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ORIGINAL ARTICLE

Impact of the COVID-19 pandemic on clinical autonomic practice in Europe: a survey of the European Academy of Neurology and the European Federation of Autonomic Societies

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Abstract

Background and purpose: The objective was to investigate the impact of the coronavirus disease 2019 (COVID-19) pandemic on European clinical autonomic practice.

Methods: Eighty-four neurology-driven or interdisciplinary autonomic centers in 22 European countries were invited to fill in a web-based survey between September and November 2021.

Results: Forty-six centers completed the survey (55%). During the first pandemic year, the number of performed tilt-table tests, autonomic outpatient and inpatient visits decreased respectively by 50%, 45% and 53%, and every third center reported major adverse events due to postponed examinations or visits. The most frequent newly diagnosed or worsened cardiovascular autonomic disorders after COVID-19 infection included postural orthostatic tachycardia syndrome, orthostatic hypotension and recurrent vasovagal syncope, deemed to be likely related to the infection by ≥50% of the responders. Forty-seven percent of the responders also reported about people with new onset of orthostatic intolerance but negative tilt-table findings, and 16% about people with psychogenic pseudosyncope after COVID-19. Most patients were treated non-pharmacologically and symptomatic recovery at follow-up was observed in ≥45% of cases. By contrast, low frequencies of newly diagnosed cardiovascular autonomic disorders following COVID-19 vaccination were reported, most frequently postural orthostatic tachycardia syndrome and recurrent vasovagal syncope, and most of the responders judged a causal association unlikely. Non-pharmacological measures were the preferred treatment choice, with 50%–100% recovery rates at follow-up.

Conclusions: Cardiovascular autonomic disorders may develop or worsen following a COVID-19 infection, whilst the association with COVID-19 vaccines remains controversial. Despite the severe pandemic impact on European clinical autonomic practice, a specialized diagnostic work-up was pivotal to identify non-autonomic disorders in people with post-COVID-19 orthostatic complaints.

KEYWORDS
autonomic nervous system, COVID-19 infection, COVID-19 vaccination, orthostatic hypotension, postural orthostatic tachycardia syndrome, syncope, telemedicine

INTRODUCTION

Since 2019, over 600 million people worldwide suffered from a coronavirus disease 2019 (COVID-19) infection [1], with major impacts on society and healthcare systems. Not only emergency care [2, 3], but also services for people with chronic conditions were hit hard by the pandemic [4, 5], resulting in increased healthcare burden, especially for neurological patients [6].

Several consortia consistently reported that people with COVID-19 may develop multiple complications, both in the acute phase [7, 8] and in the so-called *post-COVID-19 condition*, characterized by signs and symptoms developing during or after a COVID-19 infection, continuing >12 weeks and not explained by alternative diagnoses [9]. Many post-COVID complaints are neurological in nature [10–12] and may persist over time [13].

With the introduction of various COVID-19 vaccines, concerns have been raised about possible worsening or new onset of both peripheral and central nervous system disorders in vaccinated individuals [14, 15].

Several case reports and case series described cardiovascular autonomic disturbances following COVID-19 infection or vaccination, but methodological heterogeneities and limited clinical information prevented clear conclusions about the causal relationship in many of them [16–20]. In order to fill these gaps in knowledge, the European Academy of Neurology (EAN) Scientific Panel for Autonomic Nervous System Disorders and the European Federation of Autonomic Societies (EFAS) initiated a survey amongst European autonomic centers on the impact of the COVID-19 pandemic on clinical autonomic practice, and on newly diagnosed or worsened cardiovascular autonomic disorders following a COVID-19 infection or vaccination.

METHODS

Participants

A detailed description of the survey methodology was previously published [21]. Briefly, a three-stage search was conducted amongst European neurological and autonomic professional networks to localize neurology-driven or interdisciplinary autonomic centers throughout Europe and they were invited to answer a web-based survey between September and November 2021.

Questionnaire

The questionnaire covered the following topics (full text in Appendix S1):

(i) impact of the pandemic on clinical autonomic laboratories, outpatient and inpatient clinics and lessons learnt for an improved practice;
(ii) telemedicine use in clinical autonomic practice;
(iii) new diagnosis or worsening of previously diagnosed cardiovascular autonomic disorders after COVID-19 infection or vaccination, including information on the likelihood of a causal association, recommended treatment, follow-up availability and symptomatic recovery rate;
(iv) worsening or amelioration of previously diagnosed cardiovascular autonomic disorders due to pandemic measures.

Statistical analysis

Statistical analysis was performed with IBM SPSS, version 25. Data distribution was assessed using the Kolmogorov–Smirnov test. Qualitative variables were summarized as number (percentage), quantitative variables as median (first–third quartile). In the case of missing answers or sub-questions (e.g., only asked if the responder answered "yes" to former questions), the number of actual responders was specified in parentheses. Differences in the distribution of qualitative variables were assessed with the chi-squared, Fisher exact or McNemar test. The Wilcoxon rank-sum and the Mann–Whitney *U* test were used to compare paired and unpaired non-Gaussian-distributed quantitative variables, the *t* test for Gaussian-distributed ones. Associations between variables were analyzed with the Spearman's correlation coefficient. Two-sided *p* values <0.05 were considered statistically significant.

First, the impact of the pandemic on European autonomic practice was analyzed and it was determined whether age or gender of survey participants, pre-pandemic case-load and centers' localization (in southern/eastern vs. northern/western Europe following the United Nations geoscheme [21]) were associated with center closure, pre-to-pandemic reduction in the number of tilt-table tests, outpatient/inpatient visits, reporting a negative impact of the pandemic on autonomic healthcare provision or occurrence of major adverse events. Open-ended questions were analyzed in a semi-quantitative way.

Secondly, telemedicine use in European autonomic centers was examined and it was determined whether any responder or center characteristics were associated with the perceived degree of effectiveness, satisfaction (for physicians and patients, in the responder's view), reimbursement availability and appropriateness.

