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Research article

# Nocebo effects and health perception during infectious threats: A pandemic lesson

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ABSTRACT

Nocebo effects encompass psychophysiological, and neurobiological responses stemming from negative expectations and perceived harm. COVID-19 pandemic has created a context of infectious threat placing individuals at risk of a powerful nocebo effect. This cross-sectional study aims to investigate the specific impact of fear and expectations on self-perceived health among individuals who suspect COVID-19 infection but test negative, and to explore how personality traits and distrust in institutions mediate these impacts. To achieve this, 967 citizens with suspected COVID-19 symptoms who sought testing were surveyed online. Data from 523 individuals (283F), testing negative for COVID-19, were entered into a structural equation model. Individuals who strongly expect to have COVID-19 infection, coupled with a heightened fear of contagion, significantly contribute to a substantial portion (i.e., 60%) of the variance in perceived health status (i.e., general health condition and number of COVID-like symptoms). The model identifies an indirect effect of personality traits (i.e., pain catastrophizing and perceived vulnerability to disease), emphasizing their role as mediators, influencing susceptibility to nocebo effects. This study highlights how negative expectations related to infectious threats alter the perception of bodily experiences, reducing perceived health status and exacerbating symptoms. Understanding the interplay between these psychological factors and personality traits is essential for designing effective public health strategies during disease outbreaks. As such, this study also underscores the need for tailored interventions and educational programs for healthcare providers that focus on the psychological aspects of infectious threats. By addressing fear and negative expectations, these programs can help mitigate nocebo effects, improve patient outcomes, and promote overall well-being for individuals and communities during disease outbreaks.

## 1. Introduction

Over the past two decades, there has been consistent behavioural and neurobiological evidence demonstrating the influence of the general psychosocial context surrounding the patient on clinical outcomes. These effects can occur through various mechanisms,

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including placebo and nocebo effects [1–3]. Placebo effects, which primarily stem from positive expectations, can lead to improvements in health status and enhance the effectiveness of therapies [4]. Conversely, nocebo effects, the negative counterparts, arise from negative expectations, resulting in a worsening of the disease and reduced treatment effectiveness [5]. These effects are significantly influenced by prior experiences, emotions, and contextual factors that shape individuals' perceptions and reactions. Specifically, placebo and nocebo effects result from top-down modulation of the sensory transmission. Cognitive and affective processes (e.g., associative and social learning, expectations and beliefs, emotions) [6,7], individual personality traits (e.g., anxiety, optimism and pessimism, catastrophizing), social and contextual factors (e.g., doctor-patient relationship, information, trust in healthcare professionals, treatment and clinical milieu) [8], and genetic characteristics (e.g., genetic variants associated with dopaminergic, opioidergic, serotoninergic, and endocannabinoidergic pathway) [9] are at work in placebo and nocebo mechanisms affecting bodily perception.

While the placebo effect confers an evolutionary benefit and additionally offers an advantage that can be leveraged in clinical practice [10,11], the nocebo effect has detrimental physiological consequences that must be minimized to avoid worsening an individual's health [12–16]. Studies have shown that uncertainty, fear, anxiety, lack of trust, and misinformation play crucial roles in activating nocebo effects [17,18], and their impact is even more pronounced when these factors are widely disseminated across a population [19].

Due to the coronavirus disease 2019 (COVID-19) pandemic, we have faced a health emergency characterized by high clinical uncertainty and overwhelming demand for medical services that the healthcare system could not effectively handle. People worldwide dealt with the high probability and fear of contracting the virus, concerns about the adequacy of healthcare institutions, the absence of proven therapies for COVID-19, and the possibility of a grim prognosis [20–22]. Various sources of public communication, such as the web, TV, and newspapers, have made COVID-19 even more dominant and worrisome through an overload of information, misinformation, and rumours, as highlighted by scientific literature [23], the European Commission [24], and the World Health Organization [25]. The COVID-19 pandemic has been considered to be an ecological circumstance characterized by an infection threat that places individuals at risk of experiencing powerful nocebo effect [26–28]. While fear of infection and the ability to predict the likelihood of an unpleasant event are important adaptive behaviour in a healthy organism [29], and, in this case, they have been helpful in complying with social distancing before the availability of vaccines [30,31], they can also contribute to nocebo effects and thus the potential worsening of health conditions during the disease [32].

