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Long COVID: A biopsychosocial perspective

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1. INTRODUCTION

"Because of long COVID's diverse symptomatology, reliance on self-reported symptoms, and a lack of diagnostic tests and consensus definition, many patients struggle to obtain a definitive diagnosis. As a result, long COVID is often easily dismissed as a psychosomatic condition. Given what we now know about the effects of long COVID and its biological basis, it must be taken seriously."

Long COVID: 3 years in. Editorial, The Lancet. Volume 401, Issue 10379, 11–17 March 2023, Page 795.

In December 2019, the first case of a novel and potentially life-threatening coronavirus has been registered in the city of Wuhan, China. Soon after, the virus spread rapidly due to its high transmissibility, resulting in a huge global health crisis. As of June 2024, more than 775 Million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally[1].

After the World Health Organization (WHO) had declared the outbreak of coronavirus disease 2019 (COVID-19) a pandemic in March 2020, various policy measures have been taken to contain the virus. Although many of these measures were very effective in this respect, they were also frequently described as triggers for mental health consequences after COVID-19, but also in the general public[2,3]. An increase in psychopathological symptoms and psychological distress in the general population due to containment measures is now undisputed[4-6]. Social distancing requirements like lockdowns and quarantine, school and business closures, and the associated societal and economic challenges, uncertainty about the course of the pandemic, or concern for family members can be considered potential stressors for psychological impairment[7]. While both psychological distress and the proportion of adults with clinically relevant mental illness initially increased during the early course of the pandemic, meta-analyses synthesizing longitudinal cohort studies of both infected and uninfected individuals showed a decrease of adverse psychiatric outcomes to pre-pandemic levels over time[6,8]. Other findings confirm that the initial outbreak of the pandemic was associated with a significant but statistically small increase in mental health symptoms such as symptoms of anxiety and depression[9,10]. While such trajectories of recovery appear to be indicative of resilience in adult populations[11], the situation is different for persistent somatic symptoms after SARS-CoV-2 infection.

After acute somatic symptoms of COVID-19, like cough, fever, and myalgia[12], a substantial proportion of individuals report to suffer from ongoing health complaints after the infection has abated. To describe this phenomenon, the term "Long COVID" first emerged from Twitter by affected patients[13] and has since been used by the British National Institute for Health and Care Excellence (NICE) to describe a health problem that is now occurring worldwide, i.e., primarily somatic symptoms lasting at least four weeks after an infection with SARS-CoV-2, which cannot be explained by another diagnosis. In case symptoms persist for more than three months after the infection, the term "post-COVID-19 syndrome" is proposed[14]. Based on a Delphi consensus, the WHO similarly defines "post COVID-19 condition" as symptoms which occur three months after the onset of SARS-CoV-2 infection and last for at least two months. Again, symptoms must not be otherwise explainable, and they ought to impact everyday functioning[15]. In both the NICE and WHO definitions, it is essential that the relevant symptoms of LC did not exist prior to SARS-CoV-2 infection, so that prior medical findings are of central importance. Thus, in many cases, LC represents a diagnosis of exclusion. As it is the term originally coined by patients, this dissertation will use "Long COVID" (LC) to refer to burdensome persistent somatic symptoms (PSS) of at least four weeks following SARS-CoV-2 infection.

As with other PSS, it is now also known for LC that psychological features are involved in the development and maintenance of symptoms. However, the role of psychosomatic medicine in research and treatment of LC has been viewed critically both by some in the field as well as some of those affected[16,17]. Reflecting the fundamental understanding of psychosomatic medicine and contrasting the opening quotation, this dissertation argues for the recognition of a biopsychosocial perspective on LC, i.e., to not consider LC as "psychogenic" but as a condition that encompasses both biological and psychosocial mechanisms.

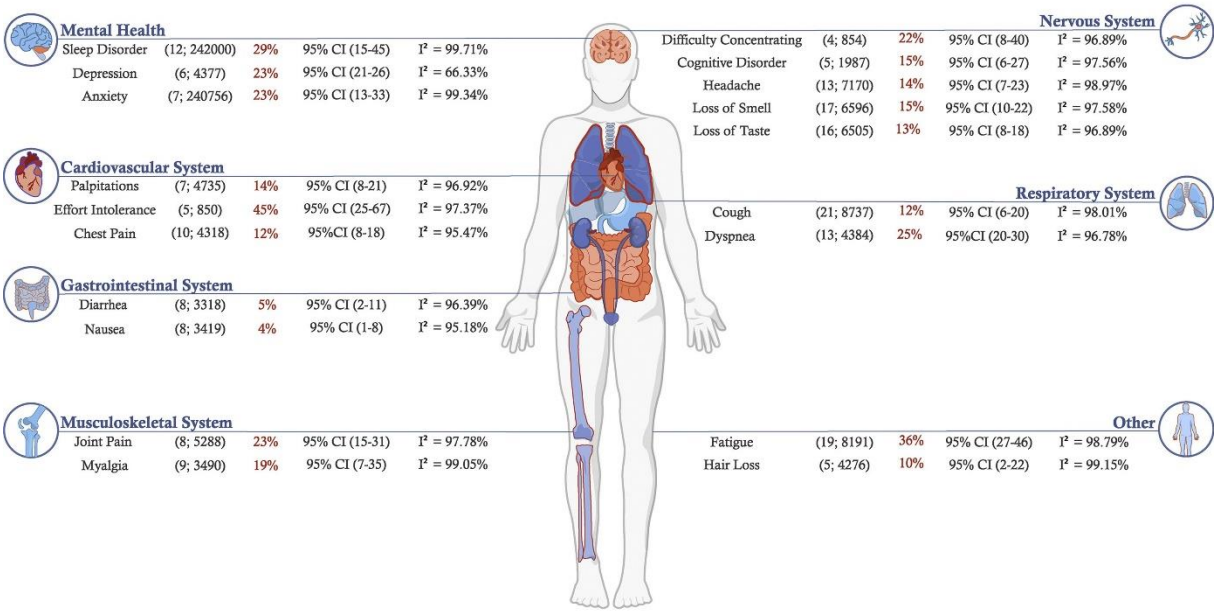
2. THEORETICAL BACKGROUND

2.1. Characteristics of Long COVID

Symptoms

So far, LC remains poorly understood, with no definitive etiology, prevention, or treatment. It is considered a heterogeneous multisystemic condition comprising a variety of symptoms[18,19] which can affect patients of any severity of preceding SARS-CoV-2 infection[20-22]. Recent meta-analytical as well as longitudinal data from controlled studies with follow-up periods of at least 6 months confirm the most common LC symptoms to include fatigue, dyspnea, anosmia and ageusia, and pain (especially headache, chest pain, myalgia, and joint pain; see Figure 1). LC can also include deficits of cognitive functions like attention, memory and concentration, often called "brain fog"[23-25]. As LC symptomatology can fluctuate greatly[26,27] with fatigue being the core symptom[28,29], a growing body of research is addressing the resemblance and overlap between LC and chronic fatigue syndrome (CFS), also called myalgic encephalomyelitis (ME[30-32]). ME/CFS is a debilitating condition of at least 6 months mainly characterized by persistent severe fatigue and exhaustion which often exacerbates after minimal physical or mental effort (so-called post-exertional malaise; PEM), does not improve by rest and has a detrimental effect on functioning as well as quality of life[33,34]. Besides persistent fatigue, PEM has been listed as a frequent sequelae of COVID-19 in a subset of patients[18,25]. Since the etiology of ME/CFS is not well understood and diagnostic biomarkers have not been identified yet[35], ME/CFS is sometimes considered a functional somatic disorder[36,37] with a multifactorial genesis[38]. ME/CFS is thought to be commonly triggered by infectious diseases[39-42] and is often associated with depression[22,43,44]. Among others, perpetuating factors can be low physical activity or dysfunctional beliefs[45].

Figure 1. Symptoms of Long COVID



Note. Illustration of meta-analysis results with estimated prevalence of symptoms following acute SARS-CoV-2 infection across follow-up intervals of 6 to < 9 months (from Alkodaymi et al. *Clin Microbiol Infect*, 2022[23]); in parentheses: number of studies, size of population used to calculate point estimate.

Prevalence

An exact estimation of the frequency of COVID-19 sequelae in adult patients is difficult and numbers provided so far are to be regarded as preliminary[46]. Definite prevalence rates are not available both due to the novelty of the condition as well as due to methodological limitations of previous publications that need to be acknowledged. Studies have reported widely varying estimates of symptom prevalence due to different study designs (e.g., cross-sectional vs. longitudinal data), follow-up periods, sample characteristics (e.g., initial disease severity, sample size), recruitment (e.g., self-selection vs. patient records), means of data collection (e.g., non-validated instruments, confirmed testing of COVID-19 vs. self-report only), inconsistent terminology (e.g., definitions of LC and symptoms), and lack of control groups[47]. Early studies on mostly hospitalized patients estimated prevalences of more than 70% around four months after the infection[48,49]. In a Chinese cohort of hospitalized patients, 68% stated at least one sequelae symptom at six months and 55% at two years[21]. As frequently documented LC symptoms are nonspecific and also common in the general population irrespective of SARS-CoV-2 infection[50], it is crucial for studies on LC to adjust for pre-existing symptoms and comorbidities and to include control groups with no history of SARS-CoV-2 to differentiate effects of the infection from those of pandemic-related stressors (e.g., fear of

becoming infected, worries about long-term effects of the infection[51]), thereby avoiding an overestimation of the frequency of LC[23,47,52]. For instance, in a Scottish general population cohort study with 23,973 participants, similar symptoms (e.g., tiredness, headache, joint pain) were highly prevalent in patients with previous laboratory-confirmed SARS-CoV-2 infection as in a PCR-negative matched control group. Interestingly, only the healthy control group reported an increase in symptom burden after 12 months[53].

Compared to initial reports, recent publications with large population-based data sets suggest a lower prevalence of LC of around 10-13%[20,54-56]. In a recent controlled prospective observational cohort study with 9,764 adults with and without prior SARS-CoV-2 infection, 10% of infected individuals developed LC at six months after the infection[25]. Similarly, Hartung et al.[20] reported persistent fatigue nine months after SARS-CoV-2 infection assignable to COVID-19 in 11% of patients in a population-based, controlled prospective multicenter study. In a multidisciplinary, prospective, population-based, observational cohort study of 76,422 participants in the Netherlands consisting of 4,231 patients with a previous SARS-CoV-2 infection who were matched to 8,462 COVID-19-negative controls, 12.7% of patients experienced symptoms attributable to LC after 8 months[54]. In the UK, the Office for National Statistics estimated the prevalence of LC three to four months after infection to be only 1.6% based on self-report data of survey participants with (5.0% reported symptoms) and without (3.4% reported symptoms) laboratory-confirmed COVID-19[57]. A retrospective cohort study that took into account the medical records of 388,980 US Veterans with a positive SARS-CoV-2 test found a documented ICD-10 code U09.9 for post COVID-19 condition in 4.79% of patients at six months and 5.28% at 12 months after infection[58]. However, the long-term evolution of LC is still unknown.

Consequences

With millions of people affected by COVID-19[1], even a small percentage of individuals who develop LC implies detrimental effects on society and public health, with many people in need of long-term follow-up, management, and support. For those affected, the symptoms associated with LC can lead to severe impairment in everyday life and reduced quality of life[53,59]. Although the magnitude is not yet fully predictable, studies to date suggest increased health care utilization of patients with LC and a large economic burden on health care systems[60,61] which may even exceed the temporary overuse of health care resources by acute cases of the disease.

2.2. Etiology of Long COVID

Pathophysiology

Despite knowledge on the clinical appearance and impact of LC, little is known about its pathophysiology and findings of clinical examinations often do not match reported disability[62,63]. Heterogeneous pathophysiological mechanisms across multiple organ systems have been postulated for LC. These include: virus-triggered inflammatory processes[64], autoimmunity[65-67], the persistence of viral reservoirs[68-70], microbiota dysbiosis[71], and microvascular blood clotting with endothelial dysfunction (for a review, see [19,40,72,73]). To date, no specific diagnostic markers (for example, in the blood) or characteristic imaging findings are known to fully explain LC[65], so that the diagnosis is assigned clinically and purely descriptive.

General risk factors

Since the outbreak of the COVID-19 pandemic, certain general risk factors for LC could repeatedly be identified in research studies. These factors are mainly sociodemographic and illness-related. In a retrospective matched cohort study based on a primary care database in the UK, female sex, obesity, and several medical comorbidities were found to be predictive of persistent symptoms 3 months after SARS-CoV-2 infection in a sample of 486,149 non-hospitalized adults with confirmed infection[74]. The virus strain also seems to play a role: Studies suggest lower rates of LC following infection with more recent variant waves, e.g., Omicron compared to Delta[75,76]. SARS-CoV-2 vaccination seems to be an effective preventive strategy against LC, but its impact on pre-existing LC symptoms has not been clarified yet[77]. Table 1 shows an overview of established general risk factors for LC including supporting references according to the current state of knowledge.

Table 1. Current evidence on general risk factors for Long COVID based on a scoping literature search

Risk factor		Reference
higher age		Frontera et al. *J Neurol Sci*, 2022[78] Kessler et al. *J Clin Med*, 2023[79] Shi et al. *Infection*, 2023[80] Sudre et al. *Nat Med*, 2021[81] Tene et al. *Int J Infect Dis*, 2023[61] Thompson et al. *Nat Commun*, 2022[82] Tsampasian et al. *JAMA Intern Med*, 2023[83]
female sex		Frontera et al. *J Neurol Sci*, 2022[78] Kessler et al. *J Clin Med*, 2023[79] Shi et al. *Infection*, 2023[80] Subramanian et al. *Nat Med*, 2022[74] Sudre et al. *Nat Med*, 2021[81] Tene et al. *Int J Infect Dis*, 2023[61] Thompson et al. *Nat Commun*, 2022[82] Tsampasian et al. *JAMA Intern Med*, 2023[83]
severe COVID-19 / high symptom load during the acute phase of COVID-19		Bahmer et al. *EClinicalMedicine*, 2022[62] Frontera et al. *J Neurol Sci*, 2022[78] Huang et al. *Lancet Respir Med*, 2022[21] Sudre et al. *Nat Med*, 2021[81] Tene et al. *Int J Infect Dis*, 2023[61] Tsampasian et al. *JAMA Intern Med*, 2023[83]
pre-existing medical conditions	high BMI/obesity	Subramanian et al. *Nat Med*, 2022[74] Sudre et al. *Nat Med*, 2021[81] Thompson et al. *Nat Commun*, 2022[82] Tsampasian et al. *JAMA Intern Med*, 2023[83]
	smoking	Subramanian et al. *Nat Med*, 2022[74] Tene et al. *Int J Infect Dis*, 2023[61] Tsampasian et al. *JAMA Intern Med*, 2023[83]
	asthma	Kessler et al. *J Clin Med*, 2023[79] Thompson et al. *Nat Commun*, 2022[82] Tsampasian et al. *JAMA Intern Med*, 2023[83]

	migraine	Kessler et al. *J Clin Med*, 2023[79] Subramanian et al. *Nat Med*, 2022[74]
	COPD	Subramanian et al. *Nat Med*, 2022[74] Tsampasian et al. *JAMA Intern Med*, 2023[83]
	type 2 diabetes	Tsampasian et al. *JAMA Intern Med*, 2023[83]
	chronic kidney disease	Tsampasian et al. *JAMA Intern Med*, 2023[83]
	multiple sclerosis	Subramanian et al. *Nat Med*, 2022[74]
	ischemic heart disease	Tsampasian et al. *JAMA Intern Med*, 2023[83]
	back pain	Kessler et al. *J Clin Med*, 2023[79]
SARS-CoV-2 infection with early virus strain		Antonelli et al. *Lancet*, 2022[75] Perlis et al. *JAMA Netw Open*, 2022[76]

Psychosocial risk factors

In addition to biomedical attempts at explaining LC, there is increasing evidence on the involvement of psychosocial factors in the maintenance of somatic symptoms after COVID-19 such as psychological distress previous to infection. By far most evidence is currently available for anxiety and depression[38]. Table 2 provides exemplary studies indicating anxiety and depression to be of relevance for LC. Protective factors for LC, on the other hand, seem to be pre-infection lifestyle factors including at least moderate physical activity, a healthy diet, adequate sleep, and trait forgiveness (an individual's tendency to forgive themselves, other people, and/or situations)[84,85]. Even for acute SARS-CoV-2 infection, psychological factors were found to influence the disease: In a meta-analysis of 23 studies, the presence of any mental disorder was associated with a heightened risk for COVID-19 mortality[86]. An analysis of primary care medical records comprising more than 11 million patients in the UK reported an association between pre-existing neuropsychiatric conditions and more severe acute respiratory infections including COVID-19[87]. This is in line with research demonstrating negative effects of high psychological distress on inflammation and immune system functioning[88-92] as well as regulation of the autonomic nervous system[93].