Thirdly, the cumulative number of newly diagnosed cardiovascular autonomic disorders following COVID-19 infections was estimated by multiplying the number of positive responders by the median number of diagnosed cases in the responder's center (e.g., if the responder answered "yes" to a new diagnosis of postural orthostatic tachycardia syndrome [POTS] after COVID-19 infection and reported 5–10 cases, 1 ×7.5 newly diagnosed POTS cases were calculated for that center). Afterwards, descriptive analyses were conducted on the likelihood of causal association, adopted treatment, follow-up availability and recovery rates. If the number of responders making a new diagnosis of any cardiovascular autonomic disorders after COVID-19 infection was ≥8, it was assessed whether any center or responder characteristic was associated with the likelihood of association between the autonomic diagnosis and COVID-19 infection, treatment choices, availability of follow-up visits and recovery rates.

The same procedure was applied to analyze questions about:

(i) worsening of previously diagnosed cardiovascular autonomic disorders following COVID-19 infection;
(ii) new diagnosis or worsening of cardiovascular autonomic disorders following COVID-19 vaccination;

(iii) previously diagnosed cardiovascular autonomic disorders that worsened or improved due to pandemic-containment measures.

RESULTS

Participants

Forty-six out of 84 (55%) autonomic centers in 22 European countries responded to the survey. Detailed information on the survey responder and autonomic center characteristics has been published previously [21].

Impact of the COVID-19 pandemic on European clinical autonomic practice

The majority of the survey participants reported an overall negative impact of the pandemic on European clinical autonomic practice (Figure 1).

By the end of 2021, 96% ($n = 43/45$) of the autonomic diagnostic laboratories were examining patients, but 69% ($n = 31/45$) had been closed for a median of 5 (2–9) months during the pandemic, with a 50% (21%–74%) pre-to-pandemic annual reduction in the number of performed tilt-table tests ($n = 4872$, altogether).

Sixty percent ($n = 27/45$) of the autonomic outpatient clinics were also closed for a median of 5 (2–9) months since the pandemic beginning, with a 45% (12%–63%) reduction in the annual number of outpatient visits ($n = 8766$ cumulative autonomic outpatient visits during the first pandemic year).

Inpatient admissions of people with autonomic disorders were not possible in 44% ($n = 20/45$) of centers for 2 (2–9) months following the pandemic outbreak, with 53% (16%–87%) annual decrement of inpatient stays ($n = 1138$ cumulative inpatient stays during the first pandemic year). Age and gender of the survey participants and the pre-pandemic center case-load showed no association with its pandemic-related closure. However, more autonomic outpatient clinics located in southern/eastern Europe were closed during the pandemic than in northern/western Europe (88% vs. 49%, $p = 0.01$). Centers located in southern/eastern Europe also experienced higher pre-to-pandemic reductions in the number of performed tilt-table tests ($p = 0.006$) and autonomic outpatient visits ($p = 0.002$).

Twenty-seven percent ($n = 12/45$) of the centers reported 3 (3–3) major adverse events due to missed or postponed diagnostic work-ups or visits, including syncope-related femur fractures and significant disability due to symptomatic worsening or increased anxiety.

Telemedicine in European clinical autonomic practice

Thirty-seven percent ($n = 17/46$) of the autonomic centers already used telemedicine before the pandemic, with a 38% (13%–88%) increase of telemedicine visits during the pandemic. Forty-one percent ($n = 19/46$) of the centers implemented telemedicine measures during the pandemic. The most frequently used telemedicine tools were phone calls ($n = 17/36$), followed by video calls ($n = 11/36$),

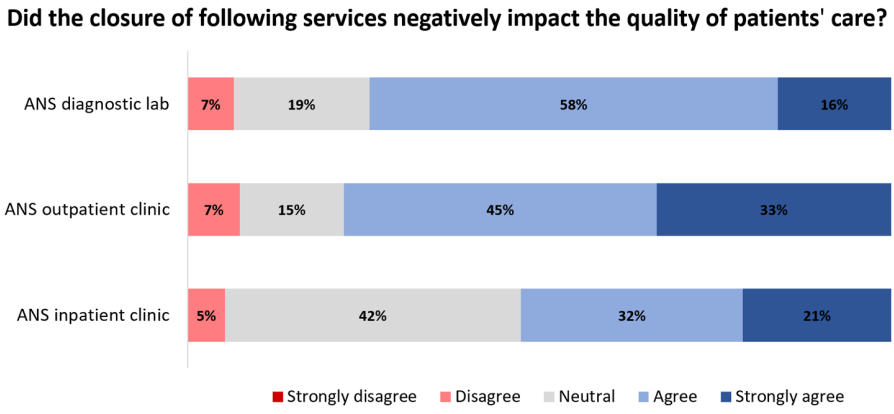

FIGURE 1 Impact of the pandemic on clinical autonomic practice in Europe and lessons learnt for an improved practice. Survey responders reporting a negative impact of the pandemic on autonomic outpatient practice had a lower number of tilt-table tests during the first year of the pandemic (50 [10–93] vs. 187 [30–403], $p = 0.041$); those reporting a negative impact on autonomic diagnostic laboratories had a higher pre-to-pandemic reduction in the number of tilt-table tests performed per year (−67% [−82% to −43%] vs. −38% [−50% to −7%], $p = 0.013$). Sixteen responders answered the open-ended questions on lessons learnt during the pandemic for clinical autonomic diagnostic laboratories. Five of them considered telemedicine useful for urgent consultations and remote monitoring. Six participants stated that there is an urgent need for safety protocols for guaranteeing autonomic testing during pandemic times (especially for aerosol generating procedures, like the Valsalva maneuver and deep breathing). Other participants highlighted the need for standardized test batteries and online audiovisual educational material. Eighteen participants shared their opinion on lessons learnt for autonomic outpatient clinics: 14 rated teleconsultations and telemonitoring strategies as highly valuable, whilst others emphasized the need for hygiene measures also for outpatient visits and online learning aids (e.g., well-illustrated, interactive cases). Seven responders made suggestions on how to improve autonomic inpatient stays, highlighting the need for dedicated autonomic educational programs for healthcare professionals, standardized hygiene measures and telemonitoring facilities to follow up patients after discharge.

remote monitoring (n = 5/36), emails, e-prescriptions and e-referrals (n = 1 each).

Seventy-one percent of responders (n = 15/21 responders for this question) reported that telemedicine services were reimbursable in their country and 67% (n = 10/15) considered the reimbursement fee adequate. No association was found between responder or center characteristics, reimbursement availability or adequateness and use of telemedicine in clinical practice.