Among the numerous challenges posed by the COVID-19 outbreak, a critical question that needs further exploration is whether and to what extent the fear and expectations of being infected by SARS-CoV-2 may influence the individual's perception of health conditions. Existing research has shown that fear and expectations surrounding COVID-19 can significantly influence health perceptions and increase stress levels, particularly among individuals with pre-existing anxiety or vulnerable health conditions [27,28,33–35]. However, these studies have primarily concentrated on populations diagnosed with COVID-19 or those at high risk, without specifically evaluating individuals who fear having contracted the virus. In contrast, our study targets a unique cohort: individuals who have the suspicion of being affected by COVID-19, yet have tested negative for the virus.

Specifically, this study aimed to investigate the influence of fear, and expectation of being infected by SARS-CoV-2 on the health status (defined as the individuals' overall well-being and the number of COVID-like symptoms reported) of individuals who tested negative for COVID-19. Additionally, we explored the mediating role of distrust in institutions and personality traits, such as pain catastrophizing, optimism, and perceived vulnerability to disease. To disentangle the complex interplay of these variables and offer nuanced insights, we used a Structural Equation Model (SEM). This analytical framework allowed us to assess both the expected direct impact of the expectation and fear of viral infection on perceived health conditions, as well as the intricate pathways wherein personality factors act as mediators, by making certain individuals more susceptible to experiencing nocebo effects. We hypothesized that individual traits and trust in institutions mediate the relationship between fears, expectations, and perceived health, thus adding depth to our model. The study was conducted in a clinical setting during the second wave of the COVID-19 pandemic in Europe, before vaccines became available. Since both COVID-19 and flu-like illness share similar clinical manifestations, it is reasonable to expect that individuals who interpret their symptoms with a stronger fear of being infected with COVID-19 would have worse health outcomes compared to those who do not have such expectation.

## 2. Materials and methods

### *2.1. Participants*

The target population included all citizens with suspected COVID-19 symptoms coming consecutively to point-of-care testing for COVID-19 between February 19 and March 25, 2021 (corresponding to the second COVID-19 wave in Europe, before the vaccination campaign). During the data collection, the north of Italy, where the study was conducted, experienced various levels of COVID-19 restrictions under a color-coded system. The region was classified as a yellow zone initially, transitioned to an orange zone, and finally a red zone. Each level included specific measures, with red zones enforcing the strictest limitations such as school closures and travel restrictions, and yellow zones allowing more freedom with safety protocols in place. Across all zones, wearing masks was mandatory, remote work was recommended, and social gatherings were limited to mitigate virus transmission.

Exclusion criteria were age under 18 and over 75 years old, people who were not able to complete the survey independently, such as individuals with cognitive impairment accompanied by a caregiver.

### 2.2. Procedures

At the point-of-care COVID-19 testing site, nursing staff, by giving an information card, invited citizens to take part in an online self-report survey. Participants were asked to complete the survey by the end of the day by scanning a QR code or typing the Web address with their phone or other devices into an Internet browser.