Table 2. Exemplary studies with evidence for the role of anxiety and depression in LC based on a scoping literature search

Psychological factor	Reference
(illness-related) anxiety	Bahmer et al. *EClinicalMedicine*, 2022[62] Bobak et a. *Psychosom Med*, 2024[94] Greißel et al. *Sci Rep,* 2024[95] Joli et al. *Front Psychiatry*, 2022[38] Milde et al. *Psychosom Med*, 2023[96] Nishimi et al. *Psychol Med*., 2024[97] Subramanian et al. *Nat Med*, 2022[74] Thompson et al. *Nat Commun*, 2022[82] Tsampasian et al. *JAMA Intern Med*, 2023[83] Wang et al. *JAMA Psychiatry*, 2022[17]
depression	Bobak et a. *Psychosom Med*, 2024[94] Durstenfeld et al. *Open Forum Infect Dis*, 2023[98] Greißel et al. *Sci Rep,* 2024[95] Joli et al. *Front Psychiatry*, 2022[38] Mazza et al. *J Psychiatr Res*, 2022[29] Milde et al. *Psychosom Med*, 2023[96] Nishimi et al. *Psychol Med*., 2024[97] Subramanian et al. *Nat Med*, 2022[74] Thompson et al. *Nat Commun*, 2022[82] Tsampasian et al. *JAMA Intern Med*, 2023[83] Wang et al. *JAMA Psychiatry*, 2022[17]

Biopsychosocial view on Long COVID

In line with the observation that most LC symptoms are unspecific and also common in the general population[50,99,100] as well as in other long-term medical conditions[101], studies investigating LC often find similar symptom reports of participants with and without a history of SARS-CoV-2 infection with only subtle differences. In a prospective cohort study of nonhospitalized individuals who underwent PCR testing, 382 individuals with and 85 without prior COVID-19 who were comparable in terms of sex and age were evaluated. When applying the WHO definition of post COVID-19 condition, prevalence at six months was 48.5% in the infected group, but was comparably high (47.1%) in the control group. In a

multivariable model, neither SARS-CoV-2 positivity nor biological markers were associated with the development of post COVID-19 condition. Instead, symptom severity at baseline as well as psychosocial factors like loneliness and low physical activity were significant predictors of LC[63]. In a recent German cohort study of statutory health insurance data, pre-existing mental health diagnoses were associated with an increased risk of somatic symptoms consistent with LC both in patients after COVID-19 and in controls without SARS-CoV-2 infection[95]. Also, negative expectations have repeatedly been shown to be linked to adverse health outcomes like worse somatic symptoms and increased disability[102,103]. Correspondingly, a large cross-sectional population-based French cohort study with 26,823 participants came to a similar conclusion: The self-reported belief of having had COVID-19 was more relevant for experiencing PSS than actual serological evidence[104]. In a German multicenter, population-based cohort study, functional and laboratory parameters of patients with LC fell within the normal range 6-12 months after infection, ergo patients' subjective complaints did not match somatic diagnostics[62]. Several other studies did not find relevant pathological abnormalities in LC either[30,105-107]. While in a follow-up study on neurocognitive complaints in relation to previous SARS-CoV-2 infection, individuals with a self-reported COVID-19 history stated worse selective attention, this could not be objectified by neuropsychological test performance[108]. In an experimental study comparing differences in perceived and objective fatigability between people with and without LC, participants with LC reported increased fatigue and perceived fatigability, but did not show objective fatigability in an isokinetic fatigue task[109].

Due to the absence of specific markers, findings like these suggest that PSS attributed to COVID-19 may in fact not be specific to SARS-CoV-2 and that, at least for some patients, there are more factors contributing to symptoms of LC than the triggering SARS-CoV-2 infection and the resulting biomedical mechanisms[110,111]. Accordingly, LC can occur regardless of severe, mild, or even asymptomatic acute illness as well as vaccination status[20-22,112-114]. Medical comorbidities being risk factors for LC make it extra difficult to differentiate COVID-19-specific sequelae from an exacerbation of the underlying disease. Meanwhile, there are more and more scientific advocates for a biopsychosocial understanding of LC[110,111,115,116]. In light of the current state of research with supporting evidence for a role of psychological constructs, the biopsychosocial model seems to be an appropriate explanatory model for the development of LC[51]. On the one hand, a biopsychosocial perspective on LC can facilitate appropriate preventive strategies, while it can also lead to optimized treatment approaches by involving the expertise of multiple professions into

multimodal therapy[51]. Gaining a better understanding of psychological factors in LC can also help differentiate between patient subgroups and thereby support the identification of meaningful biomarkers[110].

2.3. Treatment of Long COVID

LC is now recognized as a major public health problem and in several countries, management guidelines have been published[14,117]. Assuming that LC is a multisystemic condition, multimodal treatment seems to be a logical consequence[118]. However, research into effective treatment approaches for LC is still in its infancy and there is no causal therapy available. Since many psychological variables are modifiable, existing evidence-based therapeutic interventions might also be suitable for LC. For instance, several randomized controlled trials (RCTs) found that cognitive behavioral therapy (CBT) can significantly reduce severe post-infectious fatigue (e.g.[119-121]). Therefore, psychotherapeutic interventions aiming to reduce psychological burden should be investigated as potential treatments of LC[17,38]. A two-arm multicenter RCT conducted in the Netherlands provided first evidence for the positive effect of CBT in patients with severe fatigue three to twelve months after COVID-19. Patients who received CBT were significantly less fatigued directly post treatment as well as six months later compared to patients receiving care as usual[122]. A German feasibility trial found high acceptance of CBT and high satisfaction with the therapy sessions among patients with LC[123]. Currently, most trials that have been registered at the WHO Internal Clinical Trials Registry Platform (ICTRP) investigate rehabilitation measures including exercise[124], with preliminary evidence of positive effects on LC symptomatology[125,126]. Beyond that, many studies deal with alternative medicine like homeopathy, Ayurveda, or dietary supplements[124]. Empirical evidence of such interventions is presently limited due to mostly small and uncontrolled studies[38]. A recent Cochrane Review found no reliable scientific evidence for the contribution of clotting abnormalities to the pathophysiology of LC and therefore recommends against the application of plasmapheresis outside the context of research[127]. In light of insufficient diagnostic and treatment options, clinical trials should be prioritized in order to establish structured diagnostic and therapeutic algorithms.

2.4. Aims of this dissertation

Taken together, LC can be considered a massive worldwide health problem for which there is still a great need for research. Following a biopsychosocial perspective, research into the relevance of psychological factors appears to be a promising approach alongside the investigation of pathophysiological changes. To date it is unclear how psychological variables contribute to the development, maintenance, and deterioration of PSS after SARS-CoV-2 infection. Consequently, more knowledge on the role of psychological characteristics is needed in order to improve diagnostic guidelines as well as to install preventive strategies and treatment options for LC. Given the enormous societal and economic impact of LC and the massive burden on affected individuals, supporting patients with LC is a major challenge for health care systems worldwide. One approach to this is research into psychological interventions.

The aim of this dissertation is to investigate psychological factors in patients with LC and contribute to the question of how to support individuals with LC through psychological interventions. With the overall aim of deriving implications for comprehensive health care, the objectives of this dissertation were: (1) to investigate psychological risk factors for somatic symptoms during the COVID-19 pandemic, (2) to present a new treatment approach for LC based on the found psychological factors, and (3) to identify further psychological factors related to LC by synthesizing the available evidence in the literature.

3. METHODS

3.1. The project

This dissertation largely emerged from the research project SOMA.COV ("Long COVID: psychological risk factors and their modification"), which has been conducted at the University Medical Center Hamburg-Eppendorf since April 2023. The project is funded by the German Research Foundation (Deutsche Forschungsgemeinschaft; project number: 508447247) and aims to investigate whether overall somatic symptom severity in patients with LC can be improved via the modification of illness-related anxiety and dysfunctional symptom expectations. Additionally, the project aims to prospectively identify further risk factors involved in the persistence of LC and compare them to the medical conditions under investigation in the Research Unit SOMACROSS[128]. The Local Psychological Ethics Committee at the Center for Psychosocial Medicine of the University Medical Center Hamburg-Eppendorf approved the project on 14 February 2022 (approval number LPEK-0446). Principal investigators are the author of this dissertation, Dr. Petra Engelmann, who already holds a doctorate (Dr. phil.) in another subject area, as well as Prof. Dr. med. Dipl.-Psych. Bernd Löwe (Department of Psychosomatic Medicine and Psychotherapy) and Prof. Dr. Antonia Zapf (Institute Medical Biometry and Epidemiology). The first study of this dissertation can be considered preliminary work leading up to the project proposal. The second study of this dissertation is the SOMA.COV study protocol. The third study of this dissertation is not directly related to SOMA.COV, however still adds to the project objective of gaining knowledge on psychological factors with relevance to LC.

3.2. Overview of studies

This dissertation is based on three publications with the following objectives: (1) to investigate psychological risk factors for somatic symptoms during the COVID-19 pandemic (study I), (2) to present a new treatment approach for LC based on the found psychological factors (study II), and (3) to identify further psychological factors related to LC by synthesizing the available evidence in the literature (study III). Study I is a prospective observational cohort study with the main aim of assessing specific risk factors for somatic symptom deterioration during the COVID-19 pandemic in adults with and without prior SARS-CoV-2 infection. The results formed the basis for the SOMA.COV research project.

Study II is the study protocol of an observer-blinded, three-arm randomized controlled trial which makes up the core of SOMA.COV and aims to investigate the effects of an expectation management intervention for patients with LC compared to a non-specific supportive intervention and treatment as usual only as well to examine further psychosocial risk factors for LC. Study III is a systematic review and meta-analysis which was conducted in addition to SOMA.COV. Its primary aim was to summarize published evidence on psychological factors associated with LC, and, where possible, pool data using meta-analyses. A more detailed description of the studies' methods is listed in section 4 (summary of articles).

4. SUMMARY OF ARTICLES

4.1. Summary study I

Engelmann, P., Löwe, B., Brehm, T. T., Weigel, A., Ullrich, F., Addo, M. M., Schulze Zur Wiesch, J., Lohse, A. W., & Toussaint, A. (2022). Risk factors for worsening of somatic symptom burden in a prospective cohort during the COVID-19 pandemic. *Frontiers in psychology*, *13*, 1022203. https://doi.org/10.3389/fpsyg.2022.1022203

Background and aims

With more and more evidence on a substantial portion of COVID-19 patients not fully recovering, there is growing scientific interest in risk factors for the potential long-term effects of SARS-CoV-2. However, empirical knowledge on the differential impact of SARS-CoV-2 infection on the one hand and psychosocial distress in response to the pandemic on the other are scarce. Overarching biopsychosocial models as well as preliminary findings on LC propose a multifactorial interaction between pathophysiological mechanisms and psychosocial factors in the etiology of symptom persistence. Therefore, this study aimed at a) prospectively investigating the course of somatic and psychological symptoms as well as b) simultaneously assessing specific risk factors for somatic symptom deterioration during the COVID-19 pandemic in a cohort of German adults with and without prior SARS-CoV-2 infection. In order to further examine the role of SARS-CoV-2 infection for the self-report of symptoms, we c) aimed to compare individuals with SARS-CoV-2 positive and negative IgG antibody test results versus positive and negative self-reported SARS-CoV-2 infection in terms of psychological measures.

Methods

We conducted a longitudinal observational cohort study among German health care professionals working at the University Medical Center Hamburg-Eppendorf. Participants underwent SARS-CoV-2 IgG antibody testing and completed self-rating questionnaires at baseline and 21 months later between April 2020 and February 2022. Besides sociodemographic variables (age, gender, profession), we assessed somatic symptom burden (SSS-8), illness-related anxiety or psychological symptom burden (SSD-12), depression (PHQ-2), and general anxiety (GAD-2). Additionally, participants who had not been infected with SARS-CoV-2 yet were asked about their symptom expectations associated with COVID-

19 using a self-developed numeric rating scale ("How much do you expect to be burdened by symptoms in case of a COVID-19 infection?") with a rage from 0 to 10. At follow-up assessment only, all participants were asked if they had a history of COVID-19. Differences in psychological variables between the two time points were analyzed with paired samples t-tests. To predict somatic symptom change between baseline and follow-up as dependent variable, a multiple linear regression analysis controlling for age, gender, and somatic symptom burden at baseline was calculated. As pre-specified predictors, the regression model included confirmed as well as self-reported SARS-CoV-2 infection since baseline as well as psychological baseline measures (illness-related anxiety/psychological symptom burden, depression severity, general anxiety severity, and symptom expectations associated with COVID-19). Participants differing in terms of SARS-CoV-2 IgG antibody test result at follow-up and self-reported belief of SARS-CoV-2 infection since baseline were compared on the continuous study variables at follow-up by forming four groups ("serology and belief no," "serology and belief yes," "serology no and belief yes," "serology yes and belief no") and performing one-way ANOVA.

Results

Of N = 1,792 participants recruited at baseline, n = 751 (41.9%; mean age: M = 40.26 years, SD = 11.75; 77.9% females) completed both assessments. Between the two time points, somatic symptom burden (t (750) = -12.68, p < 0.001, d = -0.46) and illness-related anxiety/psychological symptom burden (t (750) = -10.34, p < 0.001, d = -0.38) as well as depression (t (750) = -6.03, p < 0.001, d = -0.22) and anxiety severity (t (750) = -5.50, p < 0.001, d = -0.20) increased significantly in the sample. Symptom expectations associated with COVID-19 significantly decreased over time (t (750) = 5.07, p < 0.001, d = 0.20). Significant predictors of somatic symptom deterioration between baseline and follow-up according to the regression model were illness-related anxiety or psychological symptom burden (b = 0.11, SE = 0.03, p < 0.001), symptom expectations associated with COVID-19 (b = 0.20, SE = 0.07, p = 0.004), and self-reported SARS-CoV-2 infection (b = 1.86, SE = 0.78, p = 0.017). These three variables explained 17% of the variance in somatic symptom change (adjusted R^2 = 0.167, Δ R^2 = 0.178, Δ F = 15.618, df = (9, 649), sig. Δ F = < 0.001). Participants' serologically confirmed SARS-CoV-2 infection since baseline as well as depression severity and general anxiety severity at baseline did not significantly contribute to the explained variance in somatic symptom deterioration at follow-up. Until follow-up, n = 58 participants had contracted SARS-CoV-2 confirmed by serology. Comparisons between the four groups

differing in terms of SARS-CoV-2 IgG antibody test result and self-reported belief of SARS-CoV-2 infection yielded no significant differences on any of the variables. Regarding somatic symptom burden at follow-up, there was a trend toward a significant between-group difference ($p = 0.060$) with the "serology no and belief yes" group stating the highest somatic symptom burden of all of the four groups.

