we performed manual adjudication of a subset of 50 events. Data query was performed using DBeaver Enterprise Database Manager version 22.0.0.202203131528 with data formatting by Python 3.9.0 in Jupyter Notebook 6.0.3. Analyses were performed using R/RStudio 4.1.1/2022.02.0 (ref. [41]) with open-source packages tidyverse version 1.3.1, janitor version 2.1.0, lubridate version 1.8.0, gtsummary version 1.6.1, knitr 1.39 and ggrepel 0.9.1.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The clinical data that support the findings of this study are available from Cedars-Sinai Medical Center upon reasonable request. The data are not publicly available due to the contents including information that could compromise research participant privacy/consent. Information regarding data access requests can be found at https://github.com/biodatacore/pots_vax_covid. All inquiries should be directed to biodatacore@cshs.org. The timeframe for response to requests from the authors is 4 weeks. Source data for figures and ICD codes are included in the Supplementary Materials.

Code availability

Code for the analysis conducted for the manuscript is available at https://github.com/biodatacore/pots_vax_covid.

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Author contributions

A.C.K., J.E.E., J.W., P.-S.C. and S.C. developed the initial concepts for the manuscript. A.C.K., J.E.E., D.T., P.G.B., J.N., M.D., B.C. and S.C. performed data accrual, analysis and presentation. J.E.E., J.W., C.N.L., J.R.O., R.Z., D.O., M.D., B.C., B.N.W., P.-S.C. and S.C. provided oversight and interpretation on clinical, technical, and statistical methods and results. The initial draft was written by A.C.K. and S.C., with all authors providing substantial contributions during the editing process. All authors gave final approval for publication.

Competing interests

The authors declare no competing interests.

Additional information

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Software and code

Policy information about availability of computer code

Data collection	Clinical database was queried using DBeaver Enterprise Database Manager V. 22.0.0.202203131528 with data formatting by python Python 3.9.0 in Jupyter-notebook 6.0.3
Data analysis	R/R Studio 4.1.1/2022.02.041 with open source packages tidyverse v1.3.1, janitor v2.1.0, lubridate v1.8.0, gtsummary v1.6.1, knitr 1.39, and ggrepel 0.9.1.

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Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Sex was used and reported with sex-stratified analyses performed.
Population characteristics	Population characteristics were described (age 52±20 years; 57% female; 63% white, 10% Asian, and 8.9% African American; 12% Hispanic ethnicity in 284592 patients).
Recruitment	Patients were electronically identified by history of covid vaccination or covid infection within our system.
Ethics oversight	Cedars Sinai IRB STUDY00000603

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Life sciences study design

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Sample size	No pre-determined sample size calculation was performed. The study population was a convenience sample inclusive of all of the records in a large single center in patients with history of covid infection or vaccination.
Data exclusions	In analysis related to covid vaccination, patients with covid infection prior to vaccination or within the diagnosis interval (90 days) were excluded. In analysis related to covid infection, patients with covid vaccination prior to infection or within the diagnosis interval (90 days) were excluded. These exclusions were performed to avoid confounding between the two exposures considered in analysis.
Replication	We did not replicate in external cohorts due to lack of availability of other large-volume cohorts with similar diagnosis tracking.
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☒	☐	ChIP-seq
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