### 2.3. Survey

The online survey, implemented by Qualtrics software (https://www.qualtrics.com/core-xm/survey-software/), lasted about 8 minutes and consisted of: 1) information sheet and consent; 2) HEALTH: general health status ("How do you feel at the moment, on a scale from 1 = worst possible health status to 10 = best possible health status?") and 10 symptoms (2021 WHO COVID-19 symptoms, see Table 1 in Results) checklist (yes/no) and intensity rating ("Please indicate on a scale from 1 = Not at all intense to 10 = Extremely intense how intense the symptom is"); contact with a COVID-19 positive case (yes/no); diagnosis of COVID-19 in the last months (yes/no); presence of chronic disease, by selecting from a list of chronic diseases identified by the WHO (20); 3) FEAR, and EXPECTATIONS: fear of COVID-19 ("On a scale from 1 = Not at all scared to 10 = Extremely scared, to what extent are you afraid of having contracted COVID-19?"); estimated likelihood of being affected by COVID-19 ("On a scale from 1 = Not at all likely to 10 = Extremely likely, to what extent do you expect to be affected by COVID-19?"); both of the latter scales were developed for the purposes of this study and another study from our laboratory [36] on the basis of established psychometric properties of a numerical-rating-scale format used in the placebo and nocebo literature; 4) stable PERSONALITY traits known in the literature to define high susceptibility to nocebo effects: Pain Catastrophizing Scale (PCS [37]), which measures catastrophic thoughts about pain; "catastrophizers" were described as individuals who tended to exaggerate the threat value or seriousness of pain sensations (a total PCS score, reflecting the sum of items, of 30 represents a clinically relevant level of catastrophizing); Life Orientation Test, Optimism - Pessimism Scale (LOT-R [38]), which measures individual dispositional levels of optimism (values reflect the sum of items: low optimism values range from 0 to 13, moderate optimism from 14 to 18, and high optimism from 19 to 24); subjective perception of vulnerability to disease ("On a scale from 1 = strongly disagree to 10 = strongly agree, how susceptible do you think you are to colds, flu and other infectious diseases?"); 5) TRUST in government, healthcare and scientific institutions ("On a scale from 1 = strongly disagree to 10 = strongly agree, how much do you trust in government/healthcare institutions/scientific institutions to deal with the current pandemic?"); 6) Demographic data. In this section, participants were asked to provide some information, such as their National Insurance Number. This was necessary to extract the swab reason and the swab results for COVID-19 infection from the health system database. The swab reason may have been exposure to known COVID-19 (it is important to note that, in this case, in Italy, the test was mandatory), a suspected COVID-19 case

**Table 1**
Descriptive (M ± SD; frequency) and comparison statistics of the study variables for positive and negative COVID-19 patients.

| | POSITIVE for COVID-19 (n = 93) | NEGATIVE for COVID-19 (n = 523) | Statistics (*t*-test – *z*- test) |
|---|---|---|---|
| **Health** | | | |
| Health Status | 6.23 ± 2.05 | 7.84 ± 1.88 | $t\,(614) = -7.52$, $p < .001$ |
| Nr. Of Symptoms | 3.29 ± 1.95 | 1.38 ± 1.65 | $t\,(116.6) = 8.90$, $p < .001$ |
| Fever | 44/93 (47.3%); 38.01 ± 0.57 | 77/523 (14.7%); 37.75 ± 0.59 | $z = 7.29$, $p < .001$; $t\,(119) = 2.27$, $p = .02$ |
| Dry Cough | 47/93 (50.5%) | 78/523 (14.9%) | $z = 7.87$, $p < .001$ |
| Tiredness | 62/93 (66.7%) | 154/523 (29.4%) | $z = 6.93$, $p < .001$ |
| Aches and pains | 56/93 (60.2%) | 119/523 (22.8%) | $z = 7.38$, $p < .001$ |
| Sore throat | 35/93 (37.6%) | 118/523 (22.6%) | $z = 3.10$, $p < .01$ |
| Diarrhea | 22/93 (23.7%) | 61/523 (11.7%) | $z = 3.12$, $p < .01$ |
| Conjunctivitis | 4/93 (4.3%) | 23/523 (4.4%) | $z = -0.04$, $p = .96$ |
| Headache | 48/93 (51.6%) | 150/523 (28.7%) | $z = 4.36$, $p < .001$ |
| Loss of taste or smell | 25/93 (26.9%) | 7/523 (1.3%) | $z = 10.23$, $p < .001$ |
| Rasch on Skin | 7/93 (7.5%) | 12/523 (2.3%) | $z = 2.69$, $p < .01$ |
| Swab reason (exposure to known COVID-19) | 65/93 (69.9%) | 347/523 (66.3%) | $z = 0.67$, $p = .50$ |
| **Fear And Expectations** | | | |
| Fear of COVID-19 | 5.31 ± 2.73 | 4.08 ± 2.66 | $t\,(614) = 4.09$, $p < .001$ |
| Likelihood of being affected by COVID-19 | 7.32 ± 2.22 | 3.38 ± 2.31 | $t\,(614) = 15.25$, $p < .001$ |
| **Personality Traits** | | | |
| Subjective perception of vulnerability to disease | 5.10 ± 1.97 | 5.01 ± 2.39 | $t\,(144.79) = .36$, $p = .72$ |
| Catastrophizing (PCS) | 15.60 ± 9.09 | 16.97 ± 9.54 | $t\,(614) = -1.29$, $p = .19$ |
| Optimisms (LOT-R) | 20.42 ± 1.62 | 21.12 ± 4.33 | $t\,(614) = -1.54$, $p = .12$ |
| **Trust in Institutions** | | | |
| Healthcare | 6.75 ± 2.31 | 7.11 ± 2.10 | $t\,(614) = -1.47$, $p = .14$ |
| Government | 4.59 ± 2.31 | 4.97 ± 2.46 | $t\,(614) = -1.38$, $p = .17$ |
| Science | 6.87 ± 2.39 | 7.58 ± 1.97 | $t\,(115.35) = -2.68$, $p = .008$ |
| Total | 6.07 ± 1.99 | 6.55 ± 1.80 | $t\,(614) = -2.32$, $p = .02$ |