Discussion

The results of this study indicate that worsening of somatic symptoms over the course of the COVID-19 pandemic may be more related to the pandemic's psychosocial effects than to SARS-CoV-2 infection itself. This way, this study supports the importance of disease-overarching biopsychosocial models for the development of bothersome somatic symptoms during the COVID-19 pandemic. As opposed to serologically confirmed SARS-CoV-2 infection, illness-related anxiety and dysfunctional symptom expectations seem to be relevant for somatic symptom deterioration. Consequently, these two modifiable risk factors may be promising therapeutic targets for a psychological treatment of LC. Our results of small increases in both psychological distress and somatic symptom burden over time are in line with other studies of representative German samples[129,130].

4.2. Summary study II

Engelmann, P., Büchel, C., Frommhold, J., Klose, H. F. E., Lohse, A. W., Maehder, K., Nestoriuc, Y., Scherer, M., Suling, A., Toussaint, A., Weigel, A., Zapf, A., & Löwe, B. (2023). Psychological risk factors for Long COVID and their modification: study protocol of a three-arm, randomised controlled trial (SOMA.COV). *BJPsych open*, *9*(6), e207. https://doi.org/10.1192/bjo.2023.591

Background and aims

In addition to pathophysiological mechanisms, psychological risk factors seem to be involved in the development of LC. Particularly, illness-related anxiety and dysfunctional symptom expectations appear to contribute to processes of symptom persistence after SARS-CoV-2 infection. As both factors can potentially be modified by targeted interventions, the aim of this study is to investigate defined mechanisms of action: namely, whether the clinical symptoms of LC can be improved via a targeted modification of illness-related anxiety and dysfunctional symptom expectations. Second, we aim to prospectively identify further psychosocial risk factors involved in the persistence of LC. Third, in an exploratory approach, we aim to compare risk factors leading to symptom persistence in LC with medical conditions under investigation in our Research Unit SOMACROSS.

Methods

Using an observer-blinded, three-arm randomized controlled design, 258 patients with LC will be evenly assigned to one of three groups: targeted expectation management developed together with affected patients and aiming to reduce illness-related anxiety and dysfunctional symptom expectations in addition to treatment as usual (intervention 1), non-specific supportive treatment in addition to treatment as usual (intervention 2), or treatment as usual only (control). Both active intervention groups will receive three individual online video consultation sessions at two-week intervals and a booster session after three months. Assessments will be carried out at baseline, after 6 weeks (intermediate), 3 months (post-interventional), and 6 months (follow-up). Primary outcome is baseline to post-interventional change in overall somatic symptom severity assessed with the Patient Health Questionnaire-15 (PHQ-15). Additional risk factors for symptom persistence will be identified in the untreated control group. Comparisons with risk factors for other conditions identified in our Research Unit SOMACROSS will be conducted to provide evidence of disease-specific and

generic mechanisms of actions for the persistence of somatic symptoms. Group differences in overall somatic symptom severity will be calculated using a linear mixed effects model with the change from baseline for all measured time-points, with treatment group, time and gender as fixed effect, patient as random effect, and baseline PHQ-15 as covariate. In order to analyze whether treatment effects on LC resulted through changes in illness-related anxiety or symptom expectations, mediation analyses will be conducted. Multivariate regression analyses will be used to identify further risk factors involved in the persistence of LC and the model will be compared with the results of the Research Unit SOMACROSS. The trial has been registered at ISRCTN (trial registration number: ISRCTN15068418).

Results

The results of this study will be published in peer-reviewed journals, presented at national and international conferences, and communicated in lay language to self-help groups and patient associations. Recruitment of participants started in October 2023 and is expected to be completed in November 2024. As of April 2024, more than half of the planned sample has been enrolled in the study.

Discussion

Given that a causal therapy and concrete treatment recommendations for LC are missing so far, effective and scientifically sound treatment options need to be developed for those affected. Should a targeted modification of illness-related anxiety and dysfunctional expectations of symptom severity lead to a change in LC symptoms, this would provide sound evidence for specific mechanisms of symptom persistence in LC and the effectiveness of a mechanism-based treatment approach. If the effectiveness of the intervention via the proposed modes of action can be proven, it can be used stand-alone or in the context of a broader therapeutic approach, and might thus have an important clinical and potentially socio-economic impact. Further, the results of this study will enable a better understanding of symptom persistence in LC by identifying additional disease-specific risk factors. The results of whether the mechanisms of symptom persistence are disease-specific or also effective across diseases will contribute to the further development of our etiological model for PSS across diseases.

4.3. Summary study III

Engelmann P., Reinke M., Stein C., Salzmann S., Löwe B., Toussaint A., Shedden-Mora M. (2024). Psychological factors associated with Long COVID: a systematic review and meta-analysis. *eClinicalMedicine*, *74*. https://doi:10.1016/j.eclinm.2024.102756

Background and aims

Five years after the outbreak of the COVID-19 pandemic, the etiology of LC still raises many questions. An increasing number of studies indicates that psychological factors contribute to the development and maintenance of LC in addition to pathophysiological changes. Previous reviews on risk factors for LC, for instance, confirm anxiety and depression to be of relevance. However, research in the field of persistent somatic symptoms in general suggests multiple psychological constructs might be involved in the persistence of somatic symptoms after SARS-CoV-2 infection. A systematic synthesis of available evidence on a broad spectrum of psychological variables associated with LC is lacking to date. Therefore, the aim of this study was to systematically review the literature providing original data on psychological factors associated with LC and LC-relevant outcomes and, where possible, pool data using meta-analyses.

Methods

We performed a systematic review and meta-analysis following the MOOSE guidelines. In January 2024, a database search was conducted in MEDLINE (via PubMed), PsycINFO (via OvidSP), and the Cochrane Database of Systematic Reviews (via Cochrane Library). The search string contained the terms most frequently used in the literature for LC as well as all psychological variables from the comprehensive list of the PSY-PSS framework (Hüsing et al., 2023), a framework for reviews on psychological risk factors in the field of persistent somatic symptoms and related disorders. Studies providing original, quantitative data in English from 2019 on were included. Research focused on evidence from cross-sectional and cohort designs which reported on psychological factors in the context of self-reported or clinically diagnosed LC according to the NICE guideline and condition-relevant outcomes. The primary screening against eligibility criteria of the identified studies based on titles and abstracts was conducted independently by three authors. Full manuscripts were independently reviewed twice by six initially blinded authors and data from each included study was extracted by four authors (1. study characteristics, 2. operationalization of diagnostic criteria

for LC, 3. psychological factors included in the study and operationalization of constructs, 4. condition-relevant outcomes and their assessment along with effect sizes). Study quality was assessed independently by two authors using the assessment tools of the National Institutes of Health. Results were summarized in a synthesis table and random-effects meta-analyses were conducted if valid data was available for at least five studies per psychological variable, type of data, and outcome variable. A review protocol has been published on PROSPERO (ID: CRD42023408320).

Results

Of 2,517 records identified by database search, we included 113 studies (n = 312,831 patients with LC) providing evidence on at least one psychological factor in LC, 63 in cross-sectional group comparisons, 53 in cross-sectional associations, and 18 longitudinal. Most reported findings related to anxiety and depression and, less frequently, to physical activity, posttraumatic stress disorder, stress, and history of mental illness. Meta-analyses of cross-sectional studies with control groups found depression (OR 2.35; 95% CI, 1.49-3.70) and anxiety (OR 2.53; 95% CI, 1.76-3.61) were significantly associated with LC and higher in affected patients than controls (depression: SMD 0.88; 95% CI, 0.66-1.11; anxiety: SMD 0.74; 95% CI, 0.50-0.99), while results for physical activity (p = 0.07) and stress (p = 0.10) were non-significant. Longitudinal studies showed most of the investigated psychological constructs to significantly predict LC.

Discussion

This is the first systematic review and meta-analysis of a comprehensive range of pre-defined psychological characteristics with potential relevance for the development and/or maintenance of LC. The present study confirms that, compared to controls, patients with LC are more impaired by anxiety and depression and both factors are predictive of LC. Due to the overrepresentation of anxiety and depression in studies on psychological variables in LC, reliable conclusions about the relative importance of other psychological factors for LC cannot be drawn. Future studies on LC should therefore include understudied psychological constructs, such as emotion regulation or dysfunctional symptom expectations, in order to gain more knowledge about their relevance. In addition, more longitudinal studies are needed to assess the predictive value of psychological factors in the etiology of LC. Great methodological heterogeneity between publications point to the importance of guidelines for LC research.

5. DISCUSSION

With the overall aim of deriving implications for comprehensive health care, the objectives of this dissertation were: (1) to investigate psychological risk factors for somatic symptoms during the COVID-19 pandemic, (2) to present a new treatment approach for LC based on the found psychological factors, and (3) to identify further psychological factors related to LC by synthesizing the available evidence in the literature. Using different empirical methods, three studies were conducted to assess the above-named objectives: a prospective observational cohort study (study I), the study protocol of an observer-blinded, three-arm randomized controlled trial (study II), and a systematic review and meta-analysis (study III).

5.1. Summary of the results

The aim of all three studies of this cumulative dissertation was to identify psychological factors related to the sequelae of SARS-CoV-2 infection. In the longitudinal observational cohort study (study I), illness-related anxiety or psychological symptom burden, symptom expectations associated with COVID-19, and the belief of having been infected with SARS-CoV-2 were found to be significant predictors of somatic symptom deterioration after almost two years of the COVID-19 pandemic. These results are in line with other studies that found that anxiety[74,83] and dysfunctional expectations[104,131] are risk factors for LC and led to the conclusion that illness-related anxiety and dysfunctional symptom expectations might be promising modifiable targets in a psychological intervention for patients with LC. Consequently, the observer-blinded, three-arm randomized controlled trial outlined in the study protocol (study II) investigates the effects of a psychological intervention, which has been developed together with affected patients and aims at the targeted modification of both modifiable factors on the clinical symptoms of LC. Beyond that, further psychosocial risk factors involved in the persistence of LC are examined and compared to other medical conditions under investigation in the Research Unit SOMACROSS (e.g., primary biliary cholangitis, irritable bowel syndrome, ulcerative colitis)[128].

The result of study I, i.e., that serologically confirmed SARS-CoV-2 infection was no significant predictor for somatic symptom worsening suggests the pandemic's psychosocial effects to be more relevant for somatic symptom burden than SARS-CoV-2 infection which corroborates similar research findings[63] pointing to a biopsychosocial model of LC[110,111]. In detail, experiencing somatic symptoms may have led to the belief in having had COVID-19,

especially in the context of a growing concern regarding LC. During the COVID-19 pandemic, constant confrontation with the topic and its hyperpresence in mass media might have been a triggering factor for initial or heightened illness-related anxiety[132,133], leading to fear of infection and a severe COVID-19 course, the attribution of bodily symptoms to SARS-CoV-2 infection and the belief in having had COVID-19[134,135]. In fact, several studies reported an increase in illness-related anxiety after the COVID-19 outbreak, especially during the early stages[134,136]. Illness-related anxiety, in turn, has been found a strong predictor of somatic symptoms in the general population, before as well as during the pandemic[137-139]. It is possible that such psychological factors and societal phenomena might account for the findings of study I.

In the systematic review and meta-analysis (study III), sound evidence was found that patients with LC are more impaired by anxiety and depression compared to controls. These results not only again confirm the importance of illness-related anxiety for symptom persistence in LC, but are also in line with earlier systematic reviews on general risk factors for LC[38,83] and suggest anxiety and depression should be considered in LC treatments. The scarce evidence base for other psychological variables and great methodological heterogeneity between publications, however, hinder reliable conclusions regarding their relevance and predictive value for LC. Overall, a narrative synthesis indicated the investigated psychological factors to be associated with and predictive of LC. Therefore, investigating a wider range of psychological constructs in future studies is a worthwhile endeavor in order to establish further evidence-based treatment targets and inform guidelines. To gain further insights into the predictive value of psychological factors in the etiology of LC, more prospective cohort studies using harmonized methods are needed.

Taken together, the findings of this dissertation support the relevance of psychological factors for the persistence of somatic symptoms after COVID-19. Thus, all three studies contribute to a better understanding of the etiology of LC. They also provide clear indications of possible therapeutic starting points in the multimodal treatment of LC. This is especially important given the fact that evidence-based treatment recommendations for LC are still lacking. At the same time, the results also reveal a clear research gap: In order to provide an all-encompassing understanding and scientifically sound care for patients with LC, more research is needed that considers a variety of potentially relevant psychological factors.

5.2. Strengths and limitations

This dissertation adds empirical evidence to a relatively new and still insufficiently explored research area. To the best of our knowledge, we conducted the first systematic review and meta-analysis on a comprehensive range of pre-defined psychological factors with potential relevance for LC (study III) as well as one of the first studies that simultaneously investigated risk factors for somatic symptom deterioration in a large sample including adults with prior SARS-CoV-2 infection as well as an unaffected control group (study I). Moreover, the RCT presented in study II is the first to assess the modifiability of specific psychological mechanisms of symptom persistence in LC. The prospective design of study I is particularly noteworthy as it added further evidence to previous cross-sectional results[104]. Actual SARS-CoV-2 infections were objectified by performing IgG antibody tests and, in contrast to most other published data so far, data took into account almost two years of the pandemic event. One limitation of study I, on the other hand, is the small proportion of subjects who had been infected with SARS-CoV-2 at the time, i.e. at the beginning of the COVID-19 pandemic in Germany, which limits the generalizability of the results and calls for confirmation in further studies with a higher number of formerly infected participants. In these studies, it would be important to extend the time frame examined for somatic symptoms and specifically inquire the diagnostic criteria of LC, which was not realized in study I.

While focusing on a small selection of psychological variables in study I, studies II and III cover a wide range of psychosocial features in order to maximize the informative value with regard to the importance of psychosocial characteristics in the context of LC. However, the specific intervention delivered in the ongoing RCT (study II) exclusively addresses illness-related anxiety and dysfunctional symptom expectations. Future intervention studies should pay special attention to further psychological factors (e.g., depression, emotion regulation or attributional styles). A challenge in the recruitment of patients for the RCT is potential reluctance of patients with LC to engage in a psychological intervention which might be rooted in the concern of potential stigmatization. Therefore, careful communication and the involvement of patients and patient associations is essential. The feasibility and success of conducting the described intervention cannot yet be assessed and remains to be seen.

A major strength of this dissertation is that the included studies sequentially complement each other. All studies were conceptualized with great methodological thoroughness in accordance with the respective study design and each study followed the

established recommendations for conducting and reporting (e.g., MOOSE guidelines for meta-analyses of observational studies). The forthcoming results of the SOMA.COV research project will above all allow conclusions about the efficacy and mechanisms of a targeted expectation management intervention for patients with LC, and might thus make a valuable contribution to LC treatment.

