Ann Ist Super Sanità 2025 | Vol. 61, No. 2: 125-131
DOI: 10.4415/ANN_25_02_05

Psychological distress and its impact on the onset of lasting neurological symptoms during the pandemic: evidence from the Italian Twin Registry

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Abstract

Introduction. Neurocognitive disorders are typical of older people. Psychological distress increased during the pandemic, particularly in young people. Although often underestimated, the impact of psychological distress on neurological disorders should be considered. As part of a longitudinal study conducted by the Italian Twin Registry (ITR) on the health effects of COVID-19 pandemic, we explored the onset of lasting neurological symptoms in relation with pre-existing psychological symptoms and/or SARS-Cov-2 infection.

Methods. Online surveys on adult subjects of the ITR: in June 2020 we investigated symptoms of depression, anxiety and post-traumatic distress and, in December 2021, the onset of six persisting neurocognitive symptoms. SARS-CoV-2 infection was examined in both surveys. Associations of psychological symptoms and of viral infection with subsequent neurological manifestations were tested through logistic regression analysis.

Results. Among 1,784 participants (mean age 46.6), 42.8% reported neurological symptoms and 15.7% SARS-Cov-2 infection. Odds of neurological manifestations increased in participants with depressive or anxiety symptoms (ORs: 1.44 to 3.72), and in those with COVID-19 (ORs: 1.73 to 2.32). Anxiety symptoms explained more cases of cognitive symptoms (26.9% to 37.9%) than COVID-19 (9.1% to 15.5%). Smell/taste changes were strongly associated with viral infection (OR: 43.2).

Conclusions. During the pandemic, widespread psychological distress contributed more than COVID-19 to the appearance of some cognitive symptoms in a relatively young population. Our findings indicates that preservation of neurological well-being cannot ignore mental health interventions.

Key words

- depressive symptoms
- anxiety
- neurological symptoms
- cognitive symptoms
- COVID-19

INTRODUCTION

The prevalence of neurological disorders increased over time, and this trend is expected to continue as the population ages [1]. At a time when the predictions of a worldwide increase in neurodegenerative diseases were shifting the focus to the search for solutions, studying the risk factors and the conception of adequate prevention programs [2, 3], the COVID-19 pandemic exploded, this research path was interrupted, as energies and attention were diverted to COVID-19 related studies.

Although COVID-19 primarily affects the respiratory system, it is a multi-organ disease, often involving the nervous system and brain [4, 5]. Cognitive dysfunction, for example, identified as brain fog, has been widely reported as COVID-19 sequela during the pandemic period: memory difficulties or impaired executive functions, such as focusing and planning, were common phenomena even in non-hospitalized individuals [4, 6]. Other neurological manifestations were reported worldwide: headache was among the five most common symptoms

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of COVID-19 infection, as well as fatigue [7-9]. The discovery that COVID-19 was associated with neurological sequelae spurred researchers to study this issue. Yet, these symptoms were not new, especially the neurocognitive ones, since they had already been described in the literature as subjective cognitive decline, that need to be monitored, as it may be normal for age, reversible, indicative of a psychological disorder, or point to an organic disease or dementia. On the other hand, the pandemic has led to a sharp increase in mental health problems among the population [10], even among those without the COVID-19 disease [11, 12], although positive mental changes have also been described [13]. It is known that neurological and psychological issues (such as depression and anxiety) could share common risk factors and pathogenesis [14, 15]. Moreover, previous research has shown that depression increases the risk of developing dementia and cognitive difficulties [16]. This existing link between mental health and cognitive difficulties – as also demonstrated by long-COVID syndromes [6] – is a topic that needs to be further explored.

As we had already observed an increase of depressive symptoms soon after the first Italian lockdown (March-May 2020) [17], we hypothesized that having psychological distress could facilitate the appearance of neurological symptoms. Therefore, we were interested in understanding whether the neurological manifestations described as lasting sequelae of COVID-19: i) arose de novo during the pandemic in a non-clinical population, ii) were associated with a previous SARS-CoV-2 infection, iii) were associated with pre-existing symptoms of depression and/or anxiety and/or post-traumatic stress. We addressed these aims in the context of a longitudinal survey [18] that covered the period between February 2020 and February 2022, performed on a large sample of individuals enrolled in the Italian Twin Registry (ITR), a population-based registry of volunteer twins [19].