*Note.* Data are expressed as mean ± standard deviation, otherwise indicated as frequency (number and %). PCS = Pain Catastrophizing Scale; LOT-R: Life Orientation Test–Revised.

(here, people went to take the test voluntarily, for example because they felt sick) and, finally, a healing definition, while the swab result may have been positive or negative. Healing definition and a positive result were considered as exclusion criteria.

The study was approved by the Institutional Review Board (IRB) of the University of Bologna, with the approval number 295376, dated 7/12/2020. All participants provided written informed consent to participate in the study and for their data to be published. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### 2.4. Data analyses

Initial data exploration encompassed descriptive statistics to derive concise numerical summaries of both health status and psychological variables. By means of *t*-test or *z*-test when appropriate, we explore potential health differences between the participants tested positive vs. negative for COVID-19 in health outcomes and psychological variables. The test of equal variance for continuous variables was performed before *t*-test. Modified *p*-values and degrees of freedom calculated were adapted when equal variance was not assumed.

Following the approach developed by Little and colleagues [39], patients tested negative for COVID-19 were entered into a structural equation modelling (SEM) to explore the hypothesis underlying the relations between COVID-19 fear, and expectation, stable characteristics of the individual (optimism, catastrophizing, and vulnerability to disease), trust in institutions, and the swab reasons, on individuals' health (i.e., health status and symptoms). The latent constructs, including catastrophizing, were estimated using parcelling techniques, where items were grouped based on their correlations to form more reliable indicators of the construct [39].

Estimation of the parameters was carried out by the method of a robust weighted least-squares estimator. The impact of the predictors (effect sizes) on the outcome variables was reported using both unstandardized (B) and standardized (β) estimates. The total effects were determined by summing the direct and indirect effects. Model evaluation was conducted using goodness-of-fit indices, including the comparative fit index and the root mean square error of approximation. Modification indices were analysed to identify potential model misspecifications.

The significance threshold was set at .05. All the analyses were conducted with SPSS (version 27) and Mplus software (version 6.11) [40].