5.3. Implications and outlook

Diagnosis and treatment of Long COVID

According to the results of the three studies and considering their limitations, a number of implications can be drawn from this dissertation, which can help improve comprehensive care for patients with LC. We found psychological factors, especially illness-related anxiety, symptom expectations, and depression, to contribute to the sequelae of SARS-CoV-2 infection. Considering that these factors are potentially modifiable, early detecting and treating them is critical for symptom course and quality of life. Systematically screening for illness-related anxiety, symptom expectations, and depression in patients with a history of COVID-19 as part of routine care could facilitate the selection of suitable treatment paths in the future. Validated screening tools exist for all three constructs (illness-related anxiety: e.g., SSD-12[140]; symptom expectations: e.g., EURONET-SOMA numeric rating scales[141]; depression: e.g., PHQ-9[142]). In case positive psychological criteria are fulfilled, interdisciplinary cooperation between somatic and psychosomatic medicine with the aim of multimodal treatment should be initiated. Given the long symptom burden of many affected individuals, establishing effective treatments for LC is urgent.

One psychological intervention addressing a targeted modification of illness-related anxiety and dysfunctional symptom expectations that could be carried out in the context of a broader therapeutic approach is expectation management. A brief, low-threshold, mechanism-based expectation management intervention for PSS in patients with LC is currently under investigation in comparison to an unspecific supportive intervention as well as treatment as usual only within the SOMA.COV project. Another promising psychotherapeutic treatment option is CBT[122,123]. To drive the development of holistic care for affected patients, psychological interventions should be evaluated in future longitudinal studies with long follow-up periods to be able to derive long-term effects on LC symptomatology.

Patients with LC often face a feeling of social stigmatization, which might be rooted in mind-body dualism or “psychologizing” of symptoms, and therefore exclusion and blame of

those affected[143]. Findings from qualitative research confirm patients with LC to have suffered discrimination along their medical history before having been diagnosed with LC, especially by health care professionals[144]. This phenomenon is well known from functional somatic disorders which are equally characterized by a discrepancy between the subjective experience of symptoms and objective results of physical examinations[110,145]. Unfortunately, the rationale behind psychosomatic medicine is sometimes misunderstood, not only by patients, but also by other researchers and medical disciplines[16,17].

Education of professionals and patients on updated explanatory models like the biopsychosocial perspective is therefore urgently needed. One way of explaining the persistence of somatic symptoms after COVID-19 in a comprehensible manner is predictive processing: This framework describes how the perception of physical complaints emerges from the interaction of both internal predictions about symptoms automatically generated in the brain based on prior top-down information (like previous experiences, learning processes, and expectations), as well as actual bottom-up sensory input from the organs, both of which can be differently weighted depending on their precision[146,147]. In functional somatic disorders, for instance, it is assumed that information processing in the brain is dysregulated in a way that symptom perception is mainly shaped by model-based predictions (so-called priors) as sensory input is relatively weak and inprecise[148,149]. Consequently, PSS can be ascribed to functional alterations of the brain's perception of bodily states according to the concept of predictive processing. Predictive processing might be a suitable concept for explaining the link between psychosocial variables and LC[110].

During the COVID-19 pandemic, extensive mass media reports on the potential danger of the virus might have played a role in shaping dysfunctional symptom expectations[150]. As communication of unsupported illness descriptions, symptom uncertainty, and lack of support play a role for negative symptom expectations, it is of great importance for future public health crises to share evidence-based, reliable and helpful information in a de-escalating manner[103]. Another important measure is to involve affected patients in LC research and take their needs into account when developing treatments tailored to the individual in order to increase adherence and optimize care. Recognizing patients as experts of their condition and integrating them actively in the research process can increase subjective control of patients, enhance satisfaction with the medical encounter and improve treatment outcomes. Finally, politics has a central role to play in reducing unfavorable prejudices and reservations about psychosomatic medicine. Policy makers can ease the way for a holistic health care landscape and contribute to providing the necessary financial resources to support

both biomedical and psychosocial research projects in order to improve comprehensive knowledge on LC.

In terms of accurate data on the long-term prevalence of LC, more large-scale, prospective population-based studies or studies of stratified samples including non-hospitalized individuals are needed in order to avoid selection bias due to recruitment methods. These studies should include matched SARS-CoV-2 negative control groups and take into account previous medical findings to distinguish symptoms specific to LC from pre-existing or unrelated symptoms. This will allow for more homogenous results that facilitate evidence synthesis in systematic reviews and meta-analyses. To make scientifically sound conclusions about the concrete sequelae of SARS-CoV-2 compared to other infectious diseases, infection controls (e.g., seasonal influenza) should be used. Another reason hampering the comparison of study outcomes are inconsistent LC definitions. Eventually, gaining more knowledge on the condition should contribute to the refinement of current diagnostic criteria for LC[151]. High quality study design is equally important for future research on the underlying mechanisms of LC as well as clinical trials on potential treatments for LC.

Long COVID symptom clusters

In order to make sense of the heterogeneity of the condition, an emerging body of research currently deals with clustering different phenotypes of LC. Thereby, profiling is either based on symptoms themselves[55,152-154] or on their severity[64,155]. In a longitudinal cohort study[64], cluster analysis of 1,636 recovered COVID-19 patients resulted in four clusters in terms of physical and mental health five months after discharge: very severe (19.5%), severe (30.1%), moderate with cognitive impairment (10.9%), and mild (39.4%).

Within a Dutch longitudinal population-based cohort study, Latent Profile Analysis of 642 patients with LC yielded four symptom-related subtypes three to five months after SARS-CoV-2 infection: muscle pain (55.6%), fatigue (14.3%), cardiorespiratory (5.6%), and ageusia/anosmia (24.5%)[154]. These results partly match other findings of symptom clusters. In a prospective multicenter cohort study conducted with 1,796 patients from five different countries, machine learning algorithms similarly identified four clinical phenotypes 12 months from COVID-19 diagnosis: chronic fatigue-like syndrome (42%), respiratory syndrome (23%), chronic pain syndrome (22%), and neurosensorial syndrome (11%[156]).

Canas et al.[152] identified three symptom profiles in a prospective cohort study of 1,513 patients with LC from the UK around three months after the infection: a cardiorespiratory

cluster, a central neurological cluster, and a multi-organ systemic inflammatory cluster. Pooling the data of 1.2 million individuals with a history of symptomatic COVID-19 from 22 countries led to an estimated 6.2% experiencing LC three months after symptom onset. Of those, 51.0% belonged to a fatigue symptom cluster, 60.4% to a cluster of respiratory problems, and 35.4% to a cluster of cognitive problems[55]. A multicenter prospective cohort study by Kenny et al.[153] involving 233 patients with LC beyond 4 weeks revealed one cluster dominated by pain and another cluster of predominantly cardiovascular symptoms. Reasons for differences between studies might include different study designs and sample sizes[154].

Therefore, in future research, symptom profiles of LC should be further characterized using large data sets and long follow-up periods to identify risk factors, implications, and trajectories of these clusters over time. Potentially, phenotyping could also provide relevant insights into different pathophysiological mechanisms in LC[152]. Finally, clinical interventional trials of interventions could then be tailored to patients belonging to a specific phenotype, possibly maximizing treatment effects compared to "one size fits all"-solutions.

Long COVID and Somatic Symptom Disorder

In light of the psychosocial risk factors for LC found to date, increasing research interest is emerging in studying Somatic Symptom Disorder (SSD) in LC. SSD is a diagnosis newly introduced into the DSM-5 to describe affective, cognitive, and behavioral features associated with burdensome somatic symptoms of any etiology, and which replaces the old classification of somatoform disorders[157]. It is characterized by bothersome PSS which are accompanied by ongoing negative feelings about health or symptoms, dysfunctional thoughts regarding the seriousness of symptoms, and maladaptive health behaviors like an extraordinary amount of time and energy spent on symptoms or health concerns[158]. SSD is often associated with lower quality of life, increased functional impairment, and higher utilization of health care services[138,159]. Earlier studies from before the COVID-19 pandemic already found viral infections to be associated with a diagnosis of SSD[160]. In a recent longitudinal retrospective study of 220 patients with a history of laboratory-confirmed COVID-19, 10.4% were at risk of SSD at 8 to 10 months after the infection[161]. A single-center observational study investigating 50 patients with unexplained neurological symptoms after mild COVID-19 found a much higher rate of 64% to be at risk of SSD[30]. These preliminary findings need confirmation in studies using a structured clinical interview for a valid diagnosis of SSD in LC. Comprising psycho-behavioral criteria similar to SSD in DSM-5, Bodily Distress Disorder (BDD) has been newly introduced to ICD-11 to diagnose persistent and bothersome

somatic symptoms. While knowledge of the prevalence of BDD in patients with LC might have important implications for clinical care and also for diagnosis in the German health care system, research on the association between the two conditions is missing to date.

Post-acute infection syndromes

While LC is currently receiving a great deal of attention in research, media, as well as politics due to the massive long-lasting impact of the pandemic and the large number of people affected by LC, the phenomenon of PSS following the acute phase of an infection is not new. Earlier studies provided evidence that an acute infection is a common trigger for developing PSS[162]. Following a wide array of infectious diseases, such as mononucleosis caused by Epstein-Barr virus as well as Q fever or giardiasis, several prospective cohort studies reported moderate to severe disability and PSS, primarily fatigue[41,163,164].

Symptoms commonly seen after viral illnesses are consistent with those linked to LC[40,41,165,166]. Two examples of coronaviruses with long-term clinical outcomes similar ot SARS-CoV-2 are its predecessor severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV). Research findings on (coronavirus) infections indicate prevalence rates of persistent post-infectious fatigue similar to early numbers for LC[166-168]. In a prospective observational study of 117 formerly hospitalized patients with a history of SARS-CoV-1, more than half of the patients experienced persistent fatigue at one year follow-up. Shortness of breath and sleeping difficulties were reported with a similar frequency[169]. In a case-control study, Moldofsky & Patcai[166] found long-term fatigue to be the most common symptom more than one year after acute SARS-CoV-1 infection. In a study by Lam et al.[167], around 40% of SARS-CoV-1 survivors continued to experience fatigue more than three years after the infection.

In a systematic review and meta-analysis of 28 studies investigating hospitalized SARS-CoV-1 and MERS-CoV patients around six months after discharge, Ahmed et al.[165] found high prevalence rates of abnormal lung function and reduced exercise capacity, somatic symptoms (fatigue, pain), psychological impairment (anxiety, depression, posttraumatic stress disorder), and lower quality of life. A systematic review and meta-analysis of 72 studies on the aftermath of coronavirus infections SARS-CoV-1 and MERS-CoV corroborated a high incidence of persistent fatigue, psychological distress (anxiety, depression, posttraumatic stress disorder), and memory impairment in the post-illness stage[170]. Another more recent review on the long-term impact of SARS-CoV-1, influenza, and MERS-CoV confirmed quality of life and mental health of patients with PAIS to be highly impaired. After respiratory

sequelae, they were the second and third most common reported complications[171]. Equivalent to LC, long-lasting symptoms after SARS-CoV-1 and MERS-CoV were often independent of initial disease severity[167,172].

Other publications confirm an increase in psychological burden following prior virus outbreaks and infectious diseases similar to LC[173], like SARS-CoV-1[174], MERS-CoV[175], Ebola virus disease[176], H1N1 influenza[177], or tuberculosis[178]. For instance, illness-related anxiety was widespread in times of virus outbreaks like Ebola[179], H1N1[180], or avian influenza[181]. Psychological variables and mental illnesses have also been shown to be predictive of the development or perpetuation of PSS after an acute infection[182]. A systematic review and meta-analysis of 45 studies including a total of 21,421 individuals after infectious enteritis found anxiety, depression, somatization, and neuroticism were significant risk factors for a diagnosis of irritable bowel syndrome months after, next to female gender, antibiotic exposure, and infection severity[183]. Hulme et al.[45] summarized biopsychosocial risk factors for persistent fatigue after different infections including infectious mononucleosis, Q-fever, dengue fever, and viral meningitis in a systematic review of 17 studies. In line with current findings on LC, biological factors like pre-existing somatic symptoms and medical conditions, cognitive-behavioral mechanisms like maladaptive attributional styles and decreased activity as well as psychological distress were most consistently related to ongoing post-infectious fatigue up to six months.

Long-term somatic symptoms after an acute infection are described by the term post-acute infection syndromes (PAIS). As with LC, their underlying etiology remains poorly understood[40]. The overlap between clinical features of LC and other post-viral syndromes suggests shared etiological pathways and possibly similar disease trajectories, and calls for more research on the multifaceted sequelae of viral infections. In perspective, the combined knowledge on clinical features could facilitate tailored treatments across PAIS. Previous studies on PAIS demonstrated positive effects of CBT on symptom severity[121]. However, the field of PAIS is relatively under-researched in terms of psychological treatments. Therefore, more well-designed non-pharmacological interventional studies are needed in order to inform PAIS care and develop successful strategies to prevent adverse health outcomes. A systematic review and meta-analysis including 56 RCTs and 4,060 participants concluded that psychosocial interventions in comparison to control conditions were associated with a 14.7% improvement in beneficial immune system function and an 18.0% decrease in harmful immune system function for at least six months following treatment[184]. The best outcomes were found for CBT and multiple or combined interventions. These findings propose

psychosocial interventions to be reliably associated with enhanced immune system function and suggest psychotherapy might be an effective treatment for PAIS.

5.4. Conclusion

In a substantial proportion of adult patients, burdensome somatic symptoms persist after an acute SARS-CoV-2 infection. The dimensions of potential long-term effects of COVID-19, widely referred to as LC, put great pressure on those affected, policymakers, and health care systems worldwide. In the face of this looming health crisis of its own, numerous scientific studies have been dedicated to advancing the understanding of LC. This has sparked debates about the relevance of pathophysiological mechanisms as well as psychological factors for the development and maintenance of LC.

The findings of this dissertation underline the contribution of psychological variables to the etiology of LC. Psychological factors, especially illness-related anxiety, dysfunctional symptom expectations, and depression, are associated with LC in addition to pathophysiological changes. These features are modifiable, therefore representing a reasonable target for treatments of LC. The brief, mechanism-based expectation management intervention is one low-threshold intervention with great potential of supporting patients with LC in reducing bothering PSS.

In contrast to a dualistic understanding of illness in terms of soma versus psyche, this dissertation argues in favor of a biopsychosocial model of LC, which does justice to the true meaning of psychosomatic medicine. A biopsychosocial view of LC can help to further specify phenotypes so that individuals who meet positive psychological criteria can be screened as early as possible and provided with tailored treatments, and meaningful biomarkers can be identified more easily. Applied to other viral infections, the biopsychosocial model can serve to prevent the development of PAIS in general.

For the future, well-designed trials investigating the prevalence of LC over time, biopsychosocial mechanisms of symptom development and persistence, as well as effective therapies for LC in the sense of comprehensive, multimodal health care are of highest clinical priority in order to effectively support individuals suffering from this multisystemic condition. To facilitate the implementation of scientific evidence, education of professionals, patients, and the general population on the biopsychosocial model is needed. Further research needs, such as the active involvement of affected patients in the research process, the continued

studying of SSD in LC, and addressing the under-researched field of PAIS, are met as part of the SOMA.COV project.