METHODS

Study design and participants

This study is part of a longitudinal investigation on the effects of COVID-19 pandemic on physical and mental health that was carried out by a survey in three waves (June 2020, i.e., at the end of the Italian lockdown, December 2020, and December 2021). All adult twins (age 18-92 years) enrolled in the ITR, residing in Italy at the time of the pandemic and contactable by email, were invited to participate. For the purposes of this study, only data collected in the first and third wave surveys were used, and only participants responding to both surveys were included in the analyses.

The longitudinal survey, in which this specific study is nested, was reviewed and approved by the Ethical Committee of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) (PRE BIO CE n. 0020797, June 6, 2020). Participants provided written informed consent to participate in this study.

Measurements

Recruited twins filled out survey questionnaires using the LimeSurvey platform. Participants were given approximately a 2-month window to reply to each iteration of the survey, such that the last wave was closed in February 2022. Socio-demographic characteristics of the respondents were investigated during the first wave of the study; each wave investigated COVID-19 positivity (defined by molecular or antigenic swab), the month and year of diagnosis and whether hospitalization or admission to Intensive Care Unit had been required. In the third wave, participants reported if, since the beginning of the pandemic (February 2020), they have ever suffered for at least one month from any of the six following symptoms: headache, memory problems, difficulty concentrating, excessive tiredness, confused/heavy/empty head (also referred to as brain fog), reduction or loss of taste and smell. From now on, these six symptoms will be collectively defined as "lasting (or enduring or persisting) neurological symptoms", while we will use the term "cognitive symptoms" to refer only to memory problems, difficulty concentrating and confused/heavy/empty head. To avoid misinterpretation of the question, and in line with other articles [20], the investigated symptoms were deliberately presented in a straightforward and easy-to-understand wording. If appropriate, the month and year of onset had to be reported. One-month duration for the lasting symptoms was chosen according to NICE guidelines [21].

Validated self-reported questionnaires on mental health were administered at each wave: 1) Patient Health Questionnaire (PHQ-9) [22], for symptoms of depression in the previous two weeks; 2) State-Trait Anxiety Inventory (STAI-6) [23], that measures the presence of current symptoms of anxiety; 3) Impact of Event Scale-Revised (IES-R) [24], to assess pandemic-related subjective distress.

Higher total scores of the three above-mentioned scales corresponded to a poorer mental health status. Participants that scored above the thresholds of 10 for PHQ-9, 40 for STAI-6, or 33 for IES-R, were categorized as having symptoms of depression, anxiety, or post-traumatic stress disorder, respectively.

Statistical analysis

Descriptive statistics were used to analyse the characteristics of the sample. Continuous variables were presented as mean±standard deviation (SD) and compared by paired or unpaired Student's t-test. Categorical variables were showed as percentage and significant differences were examined using Chi-squared test. All analyses used twins as individuals.

The psychological assessment of twins – as measured in June 2020 – was described by the mean score of each scale, alongside the prevalence of symptoms of depression, anxiety, and stress, and was used for subsequent analyses.

The association between each lasting neurological symptom with COVID-19 exposure or with the measures of psychological distress was tested with logistic regression. Gender, age, area of residence, marital status, and educational level were included in the model as covariates. All subjects who reported having had enduring neurological symptoms before psychological assessment and before the diagnosis of COVID-19 were excluded from the multivariate analysis. P-values

and standard errors were adjusted for the non-independence of observations because of twin relatedness.

Furthermore, the proportion of cases of each lasting neurological symptom that can be attributed to depression, anxiety and Coronavirus infection within the entire population, was also estimated. All analyses were performed using Stata software version 16 (Stata Corporation, College Station, TX, USA), and p-value <0.05 were considered statistically significant.

RESULTS

Overall, 1,784 twins took part in both surveys (June 2020 and December 2021). Mean age was 46.6 years (range 18-92) and 64.5% were female. Socio-demographic characteristics are shown in *Table 1*.

In the whole observation period (February 2020-February 2022) 42.8% of participants reported having had one or more persistent neurological symptoms, and most of them traced the onset to the early months of the pandemic (February-April 2020) (*Figure 1*).

In the following months, instead, the appearance of these symptoms was almost evenly distributed; an exception was given by persistent change of smell and/or taste that closely followed the distribution of COVID-19 cases (*Figure 1*). Excessive tiredness was the most frequent symptom (28.0%), followed by difficulty in concentrating, headache, confused/heavy/empty head, memory problems, and alteration of smell or taste (*Table 2*).