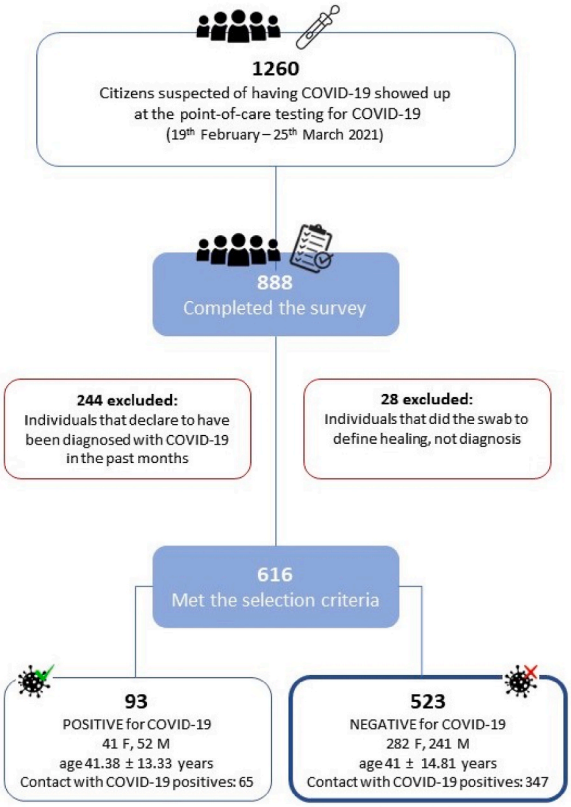


**Fig. 1.** Participants' recruitment.

## 3. Results

### 3.1. Descriptive statistics

Of the 1260 citizens invited to participate in the study, 888 completed the survey, yielding a 70% response rate. 244 were excluded from the main analyses because they had a COVID-19 diagnosis in the last few months (this information was gained asking participants: "Did you have a previous COVID-19 diagnosis confirmed by a molecular swab or serological test?"), while 28 were excluded because they did the swab to define the healing (not a diagnosis). Thus, 523 citizens (age: $M = 41$ years, $SD = 14.81$, range = 18–75; 241 men) were included in the analysis. Fig. 1 shows the participants' recruitment. Participants were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Table 1 shows the descriptive and comparison statistics (Mean ± Standard Deviation (SD); number (nr.) of cases/ %) of outcomes variables and predictors for positive and negative COVID-19 patients. The internal reliability of the PCS and LOT-R scales in our sample (as measured by α coefficients) were .92 (13 items) and .79 (6 items), respectively.

Finally, we examined the correlation between age and the dependent variables, as well as potential gender differences. We found that age was not significantly correlated with the number of symptoms ($r = -0.05$, $p = 0.24$) or with the mean general health status ($r = -0.06$, $p = 0.14$). Furthermore, there were no significant gender differences in either the number of symptoms (males: $M = 1.27$, $SD = 1.56$; females: $M = 1.47$, $SD = 1.71$; $t\,(521) = 1.37$, $p = .17$) or the mean general health status (males: $M = 7.90$, $SD = 1.86$; females: $M = 7.79$, $SD = 1.90$; $t\,(521) = -0.69$, $p = .49$). Based on these results, we decided not to include age and gender in our SEM model, as they did not significantly influence the primary outcomes of interest.

### 3.2. Structural equation model

The structural equation model, described in detail in Fig. 2, has satisfactory goodness-of-fit indexes (CFI = .95; TLI = .94; RMSEA = .05; 90% C.I. = .04 - .06; SRMR = .05) and explained 60% of the self-reported individuals' health variance. While greater fear, and expectation of being infected by the virus were strongly associated with a poorer health status ($\beta = .69$, $p < .001$), personality traits and trust in institutions were not significantly associated. However, personality traits, particularly pain catastrophizing ($\beta = .27$, $p < .001$) and perceived vulnerability to disease ($\beta = .28$, $p < .001$), were found to be correlated with these fears and expectations. Importantly, these personality traits are indirectly associated with individuals' health through fear and expectations regarding their health condition. Trust in institutions was not significantly related to health status ($\beta = .11$, $p = .056$).

Finally, the swab reason was found to be related to health status ($\beta = .42$, $p < .001$, as people who were suspected cases but had no contact with known COVID and, therefore, went to be tested voluntarily, reported a poorer health status.