6. LIST OF ABBREVIATIONS

BMI	Body mass index
CBT	Cognitive behavioral therapy
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
GAD-2	Generalized Anxiety Disorder Scale-2
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICD-11	International Statistical Classification of Diseases and Related Health Problems, 11th revision
ICTRP	International Clinical Trials Registry Platform
IgG	Immunoglobulin G
ISRCTN	International Standard Randomised Controlled Trial Number
LC	Long COVID
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
MERS-CoV	Middle East respiratory syndrome
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NICE	National Institute for Health and Care Excellence
PAIS	Post-acute infection syndromes
PCR	Polymerase chain reaction
PEM	Post-exertional malaise
PHQ-15	Patient Health Questionnaire-15
PHQ-2	Patient Health Questionnaire-2
PHQ-9	Patient Health Questionnaire-9
PSS	Persistent somatic symptoms
RCT	Randomized controlled trial
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SSD	Somatic Symptom Disorder
SSD-12	Somatic Symptom Disorder - B Criteria Scale
SSS-8	Somatic Symptom Scale-8

UK	United Kingdom
US	United States
WHO	World Health Organization

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8. APPPENDIX

8.1. Study I

Risk factors for worsening of somatic symptom burden in a prospective cohort during the COVID-19 pandemic

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Risk factors for worsening of somatic symptom burden in a prospective cohort during the COVID-19 pandemic

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Introduction: Little is known about risk factors for both Long COVID and somatic symptoms that develop in individuals without a history of COVID-19 in response to the pandemic. There is reason to assume an interplay between pathophysiological mechanisms and psychosocial factors in the etiology of symptom persistence.

Objective: Therefore, this study investigates specific risk factors for somatic symptom deterioration in a cohort of German adults with and without prior SARS-CoV-2 infection.

Methods: German healthcare professionals underwent SARS-CoV-2 IgG antibody testing and completed self-rating questionnaires at baseline and 21 months later between April 2020 and February 2022. Differences in variables between the time points were analyzed and a regression analysis was performed to predict somatic symptom deterioration at follow-up.

Results: Seven hundred fifty-one adults completed both assessments. Until follow-up, n = 58 had contracted SARS-CoV-2 confirmed by serology. Between baseline and follow-up, signs of mental and physical strain increased significantly in the sample. Symptom expectations associated with COVID-19 and a self-reported history of COVID-19, but not serologically confirmed SARS-CoV-2 infection, significantly predicted somatic symptom deterioration at follow-up. A further predictor was baseline psychological symptom burden.

Conclusions: This study supports a disease-overarching biopsychosocial model for the development of burdensome somatic symptoms during the COVID-19 pandemic and supports research findings that symptom burden may be more related to the psychosocial effects of the pandemic than to infection itself. Future studies on Long COVID should include SARS-CoV-2 negative control groups and consider symptom burden prior to infection in order to avoid an overestimation of prevalence rates.

KEYWORDS

COVID-19, Long COVID, risk factors, somatic symptom burden, persistent somatic symptoms

Introduction

In the third year of the global pandemic, there is growing interest in the potential long-term effects of SARS-CoV-2 infection, as studies indicate that a substantial portion of COVID-19 patients does not fully recover. Instead, ongoing symptoms like fatigue, shortness of breath, olfactory and gustatory dysfunction, and pain are reported (Lopez-Leon et al., 2021; Sudre et al., 2021; Seeßle et al., 2022). However, little is known about psychological predictors of symptom burden such as illness-related anxiety or expectations in patients with Long COVID. According to the British National Institute for Health and Care Excellence (NICE) COVID-19 guideline and the German Association of the Scientific Medical Societies (AWMF) S1-guideline "Post-COVID/Long-COVID," this term is currently used to describe symptoms that last more than 4 weeks after the onset of a SARS-CoV-2 infection, can affect almost every system in the body, may change over time, and are not explained by an alternative diagnosis (Carfì et al., 2020; Koczulla et al., 2021; Shah et al., 2021). Also, risk factors for the development of burdensome somatic symptoms during the COVID-19 pandemic in individuals who have not been infected with SARS-CoV-2 have hardly been investigated so far.

In terms of general risk factors for the development of persistent somatic symptoms (PSS), current disease-overarching models (Henningsen et al., 2018; Löwe et al., 2022) propose a multifactorial etiology involving psychological, sociodemographic, and biomedical factors. Regarding biomedical factors, prior medical conditions (Claassen-van Dessel et al., 2018) and immunological factors (Rief and Martin, 2014) have been found to increase the predisposition for PSS, while stressors like acute infections are considered triggering factors for short-term symptoms (Löwe et al., 2016). Maintaining/aggravating factors include psychosocial factors such as anxiety (Creed, 2019; Niles and O'Donovan, 2019; Behm et al., 2021), depression (Fischer et al., 2013; Limburg et al., 2017), and psychosocial distress (Kirmayer et al., 2004; Deary et al., 2007). Beyond that, recent studies have shown that the expectation of experiencing persistent symptoms is crucial for symptom processing and persistence (Van den Bergh et al., 2017; Kube et al., 2020). Consequently, expectations, i.e., future-directed cognitions regarding the anticipated course of symptoms, have been found to predict symptom course in a wide range of medical and psychological conditions, e.g., chronic fatigue syndrome (Moss-Morris et al., 2011).

Due to the omnipresence of the topic in personal experiences and the media, the uncertainty about the course of the pandemic, the limitations regarding social exchange and activities, and other government restrictions (Holmes et al., 2020; Hossain et al., 2020), pandemic-related distress might function as a risk factor for PSS in non-infected populations. In fact, anxiety and fear of infection have been reported to occur more frequently in response to the COVID-19 outbreak compared to before the pandemic (Gallagher et al., 2020; Jungmann and Witthöft, 2020; Sauer et al., 2020; Kibbey et al., 2021). Thus, COVID-19 related health worries might promote the tendency to ascribe certain bodily perceptions and symptoms to SARS-CoV-2 infection (Taylor et al., 2020; Tull et al., 2020). The few studies investigating PSS in populations that did not contract SARS-CoV-2 confirmed somatization to be common during the pandemic (Ran et al., 2020; Hao et al., 2021) and found an association between COVID-19 related anxiety and somatic symptoms (Liu et al., 2020). Yet, studies that explicitly examine risk factors for the development of somatic symptoms in individuals without former SARS-CoV-2 infection during the pandemic are largely missing. In the analysis of an earlier follow-up time point of the here presented sample, we found baseline somatic symptom burden, higher levels of anxiety, occupation as a nurse, younger age, higher psychological symptom burden, lower efficiency, and higher fatigability at baseline to predict somatic symptom burden in a cohort without prior SARS-CoV-2 infection after 8 weeks (Engelmann et al., 2022).

Female sex, higher age, high body mass index, specific autoantibodies, viremia, and pre-existing medical conditions including type 2 diabetes can be considered biomedical risk factors for Long COVID (Townsend et al., 2020; Lopez-Leon et al., 2021; Sudre et al., 2021; Chudzik et al., 2022; Su et al., 2022). In a recent systematic review and meta-analysis of 20 studies investigating prognostic factors for Long COVID in adults previously hospitalized for COVID-19, female sex and acute disease severity emerged as independent prognostic factors for PSS at least 12 weeks after the infection (Maglietta et al., 2022).

However, current evidence shows that also a high number of COVID-19 patients without these clinical risk factors report somatic symptoms months after the initial infection (Moreno-Pérez et al., 2021). Besides, several studies indicated a small or no association between Long COVID and initial disease severity (Townsend et al., 2020; Sudre et al., 2021; Sykes et al., 2021; Bungenberg et al., 2022; Huang et al., 2022). Many symptoms of Long COVID are unspecific (Davis et al., 2021) and have been shown to frequently occur in the general population prior to the COVID-19 pandemic (Hinz et al., 2017). Therefore, it seems reasonable to assume a biopsychosocial perspective in explaining Long COVID, i.e., an interplay between pathophysiological mechanisms and psychological factors (Yelin et al., 2020; Sykes et al., 2021). Still, only a few studies have been conducted on psychological risk factors for Long COVID. Preliminary evidence points to the importance of anxiety, depression, and symptom expectations (Townsend et al., 2020; Taquet et al., 2021; Matta et al., 2022). In a recently published large cross-sectional cohort study, the self-reported belief of having been infected with SARS-CoV-2 in the past was significantly associated with somatic symptoms persisting for at least 8 weeks, while a positive serology test result was only positively associated with anosmia, with no significant interaction between

self-reported COVID-19 and serology test results (Matta et al., 2022).

The congruence between risk factors described in overarching disease models for the etiology of PSS (Henningsen et al., 2018; Löwe et al., 2022) and those that have been found for Long COVID so far suggests the investigation of potential psychological predictors of worsening of somatic symptoms over the course of the pandemic in both individuals formerly infected with SARS-CoV-2 and individuals without a history of COVID-19 to be highly relevant. Most studies on Long COVID lack adequate control groups (Amin-Chowdhury and Ladhani, 2021) and simultaneous investigations of predictors of PSS in affected and unaffected populations have not yet been conducted. With regard to observation periods, the data basis of most publications refers to the first wave of infection in 2020 (Mauz et al., 2021). Follow-up assessments are necessary to identify symptom development and predictors of symptom change ever since, as the pandemic's effect may have evolved over time.

Therefore, the objective of the present study was to prospectively examine the course of somatic and psychological symptoms as well as specific risk factors for somatic symptom deterioration after 21 months in individuals with and without SARS-CoV-2 infection since baseline. To further assess the role of SARS-CoV-2 infection for self-reported somatic and psychological symptoms, we aimed to compare participants with SARS-CoV-2 positive and negative IgG antibody test results and positive and negative self-reported SARS-CoV-2 infection. In general, it was our aim to improve the understanding of some of the various hypothesized biopsychosocial risk factors involved in the development of burdensome somatic symptoms in response to the COVID-19 pandemic.

Materials and methods

Participants and study design

The current study used the first and last of four waves of data collection within a prospective cohort study to determine the seroprevalence of SARS-CoV-2 and to track bothersome somatic symptoms during the pandemic (Brehm et al., 2021; Engelmann et al., 2022). Data were collected among healthcare professionals working at the University Medical Center Hamburg, Germany. Inclusion criteria were at least 18 years of age, employment at the University Medical Center Hamburg, informed consent, and the ability to understand German. Recruitment was carried out by informing employees both in person and *via* an internal email newsletter. Prior to recruitment, written informed consent was obtained from all study participants. To promote participant retention, participation reminders were sent out before each data collection point via an email reminder as well as regularly via email newsletter. The study protocol was approved by the ethics board of the Hamburg Medical Chamber, Germany (PV 7298).

At baseline (T0), age, gender, and profession were assessed in a sociodemographic questionnaire. At baseline as well as at follow-up 21 months later (T1), participants completed a battery of self-rating questionnaires. Baseline data collection started at the end of April and was completed at the beginning of July 2020. Follow-up data collection took place between January and February 2022. The data collection period thus covered the peak phase of the pandemic in Germany to date. All participants underwent SARS-CoV-2 IgG antibody testing: Blood samples were taken at baseline and follow-up and a semi-quantitative SARS-CoV-2 immunoglobin (Ig) G enzyme-linked immunosorbent assay (ELISA) targeting the S1-Domain of the S-protein spike protein subunit (Euroimmun Medizinische Labordiagnostika, Lübeck, Germany) was performed according to the manufacturer's instructions. A stringent cut-off ratio of the extinction of the serum sample over the extinction of the calibrator of $\geq$ 1.5 for positive results was used, which has been shown to display a specificity of 100% (Pflüger et al., 2020), in order to account for the low prevalence environment.

Instruments

For a detailed description of the instruments used, see Engelmann et al. (2022). In short, somatic symptom burden was assessed *via* the Somatic Symptom Scale-8 [SSS-8 (Gierk et al., 2014)] which measures eight common somatic symptoms (e.g., shortness of breath and joint pain) on a five-point response range (0–4). Sum scores can be categorized into minimal (0–3 points), low (4–7 points), medium (8–11 points), high (12–15 points), or very high (16–32 points) somatic symptom burden. Psychological symptom burden was inquired via the Somatic Symptom Disorder–B Criteria Scale [SSD-12 (Toussaint et al., 2016)]. Consisting of 12 items, it uses four items respectively to ask about psychological burden related to the somatic symptoms on an emotional, cognitive, and behavioral level. A score between 0 and 4 is used for each of the 12 items and a total score is calculated from the sum of the items. Symptom expectations associated with COVID-19 were assessed using a self-developed numeric rating scale (NRS: "How much do you expect to be burdened by symptoms in case of a COVID-19 infection?") with a range from 0 to 10. Participants were instructed to answer the item on symptom expectations only if they had not been infected with SARS-CoV-2 yet. Depression and anxiety severity were examined with the PHQ-4 [Patient Health Questionnaire (Kroenke et al., 2009)], the ultrashort form of the Patient Health Questionnaire (PHQ–D) which consists of 4 items. We used its depression (PHQ-2) and anxiety subscales (GAD-2) where responses are scored between 0 and 3, resulting in a total score between 0 and 6. To assess the internal consistency of the used scales in our sample, Cronbach's alpha was calculated. All

reliabilities were acceptable to excellent (SSS-8: 0.79, SSD-12: 0.93, PHQ-4: 0.84).

Additionally, participants were asked by a dichotomous item if they had a history of COVID-19 ("I have been diagnosed with SARS-CoV-2 infection by nasal/pharyngeal swabbing"), and if they suffer or have suffered from Long COVID ("Do you suffer or have you suffered from Long COVID syndrome?") with three response options ("No"; "Yes, but now I have overcome Long COVID syndrome"; "Yes, I am still suffering from Long COVID syndrome"). Participants were also asked if and how often they had been vaccinated against COVID-19. Except for the items on Long COVID and vaccination, all instruments were employed at both baseline and follow-up assessment.

Statistical analyses

Statistical analyses were conducted using IBM SPSS 27. For sample characteristics, descriptive statistics were used. In order to detect potential selection bias, dropout analyses were performed. Differences between psychological variables at T0 and T1 within the study group were compared with paired samples *t*-tests.

To explore the impact of non-modifiable and modifiable factors on somatic symptom change between T0 and T1, a multiple linear regression analysis controlling for age, gender, and somatic symptom burden at T0 was conducted. As pre-specified predictors, the regression model included SARS-CoV-2 infection since T0 determined by IgG antibody test and self-reported SARS-CoV-2 infection since T0, as well as modifiable explanatory baseline measures (psychological symptom burden, symptom expectations associated with COVID-19, depression severity, and anxiety severity). The dependent variable was somatic symptom change (Δ SSS-8) between T0 and T1. Multicollinearity was examined through tolerance and variance inflation factor criteria. The assumption was not violated.

Comparisons between participants differing in terms of SARS-CoV-2 IgG antibody test result at T1 and self-reported belief of SARS-CoV-2 infection since T0 on the continuous study variables at T1 were computed by forming four groups ("serology and belief no," "serology and belief yes," "serology no and belief yes," "serology yes and belief no") and performing one-way ANOVA.