Fifty percent of responders (n = 10/20 responders for this question) judged telemedicine fairly to very effective for first visits. All (n = 20/20) agreed on telemedicine effectiveness for follow-up visits and estimated it at least fairly satisfying both for people with autonomic disorders and for autonomic specialists (Figure 2).

Newly diagnosed cardiovascular autonomic disorders after COVID-19 infection

Postural orthostatic tachycardia syndrome was the most common newly diagnosed cardiovascular autonomic disorder after COVID-19 infection (Figure 3a) and 61% (n = 11/18) of responders agreed that POTS was probably related to the COVID-19 infection. All responders (n = 18/18) recommended non-pharmacological therapeutic measures; 72% (n = 13/18) also recommended pharmacotherapy. Seventy-two percent (n = 13/18) of the survey responders had the chance to follow up their POTS cases and observed at least partial symptomatic recovery in 50% of them (25%–88%, Table 1).

Recurrent vasovagal syncope (VVS) was the second most common newly diagnosed cardiovascular autonomic disorder after COVID-19 infection (Figure 3a), judged probably related to the COVID-19 infection by 55% of the responders (n = 6/11). All responders recommended non-pharmacological interventions (n = 11/11), and 64% (n = 7/11) additional pharmacotherapy (Table 1). Nine out of 11 responders (82%) followed up these newly diagnosed VVS cases and observed symptomatic improvement in 80% (50%–100%) of them.

The third most frequent newly diagnosed cardiovascular autonomic disorder after COVID-19 was orthostatic hypotension (OH; Figure 3a), in 57% of cases of neurogenic nature. Every second (n = 6/13) responder rated the new diagnosis of OH probably associated to COVID-19 infection. All responders recommended non-pharmacological strategies, 69% (n = 9/13) also pharmacotherapy. Sixty-two percent (n = 8/13) of responders followed up the newly diagnosed OH cases, with symptomatic improvement in 45% (8%–58%) of them (Table 1). Other newly diagnosed cardiovascular autonomic disorders were, in descending frequency, initial OH (iOH), delayed OH (dOH) and autoimmune autonomic ganglionopathy (Figure 3a; Table 1).

Seven responders reported 45 cases altogether of psychogenic pseudosyncope following COVID-19, in one-third of cases deemed to be related to the infection (Figure 3a).

Forty-eight percent (n = 22/46) of responders also reported 135 cases with orthostatic complaints but negative tilt-table findings (Figure 3a); six responders identified alternative causes of orthostatic intolerance in these patients, including physical deconditioning, polypharmacy, persistent postural-perceptual dizziness and pandemic-related psychological burden.

Worsening of previously diagnosed cardiovascular autonomic disorders after COVID-19 infection

The most common pre-existing cardiovascular autonomic disorder worsening after COVID-19 infection was POTS (Figure 3b), with

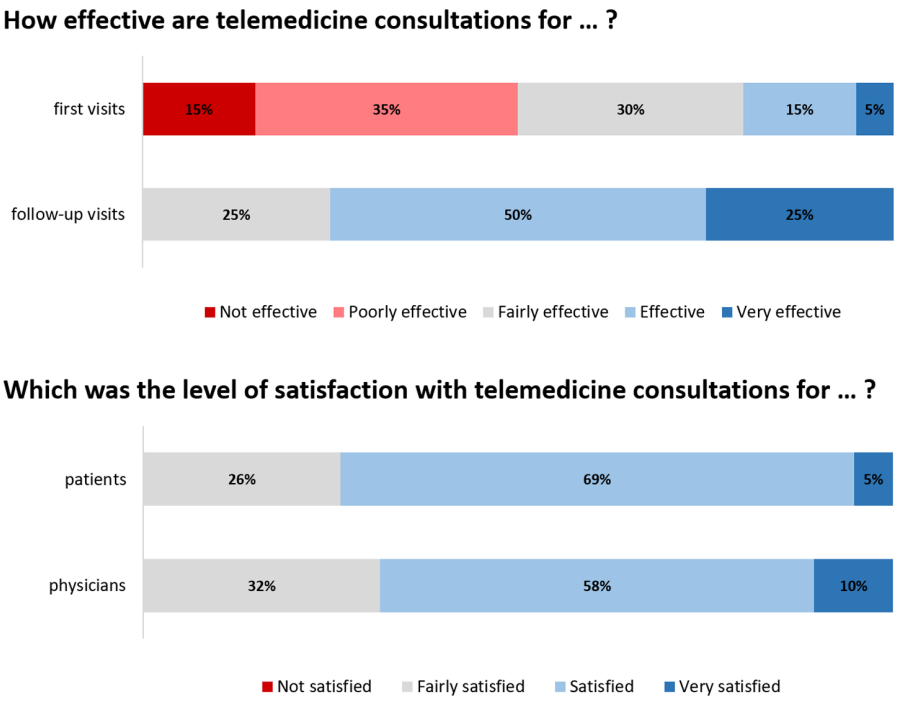

FIGURE 2 Telemedicine effectiveness for first and follow-up visits and level of physicians' and patients' satisfaction with telemedicine consultations. A moderate positive correlation was observed between the number of autonomic inpatient stays in years preceding the pandemic and a positive opinion on the effectiveness of telemedicine for the first (ρ = 0.659; p = 0.004) and follow-up visits (ρ = 0.507; p = 0.038).