In the whole time frame, 270 participants (15.7%) had contracted COVID-19 with a chronological distribution of cases (*Figure 1*) that closely resembles that of the national pandemic. Most of the COVID-19 cases (96%) in our sample were treated at home. A SARS-CoV-2 infection preceded the appearance of excessive tiredness, difficulty in concentrating, headache, confused/heavy/empty head, and memory problems in a minority (11.1-16.4%) of the participants; instead, COVID-19 was very frequent (72.4%) before the onset of persistent dysgeusia/dysosmia (*Table 2*). In most cases, SARS-CoV-2 infection preceded of less than one month the onset of lasting neurological symptoms (from 76% for memory problems to 97.4% for reduction/loss of taste and/or smell). Participants reporting any of the above neurological symptoms, apart from memory problems, were significantly younger than those who did

Table 1
Socio-demographic characteristics of participants (N=1,784)

Characteristics	N	(%)
Sex		
Male/female	634/1,150	35.5/64.5
Age		
<35	413	23.15
35-49	588	32.96
50-64	561	31.45
65+	222	12.44
Marital status		
Never married	727	42.2
Married	796	46.2
Widowed/divorced/separated	200	11.6
Education		
Up to lower secondary education	93	5.2
Upper secondary education	721	40.6
Bachelor or equivalent	198	11.2
Master or equivalent	541	30.5
Doctorate or equivalent	222	12.5
Area of residence in Italy		
North	985	55.4
Centre	518	29.1
South and Islands	276	15.5

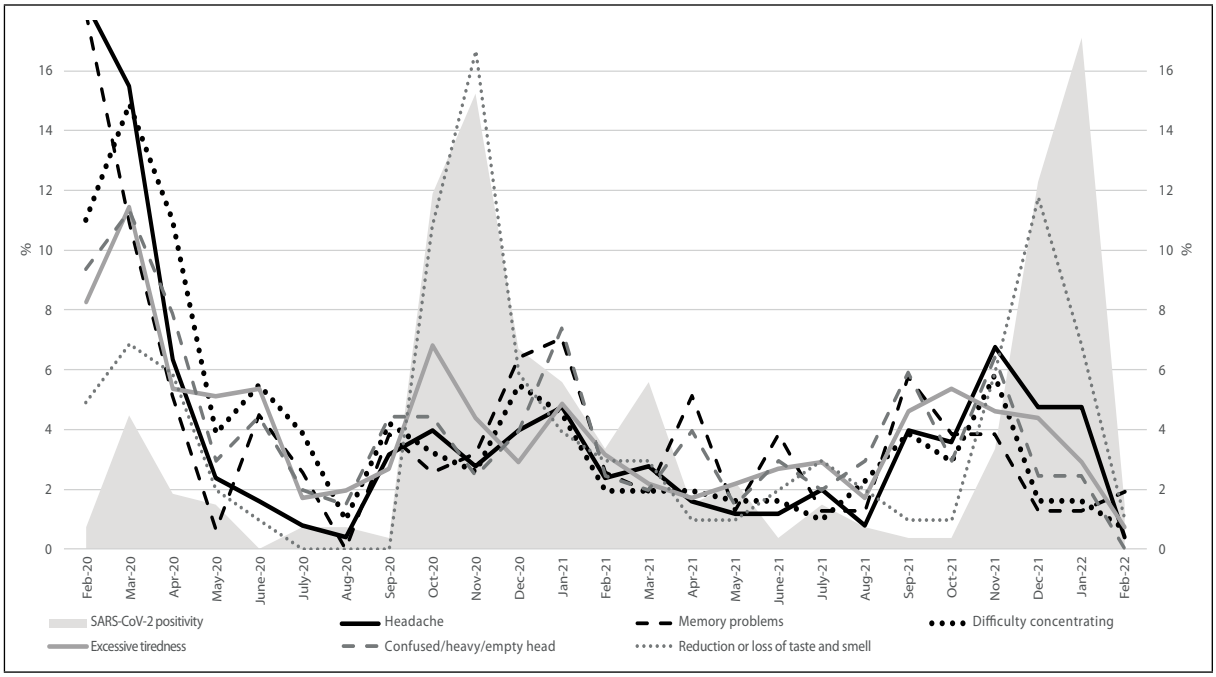

Figure 1
Monthly onset of SARS-CoV-2 positivity and of lasting neurological symptoms among participants: February 2020-February 2022.