Results

Sample characteristics

In total, $N = 1{,}792$ healthcare professionals aged ≥ 18 years (27.9% nurses, 20.5% medical doctors, 9.4% medical (technical) assistants, 6.3% scientists, 5.6% administrative employees, 20.8% others such as pharmacists, psychologists, social educations workers, students) were recruited. Of the 1,792 participants at baseline, $n = 751$ (41.9%) completed the measures at follow-up after 21 months. The mean follow-up interval was $M = 20.07$ ($SD = 0.37$) months. Compared to the dropout group, the study sample was characterized by significantly older age (study group: $M = 40.32$, $SD = 11.79$; dropout group: $M = 35.58$, $SD = 11.32$; $p < 0.001$), a higher percentage of females (study group: 77.9% females, dropout group: 65.0% females; $p < 0.001$), and a significantly lower depression severity (study group: $M = 0.88$, $SD = 1.04$; dropout group: $M = 1.02$, $SD = 1.11$; $p = 0.01$). All other scores were within similar range in both groups. The study sample had a mean age of $M = 40.26$ years ($SD = 11.75$). At follow-up, 93.3% of the study sample reported to be fully vaccinated against COVID-19, i.e., three vaccinations, according to the recommendation at that time.

Comparison between study variables at baseline and follow-up

Table 1 shows the comparison between relevant variables within the study sample at baseline and follow-up. Significant differences were found between the two time points on all variables, with significantly higher scores of somatic and psychological symptom burden as well as depression and anxiety severity at follow-up. Symptom expectations associated with COVID-19 significantly decreased over time. According to the effect sizes, all differences are of small magnitude (Cohen, 2013).

Prediction of somatic symptom deterioration

Between baseline and follow-up, participants' somatic symptom burden increased by an average of 1.74 points on the SSS-8 (range from worsening by 18 points to improvement by 11 points, $SD = 3.76$). Predictors of somatic symptom deterioration between baseline and follow-up are shown in Table 2. According to our regression model, 17% of the variance in somatic symptom change could be explained by three of the included factors. The strongest predictor of somatic symptom deterioration after 21 months was psychological symptom burden at baseline. In addition, participants with higher symptom expectations associated with COVID-19 at baseline as well as those who reported a SARS-CoV-2 infection since baseline were more likely to report somatic symptom deterioration after 21 months.

Participants' serologically confirmed SARS-CoV-2 infection since baseline determined by IgG antibody test, as well as depression severity and anxiety severity at baseline did not significantly contribute to the explained variance in somatic symptom deterioration at follow-up.

TABLE 1 Comparison between study variables at T0 and T1 ($n = 751$).

Variable	T0	T1	t; p-Value	ES
Somatic symptom burden (SSS-8), *M (SD)*	3.15 (3.41)	4.89 (4.21)	$t(750) = -12.68$; $\mathbf{p < 0.001}$	−0.46
Psychological symptom burden (SSD-12), *M (SD)*	5.28 (5.73)	7.38 (7.52)	$t(750) = -10.34$; $\mathbf{p < 0.001}$	−0.38
Symptom expectations (NRS), *M (SD)*	4.03 (2.07)	3.58 (1.92)	$t(750) = 5.07$; $\mathbf{p < 0.001}$	0.20
Depression severity (PHQ-2), *M (SD)*	0.88 (1.04)	1.14 (1.17)	$t(750) = -6.03$; $\mathbf{p < 0.001}$	−0.22
Anxiety severity (GAD-2), *M (SD)*	0.72 (1.03)	0.96 (1.23)	$t(750) = -5.50$; $\mathbf{p < 0.001}$	−0.20

M, mean; SD, standard deviation; ES, effect size (Cohen's d); SSS-8, Somatic Symptom Scale-8 (range: 0-32); SSD-12, Somatic Symptom Disorder–B Criteria Scale (range: 0–48); NRS, numeric rating scale, symptom expectations: "How much do you expect to be burdened by symptoms in case of a COVID-19 infection?" (range: 0–10); PHQ-2, Patient Health Questionnaire, 2-item depression scale (range: 0–12); GAD-2, Generalized Anxiety Disorder Scale, 2-item anxiety scale (range: 0–12); significant p-values printed in bold mark.

TABLE 2 Multiple linear regression analysis to test predictors of somatic symptom change (Δ SSS-8) at follow-up, adjusting for age, gender, and somatic symptom burden at baseline ($n = 751$).

Predictor	*b (SE)*	*ß*	*p*
SARS-CoV-2 infection since baseline determined by IgG antibody test	−1.27 (0.77)	−0.09	0.100
Self-reported SARS-CoV-2 infection since baseline	1.86 (0.78)	0.13	**0.017**
Psychological symptom burden at baseline (SSD-12)	0.11 (0.03)	0.16	**<0.001**
Symptom expectations at baseline (NRS)	0.20 (0.07)	0.11	**0.004**
Depression severity at baseline (PHQ-2)	0.21 (0.16)	0.06	0.197
Anxiety severity at baseline (GAD-2)	0.14 (0.17)	0.04	0.410

SSS-8, Somatic Symptom Scale-8; SSD-12, Somatic Symptom Disorder–B Criteria Scale; NRS, numeric rating scale, symptom expectations: "How much do you expect to be burdened by symptoms in case of a COVID-19 infection?" (range: 0–10); PHQ-2, Patient Health Questionnaire, 2-item depression scale (range: 0–12); GAD-2, Generalized Anxiety Disorder Scale, 2-item anxiety scale (range: 0–12); adjusted $R^2 = 0.167$, $\Delta R^2 = 0.178$, $\Delta F = 15.618$, $df = (9, 649)$, sig. $\Delta F = <0.001$; significant p-values printed in bold mark.

Group comparisons on study variables

At baseline, none of the participants of our study sample had a history of COVID-19 according to both SARS-CoV-2 IgG antibody test result as well as self-report. During the 2 years of the study period, $n = 58$ participants had contracted SARS-CoV-2 confirmed by positive SARS-CoV-2 IgG antibody test result, while at follow-up $n = 68$ participants reported to have been through a SARS-CoV-2 infection. Of those who reported a former SARS-CoV-2 infection, in $n = 11$ this could not be confirmed by a positive antibody test result. Of those participants with a positive antibody test result, $n = 13$ reported no history of COVID-19, i.e., had suffered from a hidden infection.

Comparisons between the four groups differing in terms of SARS-CoV-2 IgG antibody test result at follow-up and self-reported belief of SARS-CoV-2 infection since baseline ("serology and belief no," "serology and belief yes," "serology no and belief yes," "serology yes and belief no") on the study variables somatic and psychological symptom burden, symptom expectations, and depression and anxiety severity at follow-up are shown in Table 3. One-way ANOVA yielded no significant differences between groups on any of the variables. Regarding the SSS-8 scores, there was a trend toward a significant between-group difference ($p = 0.060$). The "serology no and belief yes" group stated the highest SSS-8 mean score of all of the four groups at follow-up. The second highest SSS-8 score was reported by the "serology yes and belief yes" group, followed by the "serology no and belief no" group. The "serology yes and belief no" group stated the lowest mean somatic symptom burden.

In terms of Long COVID, $n = 13$ of the $n = 58$ participants with a prior infection confirmed by positive SARS-CoV-2 IgG antibody test result stated at follow-up to suffer ($n = 7$) or to have suffered ($n = 6$) from Long COVID. Beyond that, $n = 3$ participants without a positive antibody test result reported to have experienced Long COVID in the past. Due to the small sample size of this group, we did not perform any further statistical analyses regarding Long COVID.

Discussion

Risk factors for somatic symptom deterioration during the COVID-19 pandemic

The results of this prospective cohort study indicate symptom expectations, as opposed to serologically confirmed SARS-CoV-2 infection, to be relevant for the report of worsening of somatic symptoms over the course of the pandemic. Symptom expectations as well as a self-reported SARS-CoV-2 infection

TABLE 3 Comparison between groups differing in terms of SARS-CoV-2 serology and self-reported belief of SARS-CoV-2 infection on study variables at T1 ($n = 684$).

Variable	Serology−		Serology+		$F(4, 746)$	$\eta 2$
	Belief− ($n = 615$)	Belief+ ($n = 11$)	Belief− ($n = 13$)	Belief+ ($n = 45$)		
Somatic symptom burden (SSS-8), *M (SD)*	4.82 (4.12)	7.55 (4.06)	2.85 (3.34)	5.64 (4.88)	2.27	0.01
Psychological symptom burden (SSD-12), *M (SD)*	7.35 (7.34)	10.73 (10.57)	6.15 (8.36)	7.27 (7.52)	0.64	0.00
Symptom expectations (NRS), *M (SD)*	3.56 (1.93)	–	3.42 (1.44)	–	0.47	0.00
Depression severity (PHQ-2), *M (SD)*	1.15 (1.16)	1.18 (1.78)	1.23 (0.93)	0.96 (1.21)	0.32	0.00
Anxiety severity (GAD-2), *M (SD)*	0.94 (1.19)	1.55 (1.75)	0.77 (1.24)	0.82 (1.19)	1.28	0.01

Serology test result or self-reported belief of SARS-CoV-2 infection negative (–) or positive (+); M, mean; SD, standard deviation; SSS-8, Somatic Symptom Scale-8 (range: 0–32); SSD-12, Somatic Symptom Disorder–B Criteria Scale (range: 0–48); NRS, numeric rating scale, symptom expectations: "How much do you expect to be burdened by symptoms in case of a COVID-19 infection?" (range: 0–10); PHQ-2, Patient Health Questionnaire, 2-item depression scale (range: 0–12); GAD-2, Generalized Anxiety Disorder Scale, 2-item anxiety scale (range: 0–12); missing values on symptom expectations are due to the fact that participants were instructed to answer the item only if they had not been infected with SARS-CoV-2 yet; all p-values > 0.05.

since baseline were found to be significant predictors of somatic symptom deterioration after 21 months, while actual infection confirmed by reliable SARS-CoV-2 IgG antibody testing was not. Baseline psychological burden associated with somatic symptoms emerged as a further predictor of somatic symptom deterioration at follow-up. We found an interesting, yet not significant trend in our data, revealing that individuals who had a negative SARS-CoV-2 IgG antibody test but who believed they have been infected since baseline showed higher somatic symptom burden after 21 months than individuals with a positive SARS-CoV-2 IgG antibody test who did not know about their infection. This result needs confirmation in well-powered samples, however, the results of this study support the importance of disease-overarching biopsychosocial models for the development of PSS (Henningsen et al., 2018; Löwe et al., 2022) which might also be relevant for symptom persistence in Long COVID.

Our findings are in line with a cross-sectional population-based French cohort study of $N = 26{,}823$ participants in which the self-reported belief of having been infected with SARS-CoV-2 in the past was significantly associated with symptom persistence of 8 weeks or more. Whereas, a positive serology test result was only positively associated with the symptom of anosmia, with no significant interaction between self-reported COVID-19 and serology test results (Matta et al., 2022). The present study not only supports these findings, but our prospective design provides additional corroboration of the importance of expectations for the development of bothersome somatic symptoms in response to the COVID-19 pandemic regardless of SARS-CoV-2 serology status. A missing link between self-reported symptoms and biological abnormalities has also recently been reported in a patient group with acute SARS-CoV-2 infection. In an observational cohort study of non-hospitalized adolescents and young adults involving $n = 405$ positive COVID-19 cases and $n = 111$ non-COVID-19 controls, Lund Berven et al. (2022) found a higher incidence of COVID-typical clinical symptoms among the COVID-19 cases. However, clinical symptoms were independent of objective inflammatory and pulmonary function markers. The power of expectations to predict symptom course, treatment benefit, and negative treatment side effects has been confirmed before the pandemic for a variety of medical illnesses and also for somatic symptoms relevant in Long COVID, such as pain and fatigue (Goffaux et al., 2009; Moss-Morris et al., 2011; Vase et al., 2015; Schmitz et al., 2019).

Our results are consistent with previous studies in which prior psychological symptom burden has been found to be a risk factor for PSS (Voigt et al., 2013; Klaus et al., 2015; Löwe et al., 2021). In the analysis of an earlier follow-up time point of the here presented sample, baseline psychological symptom burden was found to be a predictor of somatic symptom burden in a cohort without prior SARS-CoV-2 infection after 8 weeks (Engelmann et al., 2022). In contrast to the previous analysis, baseline anxiety did not predict somatic symptom deterioration at the 21 months follow-up, while symptom expectations did. Anxiety seems to be an important predictor of somatic symptom burden in the short term, whereas symptom expectations seem to be more relevant in the longer term. This finding may be influenced by a measurement bias. While we measured anxiety with the GAD-7, assessing general anxiety, we inquired symptom expectations specifically addressing COVID-19. Accordingly, the directly COVID-19 related question appears to better predict somatic symptom burden at longer-term follow-up than general questions on anxiety and worrying.

Development of psychological distress over time

Over the period of data collection from spring 2020 until the beginning of 2022, both psychological and somatic symptom

burden increased significantly in our sample. Publications of data collected early in the pandemic reported deleterious effects on mental health with significantly higher levels of depression and anxiety than pre-pandemic estimates in the general population (Ettman et al., 2020; Pierce et al., 2020; Nochaiwong et al., 2021; Blasco-Belled et al., 2022) and in samples of healthcare professionals (Pappa et al., 2020; Bekele and Hajure, 2021; Hao et al., 2021; Blasco-Belled et al., 2022). In contrast, some later studies suggest that after an initial peak, psychological distress gradually declined over time until almost returning to baseline levels by mid-2020 (Fancourt et al., 2021; Aknin et al., 2022; Robinson et al., 2022). The latter results cannot be confirmed by our data. However, it is to say that even at follow-up, overall somatic and psychological impairment in our study must be considered low to moderate compared to normative values (Kroenke et al., 2009; Gierk et al., 2014; Toussaint et al., 2020). Even though we did not assess symptoms before the COVID-19 outbreak in our sample, this seems to be in line with studies of representative German samples that found only small increases of symptoms of depression and anxiety during the COVID-19 pandemic in comparison to pre-pandemic levels (Entringer et al., 2020; Peters et al., 2020; Beutel et al., 2021). Recent findings suggest that vaccination against COVID-19 may have a positive impact on mental wellbeing (Babicki et al., 2021). Since almost our entire sample reported to be fully vaccinated, this could also play a role in our results.

Strengths and limitations

A particular strength of this study is its prospective design, which adds further evidence to previous cross-sectional results (Matta et al., 2022), as well as the large sample of German adults which included both participants who did and who did not contract SARS-CoV-2. Most studies on Long COVID lack adequate control groups and do not consider symptom burden prior to infection, which calls published prevalences into question (Lopez-Leon et al., 2021; Ballering et al., 2022; Seeßle et al., 2022). Therefore, it was our aim to assess somatic symptom deterioration in both individuals with and without former SARS-CoV-2 infection. Moreover, there is a lack of knowledge on potential psychosocial risk factors for both the development of Long COVID and of PSS in individuals without prior SARS-CoV-2 infection during the pandemic. This is one of the first studies to simultaneously investigate risk factors for somatic symptom deterioration in a sample of affected and unaffected individuals. In contrast to most other published data so far (Mauz et al., 2021; Matta et al., 2022), our prospective study reports data taking into account almost 2 years of the pandemic event.