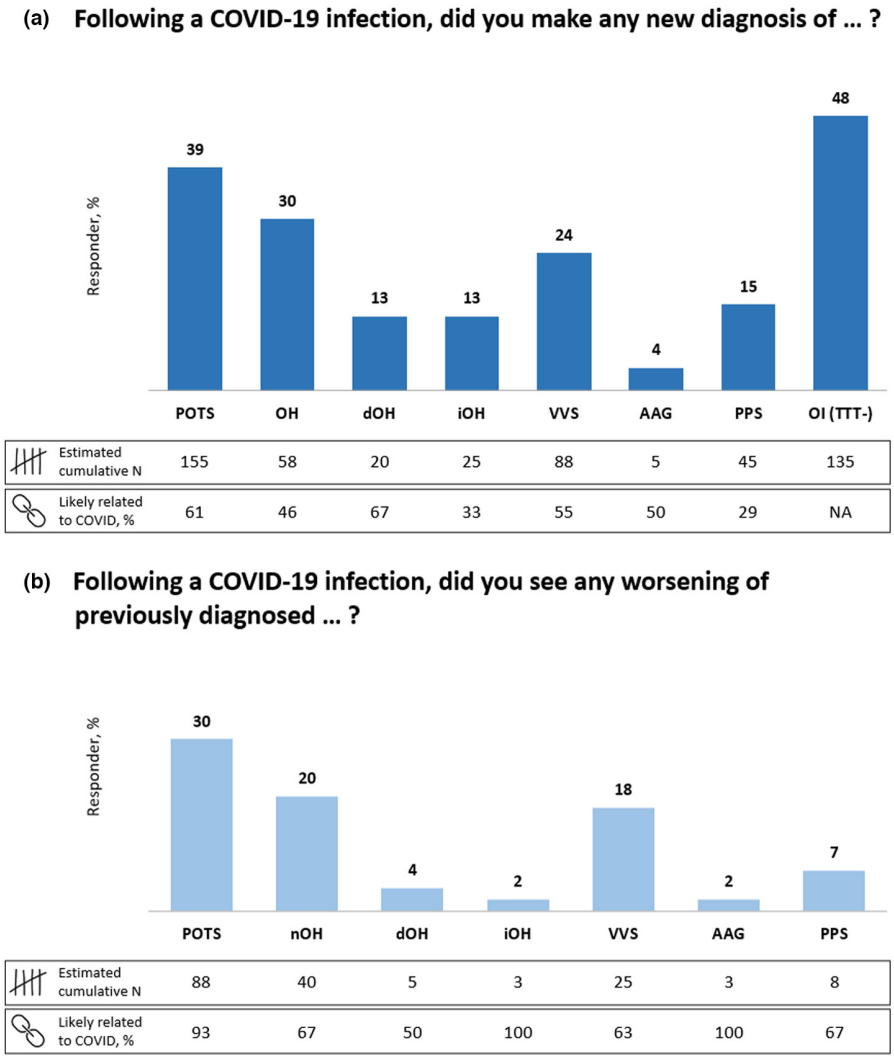

FIGURE 3 Percentage of responders reporting new diagnosis (a) or worsening of previously diagnosed (b) cardiovascular autonomic disorders following a COVID-19 infection. The lower part of each panel provides the estimated cumulative number of cases per cardiovascular autonomic disorder and the percentage of responders who deemed a causal relationship with the passed COVID-19 infection likely. Survey responders who made a new diagnosis of POTS after COVID-19 infection had a higher percentage of POTS cases in their centers' overall case mix (20% [7%–30%] vs. 3% [1%–7%], $p = 0.002$). It was found that no responder or center characteristic was significantly associated with the diagnosis of recurrent VVS diagnosis after COVID-19 infection, whilst responders who considered an association between newly diagnosed OH and the passed COVID-19 infection likely were older than those who rated the association unlikely ($\rho = 0.691$, $p = 0.009$). No association was observed between any survey participant's or center's characteristics and the reported worsening of previously diagnosed cardiovascular ANS disorders after COVID-19 infection. AAG, autoimmune autonomic ganglionopathy; ANS, autonomic nervous system; dOH, delayed orthostatic hypotension; iOH, initial orthostatic hypotension; nOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension; OI (TTT-), orthostatic intolerance but negative tilt-table test; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; VVS, vasovagal syncope.

all except one responder agreeing on some probably causal association. Non-pharmacological and pharmacological measures, and in one-third of cases both combined, were prescribed to manage POTS worsening (Table 1). Nine out of 14 responders followed up these cases and observed a symptomatic recovery in 30% (10%–63%).

The second and third most common worsened cardiovascular autonomic disorders after COVID-19 infection were neurogenic OH and recurrent VVS (Figure 3b). In both conditions, two-thirds of the responders deemed this worsening probably associated with COVID-19 infections. Pharmacological measures were the most frequent therapeutic strategy for worsened neurogenic OH, and non-pharmacological measures for worsened VVS (Table 1). Six out of 10 responders had followed up the cases with neurogenic OH worsened after COVID-19 infection, observing symptomatic improvement in one-third. Only three responders had followed up cases with increased VVS frequency after COVID-19 infection, reporting symptomatic recovery in all (Table 1).

TABLE 1 Treatment strategies, follow-up availability and percentage of symptomatic recovery at follow-up in people with new diagnosis or worsening of previously diagnosed cardiovascular autonomic disorders after a COVID-19 infection.

	Cardiovascular autonomic disorders							
Newly diagnosed after COVID-19 infection	**POTS *N* = 18**	**OH *N* = 13**	**dOH *N* = 6**	**iOH *N* = 6**	**VVS *N* = 11**	**AAG *N* = 2**	**PPS *N* = 7**	**OI (TTT-) *N* = 22**
Offered treatment								
Non-pharmacological	18 (100)	13 (100)	6 (100)	6 (100)	11 (100)	1 (50)	7 (100)	NA
Pharmacological	13 (72)	9 (69)	5 (83)	2 (33)	7 (64)	2 (100)	0 (0)	NA
Combined	13 (72)	9 (69)	5 (83)	2 (33)	7 (64)	1 (50)	NA	NA
Follow-up								
Available	13 (72)	8 (62)	5 (83)	4 (67)	9 (82)	1 (50)	3 (43)	11 (50)
Recovered (%)	50 (25–88)	45 (8–58)	90 (35–95)	85 (19–99)	80 (50–100)	100 (–; –)	50 (–; –)	67 (30–90)

Worsened after COVID-19 infection	**POTS *N* = 14**	**nOH *N* = 9**	**dOH *N* = 2**	**iOH *N* = 1**	**VVS *N* = 8**	**AAG *N* = 1**	**PPS *N* = 3**	**OI (TTT-)**
Offered treatment								
Non-pharmacological	9 (64)	4 (44)	2 (100)	1 (100)	6 (75)	0 (0)	3 (100)	NA
Pharmacological	8 (57)	6 (67)	2 (100)	0 (0)	1 (13)	1 (100)	0 (0)	NA
Combined	5 (36)	4 (44)	2 (100)	0 (0)	1 (13)	NA	NA	NA
Follow-up								
Available	9 (64)	6 (67)	0 (0)	0 (0)	3 (38)	1 (100)	1 (33)	NA
Recovered (%)	30 (10–63)	33 (0–60)	–	–	100 (–)	35 (–)	0 (–)	NA

Note: No association was found between any responder or center characteristic and treatment choices, follow-up availability or symptomatic recovery rate at follow-up of people with newly diagnosed POTS, recurrent VVS or OH after COVID-19 infection. Three out of three responders from southern/eastern Europe versus 2 out of 11 from northern/western Europe opted for combined pharmacological and non-pharmacological measures to treat people with previously diagnosed POTS worsening after a COVID-19 infection ($p = 0.027$). There was no association between any responder or center characteristics and treatment choices or follow-up availability for people with worsened cardiovascular autonomic disorders after COVID-19 infection, but responders who reported a symptomatic recovery at follow-up in people with previously diagnosed neurogenic OH worsening after a COVID-19 infection were older ($\rho = 0.840$, $p = 0.036$).