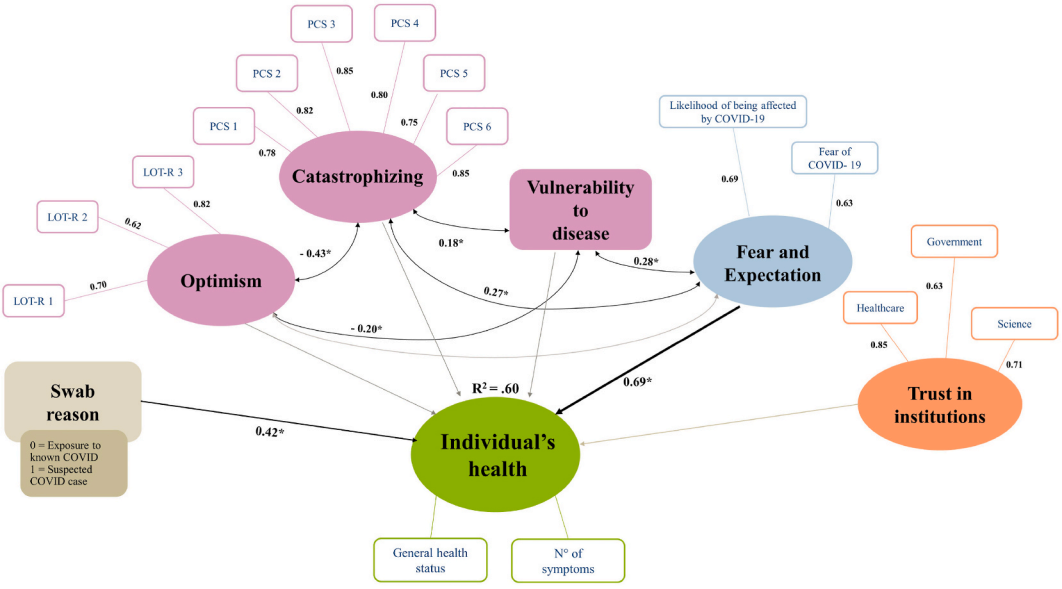


**Fig. 2.** Structural equation model.
Note. Higher scores in individual's health indicate lower health condition. Black lines represent significant associations, while grey lines represent non-significant associations. Solid lines represent direct effects. Single-headed arrows show paths, while double-headed arrows show correlations. Standardized path coefficients and partial correlation coefficients are superimposed upon the arrows and are indicative of the effect size of the relationship. Asterisks show the significance level (*p < .001), while the width of arrows is proportional to the strength of coefficients. Variable categories are indicated by colours (Green = Outcome; Light Brown = Health; Pink = Personality Traits; Light Blue = Fear and Expectation; Orange = Trust) and shapes (Oval = latent variable; Rectangle = manifest/measured variable).

## 4. Discussion

This study provides compelling evidence for the influence of nocebo effects on the health status of individuals who expect to be affected by a potentially serious disorder such as COVID-19. We found a robust association between psychological variables that contribute to the nocebo effect and the health outcomes of individuals with COVID-19-like symptoms. Notably, among citizens who came for COVID-19 test, a noteworthy 84% tested negative. Intriguingly, the fear and expectation of having COVID-19 accounted for an impressive 60% of the variance in perceived health status. Even in the absence of a COVID-19 infection, individuals who strongly expected to be infected or were fearful of being infected reported more COVID-like symptoms and worse overall health. Notably, participants who underwent testing due to legal obligations from known contact with a positive case reported better health status than those who sought testing voluntarily based on suspicions. While it is expected that individuals experiencing symptoms might voluntarily seek testing, the data underscore the significant psychological impact of fear and expectations on these behaviours, even without a known contact with a COVID-19 case. This insight enhances our understanding of how perceived health threats shape actions, reinforcing the complex relationship between psychological factors and health during the pandemic. It is worth highlighting that the extent of symptomatology reported within the present sample closely parallels the findings from clinical investigations centred on COVID-19 conducted before the advent of vaccination [41]. This parallel is further echoed by studies that have compared clinical attributes and disease outcomes between COVID-19 and seasonal influenza [42], underscoring the representativeness and generalizability of our sample within the broader context of the pandemic's impact.