The small proportion of our sample of 7.7% who has been infected with SARS-CoV-2 must be considered a limitation to our study. Consequently, our comparisons between groups of SARS-CoV-2 IgG antibody test result and self-reported belief of SARS-CoV-2 infection are only interpretable to a limited extent. The percentage of previously infected individuals in our study is comparable to other reports on healthcare professionals. A systematic review and meta-analysis of infection prevalence rates in healthcare professionals across 97 healthcare settings in Europe, the United States, and Asia found the rate to be 7% based on antibody testing and 11% using reverse transcription PCR assays (Gómez-Ochoa et al., 2021). In a longitudinal study of $N = 1{,}506$ healthcare professionals at a German General Hospital, 165 (10.6%) participants tested positive for SARS-CoV-2 infection within a one-year period between April 2020 and April 2021 (Platten et al., 2022). Further studies with a higher number of formerly infected participants would be needed in order to confirm our results. Also, since healthcare professionals represent a high-risk group for experiencing mental health issues (Maben and Bridges, 2020) and somatic symptoms like fatigue (Kawano, 2008), our study sample could limit the generalizability of our results. The discrepancy between participants in our sample with a history of COVID-19 confirmed by positive SARS-CoV-2 IgG antibody test result and those who self-reported to have previously been diagnosed with SARS-CoV-2 infection by nasal/pharyngeal swabbing cannot be fully reconstructed on the basis of our data. The swab results themselves may have been incorrect (false positive) or participants agreed to the item because they were actually convinced of an infection even without a positive test result. Another explanation could be the antibody test results. We determined prior SARS-CoV-2 infection by SARS-CoV-2 IgG ELISA. While antibody responses have been shown to maintain for more than 1 year post infection in symptomatic patients (Scheiblauer et al., 2022), serological responses in individuals with asymptomatic or mild infections are less well understood and may decline more rapidly (Efrati et al., 2021; Tian et al., 2021). Therefore, it is possible that not all SARS-CoV-2 infections in our sample have been detected by antibody testing.

We assessed somatic symptom burden at baseline and follow-up using the SSS-8, which uses a 7-day period. Accordingly, we only measured short-term symptoms at both time points and therefore, strictly speaking, cannot draw any conclusions on persistent symptoms. We did not use a Long COVID specific instrument since harmonized core outcome sets for Long COVID conditions are currently still being developed (Munblit et al., 2022). Another limitation is that we did not examine some of the previously reported risk factors for Long COVID like body mass index, autoantibodies, or pre-existing medical or psychiatric conditions (Lopez-Leon et al., 2021; Sudre et al., 2021; Su et al., 2022), and therefore do not know about their potential relevance for our sample. Future studies should take these factors into account.

Conclusion

The findings of this study provide evidence for the relevance of biopsychosocial risk factors (Henningsen et al., 2018; Löwe et al., 2022) in explaining both burdensome somatic symptoms in individuals formerly infected with SARS-CoV-2 as well as somatic symptoms that develop in response to the COVID-19 pandemic in individuals that have not been infected with SARS-CoV-2. Thus, our results are in line with current evidence which confirms that a high number of low-risk COVID-19 patients develop Long COVID (Moreno-Pérez et al., 2021) and shows little or no association between Long COVID and initial disease severity (Townsend et al., 2020; Sudre et al., 2021; Sykes et al., 2021; Huang et al., 2022). In particular, dysfunctional symptom expectations seem to play a major role for the report of somatic symptom deterioration in individuals who did and did not contract SARS-CoV-2, which indicates that symptoms that are actually associated with distress caused by the pandemic might be falsely attributed to effects of SARS-CoV-2 infection. Therefore, future studies on Long COVID should include control groups without former SARS-CoV-2 infection and consider symptom burden prior to infection in order to avoid an overestimation of the prevalence of Long COVID (Amin-Chowdhury and Ladhani, 2021; Ballering et al., 2022). This is of particular importance as media reports of excessive strains through the disease might provoke dysfunctional expectations and thereby contribute to a worsening of symptoms in those affected. In these studies, further psychological factors like catastrophizing, somatosensory amplification, and learning processes like avoidance behavior should be investigated to further expand our knowledge of biopsychosocial mechanisms involved in somatic symptom burden due to the COVID-19 pandemic.

Since dysfunctional symptom expectations seem be involved in the development of PSS during the COVID-19 pandemic, they should be addressed in corresponding interventions. Targeted expectation management has already been shown to improve clinical outcomes in several other medical conditions (Rief et al., 2017; Kube et al., 2018; Pan et al., 2020). According to our results, interventions should be made accessible especially for individuals with a history of symptom burden. Interventions trying to foster healthcare professionals' coping with infectious disease outbreaks mostly do not address somatic symptoms at all (Zaçe et al., 2021). With regard to future pandemics, it is important for healthcare organizations to preventively support healthcare professionals in dealing with burdensome somatic symptoms.

Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

The study protocol was reviewed and approved by the ethics board of the Hamburg Medical Chamber, Germany (approval number PV 7298). Written informed consent was obtained from all participants to participate in the study.

Author contributions

TB, MA, JS, and AL developed the concept and design of the study. FU was responsible for conducting the study. PE analyzed the data and wrote the draft of this manuscript. AT provided revisions. BL and AW contributed further refinements. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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8.2. Study II

Psychological risk factors for Long COVID and their modification: study protocol of a three-arm, randomised controlled trial (SOMA.COV)

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Psychological risk factors for Long COVID and their modification: study protocol of a three-arm, randomised controlled trial (SOMA.COV)

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Background

Growing evidence suggests that in addition to pathophysiological, there are psychological risk factors involved in the development of Long COVID. Illness-related anxiety and dysfunctional symptom expectations seem to contribute to symptom persistence.

Aims

With regard to the development of effective therapies, our primary aim is to investigate whether symptoms of Long COVID can be improved by a targeted modification of illness-related anxiety and dysfunctional symptom expectations. Second, we aim to identify additional psychosocial risk factors that contribute to the persistence of Long COVID, and compare them with risk factors for symptom persistence in other clinical conditions.

Method

We will conduct an observer-blinded, three-arm, randomised controlled trial. A total of 258 patients with Long COVID will be randomised into three groups of equal size: targeted expectation management in addition to treatment as usual (TAU), non-specific supportive treatment plus TAU, or TAU only. Both active intervention groups will comprise three individual online video consultation sessions and a booster session after 3 months. The primary outcome is baseline to post-interventional change in overall somatic symptom severity.

Conclusions

The study will shed light onto the action mechanisms of a targeted expectation management intervention for Long COVID, which, if proven effective, can be used stand-alone or in the context of broader therapeutic approaches. Further, the study will enable a better understanding of symptom persistence in Long COVID by identifying additional psychological risk factors.

Keywords

Long COVID; post-COVID-19 condition; persistent somatic symptoms; biopsychosocial model; risk factors.

Studies suggest that after an infection with SARS-CoV-2 has abated, a substantial portion of affected patients do not fully recover and may be at risk of persistent somatic symptoms – a phenomenon often described as 'Long COVID'. There is growing evidence that the development of Long COVID is multifactorial and involves pathophysiological, psychological and social mechanisms.[1] Among psychological risk factors, increased levels of illness-related anxiety[2–4] and dysfunctional symptom expectations[5,6] appear to contribute to processes of symptom persistence after SARS-COV-2 infection. Since both factors can potentially be modified by targeted interventions, this study will investigate a defined mechanism of action: whether Long COVID can be influenced by modifying illness-related anxiety and dysfunctional symptom expectations.

The term Long COVID has become widely used to describe persistent somatic symptoms after a SARS-CoV-2 infection has resolved. Although Long COVID syndrome still lacks specific definition, classification and diagnostic guidelines,[2] it is thought to comprise symptoms that last >4 weeks after the onset of a SARS-CoV-2 infection, can affect almost every organ system in the body, may change over time and are not better explained by an alternative diagnosis.[7] According to the UK National Institute for Health and Care Excellence (NICE) COVID-19 guideline and the German Association of the Scientific Medical Societies (AWMF) S1-guideline 'Post-COVID/Long-COVID', Long COVID subsumes both 'ongoing symptomatic COVID-19'[8] (4–12 weeks after infection) and 'post-COVID-19 syndrome' (>12 weeks after infection).[7] Thus, Long COVID falls under the umbrella term persistent somatic symptoms (PSS), which is used to describe subjectively distressing somatic complaints, irrespective of their aetiology, that are present on most days for at least several weeks.[9]

Clinical presentation of Long COVID

Long COVID is considered an unusual course of disease, as COVID-19 is usually expected to subside after 2 weeks for patients with mild manifestation, and up to a maximum of 6 weeks for those with severe disease.[10] It is associated with reduced quality of life and poses challenges to the healthcare system, e.g. through work absenteeism and increased healthcare use. According to a meta-analysis of 15 studies encompassing 47 910 patients, 80% stated at least one symptom during follow-up periods ranging from 2 weeks to 4 months post-infection.[11] In a German prospective cohort study, only 22.9% of patients indicated to be free of symptoms at 12 months after symptom onset.[12] The most frequently reported symptoms at 12 weeks in a prospective study of 4182 COVID-19 cases were fatigue, shortness of breath, loss of smell and headache.[1] A NICE rapid evidence review of three high-quality systematic reviews also found, among others, high mean percentages for fatigue (31–51%), dyspnoea (22–38%), impairment of smell (15–24%) and taste (7–16%), and muscle pain (5–22%) after at least 4 weeks.[7]

General aetiological model for PSS

Since there is no generally accepted disease-specific model for the development of Long COVID, we draw on disease-overarching models for the development of PSS by analogy. Regarding the transition from short-term to persistent disabling symptoms in general, the

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comprehensive vulnerability-stress model by Henningsen et al[13] defines predisposing, triggering and maintaining/aggravating factors that determine the transition from short-term symptoms to PSS. Based on this model and current research findings, the German Research Foundation (DFG)-funded interdisciplinary SOMACROSS Research Unit (Persistent Somatic Symptoms Across Diseases: From Risk Factors to Modification; unit identifier RU 5211), which investigates generic and disease-specific risk factors and mechanisms for the development and maintenance of PSS across ten medical conditions, developed a cross-disease working model for the aetiology of PSS. The model is described in detail in the published framework and overarching protocol of the research unit.[9] In brief, according to this model, predisposing factors for PSS comprise sociodemographic (e.g. female gender, poor education), psychological (e.g. precedent life stressors, negative affectivity) and biomedical risk factors (e.g. prior medical conditions, immunological predispositions). Triggering factors for short-term somatic symptoms include acute infections, injuries or current life stressors. Among the best-established maintaining/aggravating factors for PSS is illness-related anxiety,[14] which may be explained by its association with other cognitive-perceptual and emotional mechanisms (e.g. catastrophising, somatosensory amplification) and with behavioural processes (e.g. avoidance behaviour). Besides disease-specific (e.g. inflammation, organ damage) and overarching (e.g. treatment effects) biomedical factors, dysfunctional symptom expectations are considered highly relevant for symptom persistence.[9] Symptom expectations are defined as conscious, future-directed cognitions regarding the anticipated course of symptoms.[15] As they constitute a common denominator of many psychological risk factors for PSS, expectations are regarded as a core feature of current aetiological models for PSS.[16] They are also prominently conceptualised in new predictive processing models suggesting that symptom perception emerges through an unconscious, integrative process of sensory input, contextual cues and prior information. In these models, next to previous experiences, learning processes, context and prior knowledge, expectations are considered one form of prior information that contribute to the development of implicit predictions about the presence of symptoms.[17]

General risk factors for Long COVID

In terms of general risk factors for developing Long COVID, older age, female gender, obesity, viremia, specific autoantibodies and pre-existing medical conditions have been found.[1,11,18] However, according to current evidence, a substantial number of low-risk patients with COVID-19 report ongoing somatic symptoms months after the infection.[19] Therefore, it seems reasonable to assume that further clinical features are associated with the subsequent development of Long COVID. For example, in a recent case–control study, 443 individuals showed signs of modest subclinical multi-organ dysfunction after mild-to-moderate SARS-CoV-2 infection.[20] Although there is no doubt about the importance of disease-specific pathophysiological processes, no biomarker has yet been identified to comprehensively measure the severity of Long COVID. A reason to believe that pathophysiological damage is not the only contributor to Long COVID symptoms is that several studies indicated a small or no association between Long COVID and initial disease severity.[1] Two particularly relevant and potentially modifiable risk factors for Long COVID are discussed below.

Anxiety as a risk factor for Long COVID

In a retrospective electronic health record study including 236 379 individuals, Taquet et al[2] examined neurologic and psychiatric symptoms within the first 6 months after COVID-19 diagnosis. The highest incidence was found for anxiety disorders at 17.4%, of whom 10% had already been diagnosed before their SARS-CoV-2 infection. A recently published cohort study of 3193 individuals found anxiety and worry about COVID-19, as well as depression, perceived stress and loneliness, to be prospectively associated with an increased risk of self-reported Long COVID.[3] Further supporting the assumption that illness-related anxiety is involved in the development and maintenance of Long COVID, we found anxiety to be the strongest modifiable predictor of somatic symptom burden after 8 weeks in a prospective cohort study of 1185 healthcare professionals that did not contract COVID-19.[4] In the UK general population, COVID-19-related anxiety has also been found to predict somatic symptoms, particularly fatigue.[21] Consistent with these findings, illness-related anxiety has been found to be a risk factor for PSS before the COVID-19 pandemic in a range of medical conditions, e.g. chronic fatigue, fibromyalgia and irritable bowel syndrome.[14]

Expectations as a risk factor for Long COVID

In a recently concluded prospective cohort study of German adults, we assessed risk factors for somatic symptom deterioration after 21 months ($N = 751$). Symptom expectations associated with COVID-19 and a self-reported history of COVID-19, but not serologically confirmed SARS-CoV-2 infection, significantly predicted somatic symptom deterioration 21 months later.[5] Our findings corroborate the results of a cross-sectional population-based French cohort study including 26 823 participants, which also indicated that PSS after COVID-19 may be more strongly associated with belief in having been infected with SARS-CoV-2 than with a laboratory-confirmed infection.[6] Consequently, the expectation of symptoms could be a determining factor for symptom persistence in Long COVID. Similarly, patients' expectations of symptom severity have been found to be a crucial factor in other conditions, e.g. chronic fatigue.[22] The power of expectations to predict symptom course, treatment benefit and negative treatment side-effects has been demonstrated for a wide range of medical illnesses and somatic symptoms, such as cancer, pain, gastrointestinal and 'medically unexplained' symptoms.[23,24]

Specific aetiological model for persistent Long COVID symptoms

The above described risk factors for Long COVID are congruent with the risk factors described in the cross-disease SOMACROSS model for the aetiology of PSS.[9] Thus, we assume that this cross-disease biopsychosocial model for symptom persistence might also be applicable to Long COVID. Therefore, we adapted the working model of the SOMACROSS Research Unit by entering predisposing, triggering and maintaining/aggravating factors assumed for Long COVID (see Fig. 1).