Qualitative variables are reported as frequency (%), quantitative variables as median (first–third quartile, where applicable).

Abbreviations: AAG, autoimmune autonomic ganglionopathy; COVID-19, coronavirus disease 2019; dOH, delayed orthostatic hypotension; iOH, initial orthostatic hypotension; *N*, number of responders per cardiovascular autonomic disorder; NA, not applicable; nOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension; OI (TTT-), orthostatic intolerance but negative tilt-table test; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; VVS, vasovagal syncope.

Newly diagnosed cardiovascular autonomic disorders after COVID-19 vaccination

Postural orthostatic tachycardia syndrome and recurrent VVS were the most frequent newly diagnosed cardiovascular autonomic disorders after COVID-19 vaccination with tozinameran (Comirnaty®), ChAdOx1-S (Vaxzevria®) or elasomeran (Spikevax®; Figure 4a). None of the responders considered the association between newly diagnosed POTS and the vaccination likely. One out of four responders reporting recurrent VVS after COVID-19 vaccination deemed the association between newly diagnosed VVS and the vaccination likely (Figure 4a). Non-pharmacological strategies were recommended in all cases with post-COVID-19-vaccine POTS or recurrent VVS. Every second responder also introduced pharmacological measures (Table 2).

Postural orthostatic tachycardia syndrome was the most frequently diagnosed cardiovascular autonomic disorder after both COVID-19 infection and vaccination. However, post-vaccination POTS was diagnosed less frequently than post-infectious POTS (155 newly diagnosed POTS after COVID-19 infection vs. 13 after COVID-19 vaccination; one center diagnosing post-vaccination but not post-infectious POTS vs. 14 centers reporting post-infectious POTS only, $p = 0.001$).

When asked about any newly diagnosed cardiovascular autonomic disturbances following vaccination against other infectious diseases, 13% of responders ($n = 6/45$) reported cases of POTS, recurrent VVS and OH, in descending frequency.

Worsening of previously diagnosed cardiovascular autonomic disorders after COVID-19 vaccination

Eighteen percent of the responders ($n = 8/45$) reported worsening of previously diagnosed POTS and 9% ($n = 4/45$) of recurrent VVS following COVID-19 vaccination with tozinameran (Comirnaty®), ChAdOx1-S (Vaxzevria®) or elasomeran (Spikevax®; Figure 4b).

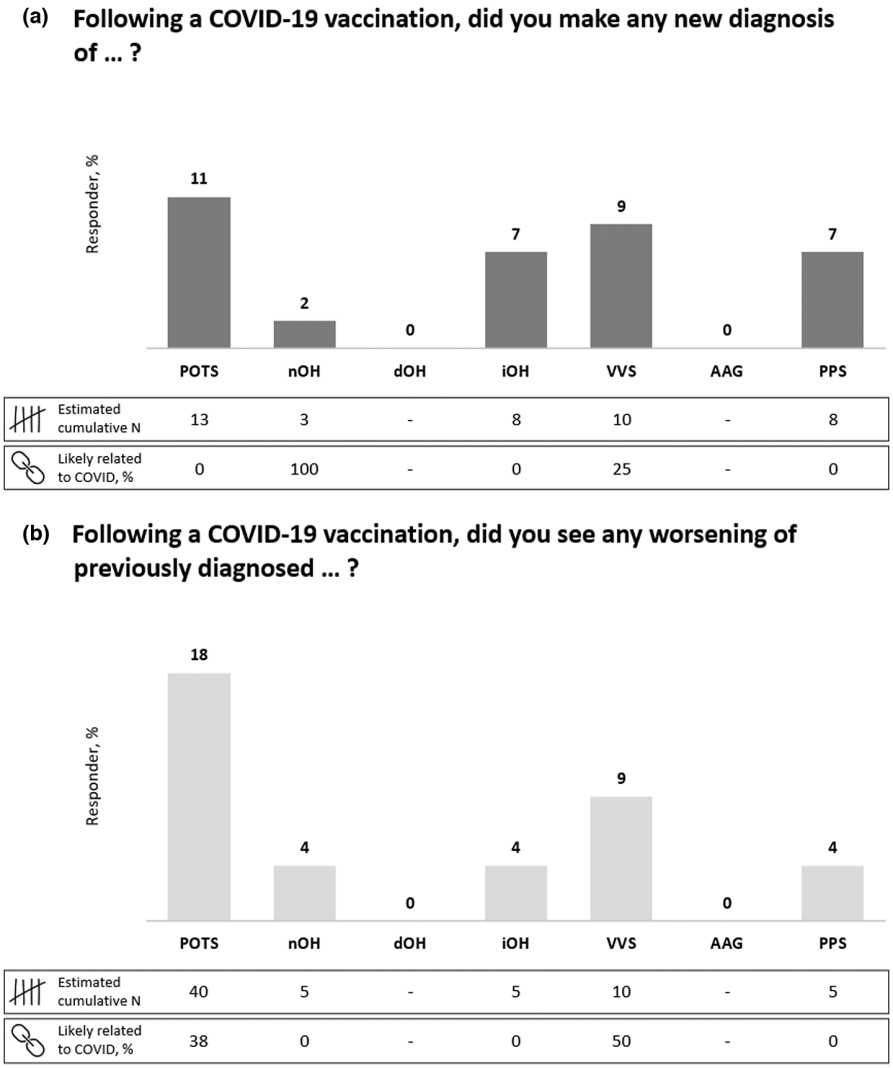

FIGURE 4 Percentage of responders reporting new diagnosis (a) or worsening of previously diagnosed (b) cardiovascular autonomic disorders following a COVID-19 vaccination. The lower part of each panel provides the estimated cumulative number of cases per cardiovascular autonomic disorder and the percentage of responders who judged a causal relationship with the received COVID-19 vaccination likely. Due to the small numbers of cases reported, no additional analysis of the responder's or center's characteristics associated with a given cardiovascular autonomic diagnosis after COVID-19 vaccine was performed. AAG, autoimmune autonomic ganglionopathy; ANS, autonomic nervous system; dOH, delayed orthostatic hypotension; iOH, initial orthostatic hypotension; nOH, neurogenic orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; VVS, vasovagal syncope.