Table 2
Individuals with or without lasting neurological symptoms (onset February 2020 - February 2022): overall number and broken down by previous SARS-CoV-2 infection

Neurological symptom	N	Yes N (%)	COVID-19 preceding onset of lasting symptom	
			Yes, N (%)	No, N (%)
Headache	1,661	282 (17.0)	39 (14.1)	238 (85.9)
Memory problems	1,662	188 (11.3)	25 (13.8)	156 (86.2)
Trouble concentrating	1,662	365 (22.0)	39 (11.1)	314 (88.9)
Excessive tiredness	1,669	468 (28.0)	66 (14.2)	398 (85.8)
Confused/heavy/empty head	1,654	242 (14.6)	39 (16.4)	199 (83.6)
Reduction/loss of taste and/or smell	1,649	112 (6.8)	76 (72.4)	29 (27.6)

not suffer from them (headache: mean age (interquartile range) 41.7 (20.4) *vs* 48.4 (23.6), p<0.001; trouble concentrating: 41.7 (21.8) *vs* 48.6 (23.7), p<0.001; excessive tiredness: 42.0 (20.8) *vs* 48.8 (23.8), p<0.001; confused/heavy/empty head: 42.7 (22.0) *vs* 47.7 (23.2), p<0.001; smell/taste problems: 42.6 (22.5) *vs* 47.3 (22.4), p<0.032). Women were more likely than men to have had each symptom (p<0.001, data not shown), with the exclusion of taste or olfaction modifications.

In the June 2020 survey, we assessed anxiety, depressive symptoms, and pandemic-related subjective distress. *Supplementary Table 1 available online as Supplementary Materials* shows the average scores and prevalence of clinically significant symptoms for each scale. Half of the participants scored above the threshold at the STAI-6 scale for anxiety symptoms; 12.5% and 9.2% of respondents obtained above cut-off scores for depression and stress, respectively.

To explore the psychological profile, beyond the Coronavirus infection, as risk factor for the appearance of the enduring neurological symptoms, we excluded from the subsequent analysis the participants who had declared the beginning of the neurological symptoms before the psychological assessment in June 2020, or that had contracted COVID-19 after the onset of the neurological symptoms. In the multivariate analysis (*Table 3*) the presence of depressive symptoms was significantly associated with headache, memory and concentration problems, confused/heavy/empty head and excessive tiredness, but did not affect the onset of lasting dysgeusia/dysosmia. Similarly, participants with anxiety symptoms were 1.44 to 2.26 times more likely to show subsequently cognitive problems, as well as tiredness. The above effects were net of the role of SARS-Cov-2 infection that, as expected, doubled the risk of suffering from all the neurological symptoms, and increased the

Table 3
Odds ratios of experiencing lasting neurological symptoms estimated by the logistic regression analysis

	Headache		Memory problems		Difficulty concentrating		Excessive tiredness		Confused/heavy/ empty head		Reduction or loss of taste and smell	
	OR	*95% CI*	OR	*95% CI*	OR	*95% CI*	OR	*95% CI*	OR	*95% CI*	OR	*95% CI*
Sex (male)												
Female	2.27***	*1.49-3.47*	2.10**	*1.28-3.44*	1.72**	*1.20-2.48*	1.74***	*1.28-2.37*	1.78**	*1.17-2.70*	1.14	*0.66-1.95*
Age (<35 years)												
35-49	1.00	*0.62-1.63*	1.20	*0.63-2.25*	0.99	*0.63-1.56*	0.87	*0.58-1.29*	1.04	*0.64-1.71*	1.10	*0.53-2.27*
50-64	0.73	*0.42-1.25*	1.61	*0.85-3.07*	1.23	*0.75-2.02*	0.85	*0.55-1.32*	0.95	*0.54-1.65*	0.93	*0.41-2.11*
65+	0.28*	*0.10-0.75*	1.15	*0.45-2.90*	0.44	*0.18-1.09*	0.65	*0.35-1.20*	0.67	*0.29-1.55*	0.24	*0.06-1.01*
Area of residence (North)												
Centre	1.54*	*1.01-2.33*	1.08	*0.68-1.72*	1.17	*0.79-1.72*	1.17	*0.85-1.60*	1.35	*0.87-2.08*	1.23	*0.69-2.20*
South and Islands	2.98***	*1.87-4.74*	1.45	*0.82-2.55*	1.70*	*1.09-2.64*	1.49*	*1.01-2.22*	2.27***	*1.42-3.61*	1.72	*0.86-3.44*
COVID-19 diagnosis	2.29***	*1.47-3.57*	2.22**	*1.36-3.61*	1.73*	*1.13-2.65*	2.02***	*1.39-2.93*	2.32***	*1.48-3.63*	43.8***	*23.4-82.1*
Anxiety symptoms	1.28	*0.87-1.88*	2.26***	*1.43-3.58*	1.95***	*1.36-2.81*	1.44*	*1.07-1.95*	1.77**	*1.17-2.65*	1.14	*0.66-1.96*
Depressive symptoms	2.33**	*1.40-3.86*	1.91*	*1.10-3.34*	2.47***	*1.60-3.83*	3.72***	*2.48-5.57*	2.47***	*1.54-3.96*	2.02	*0.97-4.20*
Post-traumatic stress disorder	1.04	*0.57-1.89*	1.19	*0.63-2.27*	1.29	*0.75-2.20*	0.88	*0.52-1.49*	1.11	*0.63-1.95*	0.75	*0.30-1.84*