This finding is in line with and expands the existing literature on the significance of expectations regarding COVID-19, utilizing a rigorous and robust methodological framework. Studies have demonstrated that post-sequelae of SARS-CoV-2 infection (PASC), also known as long COVID [43], are more strongly associated with the expectation of having been infected with the virus rather than lab-confirmed COVID-19 infection [34]. Additionally, Rozenkrantz and collaborators (2022) found that the belief regarding the severity of symptoms, if infected with COVID-19, predicted the experience of COVID-like symptoms a few weeks later. Furthermore, studies highlighted that anxiety about personal health plays a significant role in causing individuals to believe they are infected with COVID-19 [27,33,35]. However, it is important to consider that other diseases or conditions could have contributed to the symptoms reported by individuals, potentially leading to the assumption that these were indicative of COVID-19 infection. This possibility aligns with the broader context of the pandemic, where individuals may be more inclined to seek testing due to heightened awareness and concern.

Importantly, the present results are consistent with experimental laboratory and clinical evidence on nocebo effects, supporting the predictive value of negative expectations on health outcomes and indicating how nocebo effects can propagate during a pandemic [5,8,13,18,44–46]. Moreover, these findings contribute to shed light on the role of personality traits on nocebo effect. The scientific literature on this topic sometimes yields incongruent results, likely due to variations in methodological approaches, sample differences, and the inherent complexity of personality assessment itself (for a review, see Ref. [47]. However, the identified correlations among personality traits emphasize their potential relevance in shaping individuals' responses to health threats. Our results, derived from an ecological context and a large participant cohort, align with experimental studies showing that individuals with a tendency to catastrophize pain are more prone to experiencing nocebo effects [48]. Notably, our findings underscore how personality traits, such as catastrophizing tendencies and a heightened perception of vulnerability to disease, do not exert direct effects on health status. Instead, they exert their influence through fear and expectations. Individuals exhibiting elevated levels of catastrophizing and an increased sense of susceptibility to illness report a more compromised health status. This elucidates the intricate mechanism through which these personality traits are intertwined with psychological responses, ultimately shaping the perceived well-being of individuals. Contrastingly, this relationship does not manifest when considering factors such as optimism and trust in institutions.

These findings have significant clinical implications. Clinical care could greatly benefit from the assessment of fears and expectations, particularly in individuals who have a greater predisposition to develop them such as patients high in catastrophizing. This assessment can help identify patients at a higher risk of experiencing poorer health outcomes. Furthermore, interventions can be designed to mitigate fears or manage expectations in these individuals. It is crucial to invest in educational programs for clinical providers, highlighting the importance of recognizing and minimizing the nocebo effect. By training healthcare professionals in this regard, they can play a vital role in mitigating the negative impact of the nocebo effect on patients' health outcomes. In discussing the implications of our findings, it is essential to address the criticism regarding the overemphasis on psychosocial aspects of health conditions like long COVID and chronic fatigue syndrome [49]. Concerns have been raised that patients may feel their symptoms are dismissed as primarily psychological, leading to a perception of medical gaslighting [50]. This highlights the crucial role of healthcare workers in explaining how psychosocial factors and underlying brain mechanisms can modulate symptoms. By effectively communicating these concepts, healthcare providers can help patients understand the complex interplay between mind and body, thereby enhancing trust and improving clinical outcomes [51,52]. Finally, while our study does not provide direct evidence, it is theorized that nocebo effects may contribute to an increased number of individuals seeking COVID-19 testing, which could potentially lead to higher costs for the healthcare system. This theoretical perspective underscores the broader implications of psychological impacts during pandemics. These effects further highlight the need to address and manage psychological factors in healthcare settings, not only for improving patient well-being but also for optimizing resource allocation and healthcare efficiency during pandemic.