Three out of eight and two out of four responders, respectively, deemed worsened POTS and recurrent VVS probably associated with vaccinations (Figure 4b). Few responders reported post-vaccination worsening of neurogenic OH, iOH and psychogenic pseudosyncope, but in all cases the causal association with the COVID-19 vaccination was judged either neutral or unlikely (Figure 4b). The vast majority of worsened POTS and VVS cases recovered at follow-up (Table 2).

Postural orthostatic tachycardia syndrome was also the most common previously diagnosed cardiovascular autonomic disorder with symptomatic worsening following either COVID-19 infection or vaccination. However, POTS worsening after COVID-19 infection was more frequent than after vaccination ($n = 88$ vs. $n = 40$; six centers reporting only post-infectious POTS worsening, but none reporting post-vaccination POTS worsening only, $p = 0.031$).

Eighteen percent of responders ($n = 8/45$) had experience with cases of previously diagnosed cardiovascular autonomic disorders worsening after vaccination for other infectious diseases, most frequently POTS (four responders), OH and VVS (two responders each).

Worsening of previously diagnosed cardiovascular autonomic disorders due to pandemic measures

The responders reportedly observed, in descending frequency, worsening of previously diagnosed POTS, neurogenic OH, psychogenic pseudosyncope, VVS, dOH, iOH and autoimmune autonomic ganglionopathy due to pandemic-related restrictions (Figure 5). Both pharmacological and non-pharmacological measures, and sometimes combinations thereof, were offered to treat worsened symptoms (Table 3). Symptomatic recovery was observed more frequently in people with worsened neurogenic OH than in those with pandemic-related POTS, psychogenic pseudosyncope or VVS worsening (Table 3).

Amelioration of previously diagnosed cardiovascular autonomic disorders during the pandemic

Amelioration of symptoms due to pandemic-related changes in lifestyle was also observed in people with previously diagnosed cardiovascular autonomic disorders and mimicries, most frequently

TABLE 2 Treatment strategies, follow-up availability and percentage of symptomatic recovery at follow-up in people with new diagnosis or worsening of previously diagnosed cardiovascular autonomic disorders following a COVID-19 vaccination.

Newly diagnosed after COVID-19 vaccination	Cardiovascular autonomic disorders						
	POTS *N* = 5	nOH *N* = 1	dOH *N* = 0	iOH *N* = 3	VVS *N* = 4	AAG *N* = 0	PPS *N* = 3
Offered treatment							
Non-pharmacological	5 (100)	1 (100)	–	3 (100)	4 (100)	–	3 (100)
Pharmacological	3 (60)	0 (0)	–	0 (0)	2 (50)	–	0 (0)
Combined	3 (60)	0 (0)	–	0 (0)	2 (50)	–	NA
Follow-up							
Available	3 (60)	1 (100)	–	1 (33)	2 (50)	–	0 (0)
Recovered (%)	50 (–)	100 (–)	–	75 (–)	85 (–)	–	–
Worsened after COVID-19 vaccination	**POTS *N* = 8**	**nOH *N* = 2**	**dOH *N* = 0**	**iOH *N* = 2**	**VVS *N* = 4**	**AAG *N* = 0**	**PPS *N* = 2**
Offered treatment							
Non-pharmacological	3 (38)	1 (50)	–	2 (100)	1 (25)	–	2 (100)
Pharmacological	3 (38)	1 (50)	–	0 (0)	1 (25)	–	0(0)
Combined	1 (13)	1 (50)	–	0 (0)	1 (25)	–	NA
Follow-up							
Available	5 (63)	1 (50)	–	0 (0)	2 (50)	–	2 (100)
Recovered (%)	95 (60–100)	0 (–)	–	–	100 (–)	–	55 (–)

Note: Due to the small number of cases reported, no additional analysis of factors associated with a given cardiovascular autonomic diagnosis after COVID-19 vaccination, offered treatment and recovery at follow-up was performed.

Qualitative variables are reported as frequency (%), quantitative variables as median (first–third quartile, where applicable).

Abbreviations: AAG, autoimmune autonomic ganglionopathy; COVID-19, coronavirus disease 2019; dOH, delayed orthostatic hypotension; iOH, initial orthostatic hypotension; *N*, number of responders per each cardiovascular autonomic disorder; NA, not applicable; nOH, neurogenic orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; VVS, vasovagal syncope.