Subjects who had enduring neurological symptoms before the psychological assessment and before the diagnosis of COVID-19 were excluded.
Anxiety symptoms, depressive symptoms and post-traumatic stress disorders are categorical variables (scores below or above threshold for each scale). Other covariates included in the model: marital status and educational level; OR: adjusted Odds Ratio; 95% CI: 95% confidence interval; *p<0.05, **p<0.01, ***p<0.001.

probability of having persistent alterations of taste and smell by more than forty times (*Table 3*).

The occurrence of perceived stress did not seem to increase the probability of developing lasting neurological symptoms. Female gender was confirmed to be a risk factor for the neurological symptoms investigated, with the exception of dysosmia/dysgeusia. It also emerged a significant effect of the area of residence on the majority of neurological symptoms; the age effect – observed in the univariate analysis – was reduced and remains significant only for enduring headache from which the oldest age group was protected. Marital status and educational level did not influence the onset of any neurological symptom.

We then estimated, for each persistent neurological symptom, the proportions of cases that could be attributed to the presence of anxiety or depression symptoms or to a preceding SARS-Cov-2 infection. Although the ORs estimates overlapped for the three risk factors (*Table 3*), anxiety symptoms were much more prevalent and therefore explained 1.7 to 3.4 times more cases of cognitive symptoms than those attributable to COVID-19 and depression symptoms (*Supplementary Table 2 available online as Supplementary Materials*).

DISCUSSION

Neurological sequelae of COVID-19 have been demonstrated by many studies, performed mainly in hospitalized people [25, 26]. However, neurological consequences have been described also in mild COVID-19 cases. This study began with the aim of researching and describing the onset of neurological symptoms, known as sequelae of COVID-19, in a sample of the Italian population during the COVID-19 pandemic. About 40% of our responders experienced enduring neurological symptoms: the majority reported having experienced two or more. Excessive tiredness, difficulty concentrating, and headache were the most common, followed by confused/heavy/empty head, memory issues, and reduction or loss of taste and smell. These findings are consistent with previous literature regarding COVID-19 patients, that were more likely to experience a constellation of symptoms, among which fatigue and cognitive difficulties were very common [4, 27].

The detection of lasting cognitive symptoms in a large proportion of a relatively young general population was an unexpected phenomenon, especially because our survey was conducted in a non-clinical setting. Of note, although COVID-19 infection represented a risk factor for showing neurological symptoms, possibly because of endotheliitis of brain vessels and encephalopathy [4], still a larger portion of our sample manifested cognitive difficulties without COVID-19 or any specific risk factor involved. This was especially evident during the lockdown period (March-May 2020), when the prevalence of coronavirus infections was limited to some areas of northern Italy, but neurological symptoms were reported throughout Italy. We therefore hypothesized that the drastic change in lifestyle, due to the particularly restrictive measures adopted in Italy, had a strong impact on the appearance of the neurological symptoms, as a consequence of the psychological distress. Indeed, Italy was among the first European countries to introduce a strict nationwide lockdown and kept it in place for longer than other countries, introducing regional restrictions and then gradually relaxing them [28]. This was also suggested by previous data on difficulties in falling and/or staying asleep during lockdown [18], and on the significant increase of the PHQ-2 mean score in post-lockdown (June 2020) compared to pre-lockdown period [17]. In fact, from the longitudinal analysis of the data, it clearly emerged that having symptoms of depression or anxiety in June 2020 increased – in the following months – the risk of developing the enduring neurological symptoms, excluding alterations of taste and/or smell. Although suggestive, the temporal association observed does not prove a cause-effect relationship: neurological symptoms may have a psychosomatic basis, potentially arising or worsened by psychological distress, also through unhealthy behaviors (i.e., alcohol, smoking, substance abuse, eating disorder); otherwise, psychological symptoms may have simply preceded neurological manifestations. In this line of thought is also the observation that the worsening of psychosocial functioning during pandemic was associated with pre-existing mental disorders [29].