It is important to acknowledge and address some limitations of the study. Firstly, the absence of objective measures of health and reliance solely on subjective measures is a limitation, as objective measures would have provided a more comprehensive evaluation of health outcomes. However, subjective assessments remain valuable in understanding individuals' experiences and their perception of health status, especially when dealing with symptoms that are personally experienced and reported, such as those associated with viral infections. A second limitation pertains to the use of single-item measures for assessing expectations and fear. Since validated measures

for these constructs are lacking, the study used a numerical rating scale format consistent with established psychometric properties in the field of nocebo research. It's noteworthy that the brevity and simplicity of this interview likely played a significant role in achieving the high response rate observed (i.e., 70%). However, future studies may benefit from developing more comprehensive measures specifically tailored to assess expectations and fear in the context of pandemic and nocebo effects. Additionally, the potential impact of collider bias should be taken into account, as it could influence the observed relationships in our study. Finally, an inherent limitation of the study lies in its inability to disentangle the individual contributions of the emotional aspect, such as fear, and the cognitive component, in the form of expectations, to the observed health outcomes. Given their robust correlation, these elements were combined within the model. However, a promising avenue for future investigations would be to delve into the distinct impacts of these emotional and cognitive components, shedding light on their unique roles in shaping health outcomes.

Despite the acknowledged limitations, conducting a study on the nocebo effect within the real-world context of the COVID-19 pandemic has significantly contributed to our understanding of the complex relationship between fear, and expectations, and personality traits, and their influence on health outcomes. Our findings revealed that the nocebo effect stemming from the threat of infectious disease accounts for a substantial portion of the variance in individuals' perceived health (60%). Fear and expectations related to the threat of infection have played a crucial role in the survival and evolution of living organisms. As outlined by Schaller and colleagues (2010), recognition of external cues associated with infection risk triggers a cascade of emotional, cognitive, and behavioural responses aimed at minimizing that risk. Notably, fear emerges as a powerful emotional response, that prompts individuals to take precautionary measures, such as social avoidance [53]. These defensive behavioural responses are essential to protect oneself and others in a social community, and ultimately contribute to the overall well-being of the group [29]. Recognizing the significance of fear and expectations and their influence on behaviour and health is vital to shape effective public health strategies, especially during pandemics and disease outbreaks. The nocebo effect sheds light on the interconnectedness of fear and expectations related to infection with immune system function. The psychological and physiological defence actions are intricately woven, complementing and supporting each other. In-depth exploration of these mechanisms provides valuable insights into the comprehensive nature of their functional significance.

### *4.1. Conclusion*

In conclusion, our study highlights the significant impact of nocebo effects driven by the perceived threat of infectious diseases, which accounts for a substantial portion of variability in individuals' perceived health status (60%). By identifying the indirect influence of personality traits such as pain catastrophizing and perceived vulnerability to disease, we emphasize their role as mediators in susceptibility to nocebo effects. These findings underscore the evolutionary importance of fear and expectation in shaping behaviours during infectious threats. Understanding these dynamics is crucial for developing public health strategies that incorporate psychological factors, aiming to reduce the adverse effects of noceboeffects. Tailoring interventions and educational programs for healthcare providers can improve community resilience and enhance overall well-being in the face of ongoing and future infectious threats.

## CRediT authorship contribution statement

**Katia Mattarozzi:** Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Arianna Bagnis:** Writing – original draft, Visualization, Project administration, Investigation, Data curation. **Fabio Capucci:** Writing – review & editing, Investigation. **Valeria Cremonini:** Writing – review & editing, Resources. **Alessandra De Palma:** Writing – review & editing, Resources. **Roberta Mazzoni:** Writing – review & editing, Resources. **Paolo Pandolfi:** Writing – review & editing, Resources. **Paolo M. Russo:** Writing – review & editing, Formal analysis.

## Data availability statement

Data and materials are available upon request to the corresponding author.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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