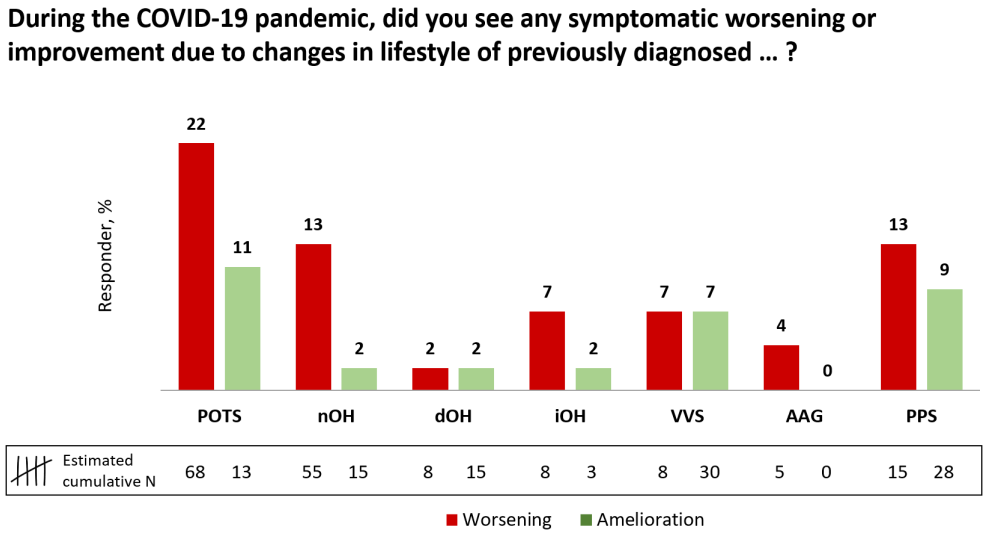

FIGURE 5 Percentage of responders reporting worsening (red) or improvement (green) of previously diagnosed cardiovascular autonomic disorders due to pandemic-containment measures and changes in lifestyle during the COVID-19 pandemic. The lower part of the panel reports the estimated cumulative number of cases per cardiovascular autonomic disorder. The responders who reported a pandemic-related POTS worsening had a higher percentage of people with POTS in their laboratory case mix (20% [9%–28%] vs. 5% [2%–10%], $p = 0.001$). Ninety percent ($n = 9/10$) of the responders who reported cases of pandemic-related POTS worsening had a research focus on POTS compared to 22% ($n = 8/36$) of the responders who did not observe any such cases ($p < 0.001$). AAG, autoimmune autonomic ganglionopathy; dOH, delayed orthostatic hypotension; iOH, initial orthostatic hypotension; nOH, neurogenic orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; VVS, vasovagal syncope.

TABLE 3 Treatment strategies, follow-up availability and percentage of symptomatic recovery at follow-up in people with pandemic-related worsening or amelioration of previously diagnosed cardiovascular autonomic disorders.

	Cardiovascular autonomic disorders						
Pandemic-related symptomatic worsening	**POTS *N* = 10**	**nOH *N* = 6**	**dOH *N* = 1**	**iOH *N* = 3**	**VVS *N* = 3**	**AAG *N* = 2**	**PPS *N* = 6**
Offered treatment							
Non-pharmacological	8 (80)	6 (100)	1 (100)	3 (100)	3 (100)	NA	6 (100)
Pharmacological	5 (50)	4 (67)	1 (100)	1 (33)	2 (67)	1 (50)	NA
Combined	3 (30)	4 (67)	1 (100)	1 (33)	2 (67)	NA	NA
Follow-up							
Available	7 (70)	4 (67)	1 (100)	0 (0)	3 (100)	2 (100)	3 (50)
Recovered (%)	50 (0–80)	65 (43–92)	20 (–)	–	30 (–)	83 (–)	50 (–)
Symptomatic improvement during the pandemic	**POTS *N* = 5**	**nOH *N* = 1**	**dOH *N* = 1**	**iOH *N* = 1**	**VVS *N* = 3**	**AAG *N* = 0**	**PPS *N* = 4**
Follow-up							
Available	2 (40)	1 (100)	1 (100)	1 (100)	2 (67)	–	4 (100)
Stable improvement (%)	50 (–)	90 (–)	90 (–)	60 (–)	60 (–)	–	48 (6–78)

Note: Qualitative variables are reported as frequency (%), quantitative variables as median (first–third quartile, where applicable).

Abbreviations: AAG, autoimmune autonomic ganglionopathy; dOH, delayed orthostatic hypotension; iOH, initial orthostatic hypotension; *N*, number of responders per cardiovascular autonomic disorder; NA, not available; nOH, neurogenic orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; VVS, vasovagal syncope.

VVS, psychogenic pseudosyncope, neurogenic OH, dOH and POTS (Figure 5). Follow-up availability was good with stable symptomatic improvement observed in ≥48% of cases (Table 3).

DISCUSSION

This survey shows the profound impact of the COVID-19 pandemic on clinical autonomic practice in Europe, with two-thirds of the centers having been closed for several months, substantial reductions in the number of performed tests and visits, and people with autonomic disorders experiencing major adverse events in every third center.

Southern/eastern European centers reported an overall higher impact of the pandemic on autonomic care than northern/western European ones, underscoring how the COVID-19 emergency further exacerbated pre-existing disparities in autonomic healthcare provision across European countries [21].

Most autonomic centers have currently resumed their activities thanks to the development of standard operating procedures for safe autonomic testing [22–24] and integration of digital healthcare solutions, which most of the survey responders judged effective and satisfying and whose clear advantages for clinical autonomic practice will last far beyond the pandemic times [25]. Teleconsultations, indeed, help abate geographical, physical and economical barriers between people with autonomic disorders and their physicians, ultimately warranting access and continuity of care. This is particularly important at advanced stages of progressive autonomic disorders, when prompt recognition of life-threatening complications may help patients to develop more effective coping strategies [26].

Postural orthostatic tachycardia syndrome, VVS and OH were the most frequent newly diagnosed cardiovascular autonomic disorders after COVID-19 infection. However, whilst VVS and OH were the most frequent autonomic diagnoses also before the pandemic [21], the perception of newly diagnosed POTS cases has considerably increased since the beginning of the pandemic. Such association was also found in a recent systematic review of published post-COVID autonomic cases, with peak incidences of POTS 4 weeks or more after COVID-19 infection, most commonly in young women [20].

Multiple mechanisms may explain cardiovascular autonomic disturbances occurring in the acute and post-COVID-19 phase. Prolonged bedrest, brainstem viral neurotropism [27], virus-mediated neuroinflammation [28, 29], disruption of the renin–angiotensin–aldosterone axis [30] or endothelial dysfunction [31] might have resulted in acute baroreflex dysfunction, impaired water–electrolyte homeostasis or altered vascular capacitance with venous and interstitial fluid pooling. All these factors might have favored the development of reflex syncope during acute COVID-19 infections [20]. On the other hand, the latency to onset of sometimes several weeks reported in the literature between the acute COVID-19 infection and the POTS symptom onset [20] might point towards additional immune-mediated mechanisms of disease. Antibodies against G-protein-coupled cardiovascular receptors have been formerly hypothesized to contribute to POTS pathogenesis [32, 33]. However, more recent studies found positive antibody titers

against G-protein-coupled cardiovascular receptors also in healthy people [34], questioning their pathogenic role in POTS settings. Interestingly, autoimmune autonomic ganglionopathy, an autonomic disorder mediated by antibodies against the α_3-subunit of the ganglionic nicotinic acetylcholine receptor, was only rarely diagnosed after COVID-19 infection by the survey responders. This observation indicates an urgent need for further studies to understand the complex interplay between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 infections, the immune and the autonomic nervous systems. Moreover, the lack of solid evidence for an immune-mediated pathogenesis calls for a very cautious attitude towards immunomodulatory therapies in people with post-COVID-19 autonomic disorders [35].