It also emerged that the risk estimates of neurological symptoms, due to preceding anxiety or depression symptoms, are similar to those due to a previous SARS-CoV-2 infection. Risk factors with similar individual association (i.e., OR) but with different prevalence explain different proportions (i.e., attributable fractions) of the outcome: thus, in our population, anxiety symptoms (prevalence 50.1%) explained a more relevant proportion of cognitive symptoms compared to that due to COVID-19 (prevalence 14.3%).

We also show that women and those living in southern Italy were more likely to have neurological symptoms. Women tend to participate to surveys more than men, and generally report more symptoms than men [30], and some biological factors could be suggested as causes. For instance, there are sex differences in immunological responses and expression/activity of certain enzymes accountable for the development of autoimmune or inflammatory diseases and post-infectious sequelae (such as endotheliitis). This was particularly important when it came to long-COVID symptomatology [4, 31, 32]. Some symptoms such as headache and fatigue are known to be particularly frequent in women [1, 33, 34]. Also, sex hormones are known for influencing neurocognitive manifestations, especially after menopause [35, 36]. In addition, a pre-COVID-19 study reported that neurological manifestations were higher in women, both in incidence and prevalence [1]. Furthermore, it must be kept in mind that the lower participation of men may have prevented the detection of some effects related to male gender.

A higher prevalence of neurological symptoms in southern Italy could be due to environmental and cultural factors, like higher unemployment rates or poverty, health disparities, and lower quality and access to care, compared to other regions [37, 38].

This study has some limitations: the non-random sampling of the participants, affects the generalizability of our results. However, the analysis of respondents and non-respondents showed no substantial differences in age, gender, residence, or education. Moreover, we cannot rule out that some participants with lasting neurological symptoms had not been diagnosed with COVID-19, due to the limited availability of swabs in the first months of pandemic, and we could not investigate whether other causes (i.e., vascular, internal, neuromuscular, neurodegenerative diseases, etc.) were at the origin of the new-onset persistent neurological symptoms. In addition, since the study does not have a further follow-up, it is not known whether neurological symptoms have regressed, still persist, or have evolved.

CONCLUSIONS

The pandemic crisis has highlighted the widespread presence of the neurological symptoms investigated. Among the associated risk factors, previous anxious symptoms precede the highest percentage of cognitive symptoms in our population. While it is true that the impact of mental health issues due to the pandemic may have been different across countries and contexts, we believe that lasting neurological symptoms deserve to be monitored over time and appropriately classified as they may regress, but they may also reveal an underlying organic or psychiatric disorder, or progress to cognitive decline. Finally, during a pandemic emergency, health policies aimed at containing the spread of the infection should also consider mental well-being especially in younger age groups, and thus also preserve brain health.

Acknowledgements

We express our gratitude to participating twins of the Italian Twin Registry and to Cristina D'Ippolito, Maurizio Ferri, Sabrina Alviti, and Miriam Salemi for their technical assistance and management of data collection.

Statement of ethics

This study was reviewed and approved by the Ethical Committee of the Istituto Superiore di Sanità (PRE BIO CE n.0020797, June 6, 2020). Participants provided written informed consent to participate in this study.

Conflict of interest statement

The Authors have no conflicts of interest to declare.

Funding sources

This study was supported by intramural funds of the Istituto Superiore di Sanità.

Authors' contributions

LV: conceptualization, interpretation of the data, drafting and reviewing of the manuscript; LN: conceptualization, interpretation of the data, drafting and reviewing of the manuscript; GG: interpretation of the data and drafting of the manuscript; AG: interpretation of the data and critical reviewing; EM: conceptualization, acquisition, analysis and interpretation of the data, drafting and reviewing of the manuscript. All Authors approved this version of the manuscript and are accountable for the accuracy and integrity of the work.

Data availability

Data underlying this article are available from the corresponding author upon reasonable request and agreement on the terms of data use and publication of results.

Received on 26 June 2024.
Accepted on 3 March 2025.

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