Symptoms suggestive of cardiovascular autonomic dysfunction have also been described following other viral pandemics such as the Russian flu in the 19th century [36] and infections with the more recent SARS-CoV-1 and Middle East respiratory syndrome virus [37–39], indicating that the mechanisms underlying post-viral cardiovascular autonomic dysfunction might not ultimately be exclusive to SARS-CoV-2.

The survey responders reported good recovery rates in people with post-COVID-19 newly diagnosed POTS at follow-up, suggesting that, irrespective of the underlying mechanism, a transient but not permanent damage to the cardiovascular autonomic nervous system had occurred in these cases. Symptomatic recovery may in fact also occur in people with POTS unrelated to COVID-19 [40].

Importantly, this survey also showed that diagnostic assessments in specialized autonomic centers revealed syncope mimicries, such as psychogenic pseudosyncope, and clinical conditions other than autonomic disorders causing orthostatic intolerance following COVID-19. The finding underscores that specialized autonomic assessments are key for proper and personalized counselling.

Postural orthostatic tachycardia syndrome and VVS were also the most frequent newly diagnosed cardiovascular autonomic disorders after COVID-19 vaccination, but the overall cumulative frequency was significantly lower than after COVID-19 infection, and a positive causal association was only seldom reported by the survey responders. The observation indicates that, from an "autonomic" point of view, the risks associated with COVID-19 infections outweigh by far the risks of adverse events following COVID-19 vaccinations. This was also the case for other neurological conditions, such as encephalopathies and Guillain–Barré syndrome, for which epidemiological studies have shown significantly higher incidence rates following COVID-19 infections than following vaccinations [41, 42]. In the present survey, people with newly diagnosed cardiovascular autonomic disorders after COVID-19 vaccination had received tozinameran (Comirnaty®), ChAdOx1-S (Vaxzevria®) or elasomeran (Spikevax®). These were reportedly also the most frequently administered COVID-19 vaccines in Europe [43], so that no conclusions regarding risks of cardiovascular autonomic complications can be derived for any specific vaccine. Cardiovascular autonomic complaints such as syncope, POTS and non-otherwise-specified orthostatic intolerance were reported for all these vaccines in the European Vaccine Vigilance Repository [44, 45], more frequently in women aged 18–64 years and by non-healthcare professionals. This observation might indicate a reporting bias, with healthcare workers eventually under-recognizing possible vaccine-related autonomic adverse effects as such, and deserves further exploration in the future.

Postural orthostatic tachycardia syndrome, VVS and OH were also the most frequently reported worsened cardiovascular autonomic disorders after both COVID-19 infection and vaccination. Worsening of cardiovascular autonomic disorders following diverse infections or other vaccines is frequently observed in clinical practice and therefore unlikely to represent a COVID-19-specific phenomenon, yet underscoring the threats imposed by the pandemic on fragile people living with autonomic disorders.

As in other chronic neurological conditions [46–48], bidirectional effects of the pandemic on symptom severity in people with previously diagnosed cardiovascular autonomic disorders were observed. Whilst the lockdown of outpatient and neurorehabilitation services, isolation and overall increased anxiety levels might have contributed to symptom worsening in people with POTS, neurogenic OH or psychogenic pseudosyncope, some pandemic measures, like home-working, might have favored a symptomatic improvement in some people, who were possibly less exposed to stressors like overcrowded places or prolonged standing whilst commuting to work.

This study has several limitations. Due to its survey design, it is based on indirect observations of the studied phenomena, reflecting the perception of the survey responders. It also provides only an estimation of possible therapeutic approaches, without signals for higher efficacy of single non-pharmacological versus pharmacological approaches. Guidelines for treating cardiovascular autonomic disorders, however, recommend a stepwise approach with non-pharmacological and behavioral strategies first, due to their favorable risk–benefit profile [40, 49, 50]. The survey also focused on a midterm estimation of the recovery rate, with longer follow-up studies warranted for a more precise prognostic assessment of people with newly diagnosed post-COVID-19 cardiovascular autonomic disorders. Finally, the survey reports the cumulative percentage of responders judging a causal association between COVID-19 infections, vaccinations and new diagnosis or worsening of cardiovascular autonomic disorders likely, but opinions on the putative mechanisms of disease might have differed amongst the responders.

In conclusion, a profound negative effect of the pandemic on European autonomic practice was observed, with silver linings like healthcare digitalization. The need for shared protocols and online-available educational material has been recognized by the autonomic professional societies and will be further worked on in the next years. Whilst the relationship between COVID-19 vaccines and the occurrence of cardiovascular autonomic disturbances remains controversial, this survey adds evidence on the importance of recognizing cardiovascular autonomic disorders in the clinical spectrum of the post-COVID-19 condition. Future studies should better characterize post-COVID-19 cardiovascular autonomic disorders and evaluate the efficacy of available therapeutic strategies. The impact

of COVID-19 vaccines and virostatic therapies in preventing post-COVID-19 cardiovascular autonomic complications also needs to be clarified.

AUTHOR CONTRIBUTIONS

Study conception: AF, JC, PC, CFP, PG, RH, MJH, VI, JJ, APLT, IR, JS, JMS, AT, GKW, EM, TB, RT, WS, MH. Study design: AF, DRC, RH, APLT, JS, TB, RT, WS, MH. Study coordination: AF, MH. Data collection: AF, FL, GCB, GC, CFP, RG, PG, VI, ECAK, AK, APLT, AT, GKW, RT, WS, MH. Data analysis: AF, FL, MKS, MH. Writing of the first draft: AF. Writing—review and editing: FL, MKS, DRC, GCB, JC, GC, PC, CFP, RG, PG, RH, MJH, VI, JJ, ECAK, AK, APLT, IR, JS, JMS, AT, GKW, EM, TB, RT, WS, MH.

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The data that support the study findings 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 at the end of this article.

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