Research needs

Empirical evidence points to a multifactorial biopsychosocial model regarding the aetiology of Long COVID. Illness-related anxiety and dysfunctional symptom expectations appear to be relevant modifiable factors contributing to Long COVID independent of initial disease severity. Thus, modifying illness-related anxiety and expectations in patients with Long COVID may be a promising approach in improving symptoms. A recent search in PubMed and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) indicated that so far, no study has investigated alleviating Long COVID symptoms by targeting these factors. Should a targeted modification of illness-related anxiety and dysfunctional expectations of symptom severity lead to a change in

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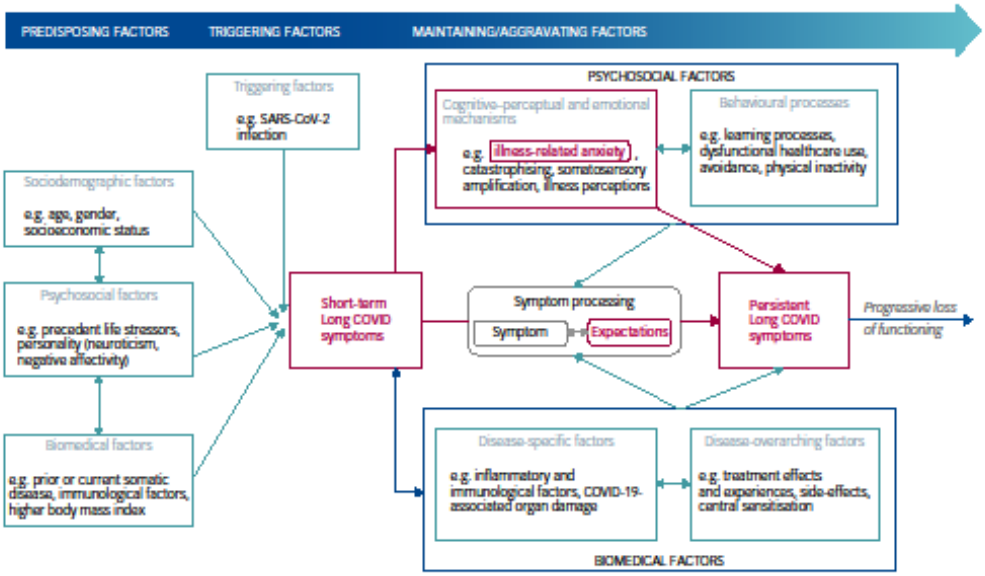

Fig. 1 General model for the aetiology of persistent somatic symptoms, developed by the SOMACROSS Research Unit[7] and adapted for Long COVID. The factors specifically investigated in this study are marked in red.

Long COVID symptoms, this would provide sound evidence for a specific mechanism of action for the development of Long COVID and the effectiveness of a mechanism-based treatment approach.

Objectives and hypotheses

Objectives

Objective 1 is to investigate whether overall somatic symptom severity in patients with Long COVID can be improved via the modification of illness-related anxiety and dysfunctional symptom expectations. Objective 2 is to prospectively identify further risk factors involved in the persistence of Long COVID, and to deduct conceptual models of symptom persistence, deterioration and improvement. Objective 3 is to compare risk factors and mechanisms of somatic symptom persistence in Long COVID exploratively with those identified in the medical conditions investigated in the SOMACROSS Research Unit.

For objective 1, a testable hypothesis can be formulated. Objective 2 will be investigated with an exploratory approach. To address objective 3, we will use data from the SOMACROSS Research Unit and compare them with our project data in an exploratory manner.

Hypotheses

Hypothesis 1 is that the therapeutic modification of illness-related anxiety and dysfunctional symptom expectations improves Long COVID symptom severity. Hypothesis 2 (exploratory) is that, in addition to illness-related anxiety and dysfunctional symptom expectations, further risk factors contributing to the persistence of Long COVID symptoms can be identified. Hypothesis 2 (exploratory, using results from SOMACROSS) is that Long COVID and other medical conditions share common risk factors for somatic symptom persistence.

Method

Study design

Study design and rationale

To identify the effect of a targeted modification of illness-related anxiety and dysfunctional symptom expectations on Long COVID symptoms, and to differentiate this effect from general modes of action, a randomised comparison between a specifically treated group, a group treated non-specifically in the same dose and a control group without additional treatment is required. A control group is necessary to test whether the experimental interventions have a positive effect compared with no intervention at all, and to investigate objectives 2 and 3. Thus, we will use the design of a three-arm randomised controlled trial, in which one third of participants will undergo targeted expectation management in addition to treatment as usual (TAU), one third will undergo unspecific supportive treatment in addition to TAU, and one third will receive TAU only. In the control group, we will additionally investigate the contribution of predefined risk factors to symptom persistence in Long COVID. The study will be fully observer-blinded with respect to all treatment conditions. It will be conducted monocentric with nationwide recruitment.

Setting

For recruitment, we will use our pulmonary out-patient clinic as well as our psychosomatic out-patient clinic and our established network of general practitioners and pulmonologists. We will also recruit via social media campaigns with support of cooperating self-help groups and patient organisations (e.g. 'Landesverband Sachsen für Prävention und Rehabilitation von Herz-Kreislauf-Erkrankungen e.V. ', 'Long COVID Vernetzungsstelle', 'Nationale Kontakt- und Informationsstelle zur Anregung und

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Unterstützung von Selbsthilfegruppen"). The experimental interventions will be carried out as personal online video consultations, which allows for a nationwide outreach of our study.

Inclusion criteria

Inclusion criteria are as follows: self-reported resolved SARS-CoV-2 infection confirmed by a positive polymerase chain reaction, serology or rapid antigen test; presence of Long COVID according to the NICE/AWMF S1-guidelines,[7] at least moderately severe ongoing symptoms (Patient Health Questionnaire 15 (PHQ-15) score ≥10),[25] aged ≥18 years and provision of informed consent.

Exclusion criteria

Exclusion criteria are as follows: acute SARS-CoV-2 infection, intensive care unit treatment for COVID-19, psychotherapeutic treatment in the past 3 months, necessity of acute emergency treatment, acute suicidality, a substance use disorder, acute psychosis, cognitive incapacity to comprehend the study materials, inability to complete outcome measures online or insufficient German language skills.

Experimental interventions and control intervention

Experimental intervention 1 (COV.EXPECT + TAU)

The experimental intervention consists of an expectation management intervention (COV.EXPECT) in addition to TAU. The manualised intervention primarily aims to reduce illness-related anxiety and optimise expectations about symptoms, treatment outcome and coping strategies.[26] The design and dose of the intervention are based on the demonstrated effectiveness of the expectation management intervention from the PSY-HEART trial (Psychological Preoperative Interventions to Improve Outcome in Heart Surgery Patients),[27] on the SOMA. GUT study (Persistence of Gastrointestinal Symptoms in Irritable Bowel Syndrome and Ulcerative Colitis: From Risk Factors to Modification) within the SOMACROSS Research Unit[28] and on other previous studies.[26] The intervention consists of three individual online video consultation sessions (conducted fortnightly) and a booster session after 3 months, with each session lasting 45 min. In the first session, the patient's expectations regarding symptoms and treatment will be assessed through a semi-structured interview so that the intervention can be adapted to the individual patient expectations within the framework of the treatment manual. The intervention components include psychoeducation aimed at developing a biopsychosocial model of Long COVID and realistic, yet functional expectations regarding symptoms and treatment outcome, visualisation techniques to foster expectations of personal control and developing personal goals in managing symptoms to improve coping expectations. In a 'toolbox', illness-specific dysfunctional expectations (e.g. 'I can't take the stairs because I'm too short of breath') are assigned to specific therapeutic interventions (e.g. cognitive restructuring, fostering positive expectations via visualisation and addressing confidence in expectations, counteracting cognitive immunisation). To deepen the acquired skills, homework will be given after each session and discussed at the beginning of the following one. The intervention thus addresses the topics 'dealing with anxiety', 'improving expectations' and the need for information about their disease. By conducting focus groups, the intervention protocol and manual will be finalised in collaboration with patients from a Long COVID group currently offered in our psychosomatic out-patient clinic.

Experimental intervention 2 (COV.SUPPORT + TAU)

The experimental intervention consists of a non-specific supportive intervention (COV.SUPPORT) in addition to TAU. COV.SUPPORT is identical to COV.EXPECT in terms of common and non-specific treatment elements (i.e. time, personal attention and emotional support), but does not use specific interventions to modify illness-related anxiety and expectations. In contrast to COV.EXPECT, which focuses primarily on changing dysfunctional symptom expectations for the future, COV.SUPPORT focuses exclusively on coping with stressful situations in the present. COV.SUPPORT is manualised and adapted from the supportive therapy we use in the PSY-HEART-II trial.[29] This unspecific intervention is needed to differentiate our proposed mechanism of action from general modes of action.

Control intervention (TAU)

The control intervention consists of TAU only. TAU in all study groups implies that the patient receives their usual treatment without any interference by the study. This group is also needed to identify risk factors for the persistence of Long COVID symptoms (objective 2) and compare risk factors for symptom persistence across conditions with results from the SOMACROSS Research Unit (objective 3).

Assessment and study outcomes

Measurement points

Assessments are carried out at baseline and after 6 weeks (intermediate), 3 months (post-interventional) and 6 months (follow-up). The intermediate assessment after 6 weeks is necessary for mediator analyses that investigate whether a change in symptom severity is mediated via changes in illness-related anxiety and dysfunctional symptom expectations. Except for an additional 12-month follow-up in the SOMACROSS Research Unit, assessment times are identical, allowing for comparison of results. Primary and secondary outcomes and mediator variables will be collected through electronic data entry by patients at home; only the diagnostic interview will be collected via telephone interview. The primary and secondary outcome variables and mediator variables will be measured at each assessment point, and are displayed in Table 1.

Primary outcome

To test the effect of the expectation management intervention on Long COVID symptoms, the primary outcome for this study is the baseline to post-interventional change in overall somatic symptom severity (3-month follow-up). As harmonised core outcome sets for Long COVID and post-COVID-19 conditions are currently still being developed, overall symptom severity will be assessed with the established PHQ-15,[25] which is validated in English and German in various diseases and has proven its sensitivity to change as an outcome instrument in many studies.[30] On a scale of 0 ('not bothered at all') to 2 ('bothered a lot'), the PHQ-15 uses 15 items to measure somatic symptom severity during the past 4 weeks. It includes most of the common Long COVID symptoms and enables us to compare our results to the SOMACROSS Research Unit, which also uses the PHQ-15 as a primary outcome instrument.[9]

Secondary outcomes

Secondary outcomes include symptoms that have been found to be of special relevance in Long COVID, such as fatigue,[31] post-exertional malaise[32] and pain.[33] We will also include a self-developed screening questionnaire on Long COVID as well as other post-infectious symptoms. This self-report instrument, called the PHQ-15 Post-Acute Infection Syndromes (PHQ-15 PAIS), is based on the PHQ-15[25] and extended for the most common symptoms in post-acute infection syndromes.[34] Illness-related anxiety (Somatic Symptom Disorder – B Criteria Scale (SSD-12)),[35] expectations of symptom

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Table 1 Outcome instruments of the SOMACOV study

Predisposing, triggering and maintaining/aggravating factors	Single constructs	Instrument	Assessment time: 0 months	6 weeks	3 months	6 months
Outcome variables (assessed via self-report/diagnostic interview)						
Primary outcome: somatic symptoms	Overall somatic symptom severity	Patient Health Questionnaire-15 (PHQ-15)	X	X	X	X
Secondary outcomes: symptom-related disability	SARS-CoV-2 infection and Long COVID	Single items	X	X	X	X
	Long COVID symptoms	Patient Health Questionnaire-15 Post-Acute Infection Syndromes (PHQ-15 PAIS)	X	X	X	X
	Fatigue	Fatigue Scale (FS)	X	X	X	X
	Post-exertional malaise	DePaul Symptom Questionnaire Post-Exertional Malaise (DSQ-PEM)	X	X	X	X
	Pain	Pain Disability Index – adapted (PDI)	X	X	X	X
	SOMACROSS core measures[9]	Self-report instruments	X	X	X	X
Diagnosis of somatic symptom disorder (DSM-5)	Diagnostic classification	Structured Clinical Interview for the DSM-5 (SCID-5)	X		X	
Prespecified mediator variables (assessed via self-report)						
Cognitive-perceptual and emotional mechanisms	Illness-related anxiety	Somatic Symptom Disorder – B Criteria Scale (SSD-12)	X	X	X	X
	Treatment expectations	Treatment Expectation Questionnaire (TEX-Q)	X	X	X	X
	Expectation of symptom severity	Numeric Rating Scale (NRS)	X	X	X	X
	Expectation of symptom burden	Numeric Rating Scale (NRS)	X	X	X	X
	Expectation of coping with symptoms	Numeric Rating Scale (NRS)	X	X	X	X

severity, burden, treatment outcome and coping with symptoms (Treatment Expectation Questionnaire (TEX-Q); European Research Network to Improve Diagnosis, Treatment and Health Care for Patients with Persistent Somatic Symptoms (EURONET-SOMA) numeric rating scales)[36,37] will be investigated as pre-specified mediator variables. The treatments received will be documented. In addition to Long COVID-specific outcome variables, we will apply the joint core measures of the SOMACROSS Research Unit to identify further risk factors and mechanisms for symptom persistence in Long COVID, and to make the results of the studies comparable. The joint core set of instruments is described in detail in the overarching protocol of the SOMACROSS Research Unit.[12] Supplements from the core set include, for example, adverse childhood experiences, negative affectivity, stigmatisation, health-related quality of life and healthcare utilisation. As in the research unit, we will also conduct the Structured Clinical Interview for the DSM-5 (SCID-5) for the diagnosis of somatic symptom disorder according to the DSM-5, to investigate the diagnosis as a potential predictor of treatment response.

Safety outcomes

To the best of our knowledge, there is no risk for serious adverse events caused by the application of expectation management interventions.[27] However, patients may develop severe somatic complications of Long COVID or other medical conditions. In these cases, patients will be informed and advised to initiate appropriate treatment. In case of an emergency, medical treatment will be initiated at the University Medical Center Hamburg-Eppendorf. Any adverse events will be systematically recorded at each follow-up assessment.

Sample size

This trial is powered with regard to the difference between intervention 1 (COV.EXPECT + TAU) and the control condition (TAU), as this is the main interest. Because of the closed testing principle, the type one error (alpha) does not need to be adjusted for multiplicity. As there are no comparable trials on Long COVID available, we based our estimation both on our DEPSCREEN-INFO trial (Increasing the Efficiency of Depression-Screening using Patient-Targeted Feedback),[38] which yielded a between-group effect size of $d = 0.33$ in PHQ-15 scores with an intervention of much lower intensity (written feedback after depression screening), and on the PSY-HEART trial,[27] which yielded a medium between-group effect size of $d = 0.71$ with an expectation management intervention, but using a different outcome instrument (modified version of the Pain Disability Index). Based on these two studies, we expect a medium effect size ($d = 0.50$) that can be detected with a power of 80%, using a two-sided alpha of 5%, by including 64 patients in each group, resulting in a total sample size of $N = 192$. Based on the results of our previous studies, we assume a loss to follow-up between baseline and the primary outcome measurement (i.e. 3-month follow-up) of 25%, resulting in a total of 258 randomised patients. Assuming that 50% of patients will meet the inclusion criteria, a total of 516 patients will be assessed for eligibility. Figure 2 shows the anticipated flow of participants throughout the trial.

Statistical methods

The primary analysis and all prespecified secondary analyses will be conducted in the intention-to-treat sample consisting of all randomised patients with the full analysis set, which is as close as possible to the intention-to-treat population. In secondary analyses, the data of the per-protocol population (subgroup of patients without major protocol violations) will be used and multiple imputation will be applied.

For objective 1, a linear mixed-effects model with the change from baseline for all measured time points will be used to investigate the group differences in the PHQ-15, with treatment group, time and gender as fixed effects, patient as the random effect and baseline PHQ-15 score as the covariate. The interaction between time and treatment group will be tested and excluded from the model if $P \geq 0.05$. For primary hypothesis, the global treatment effect after 3 months will be considered first. If the two-sided P-value is

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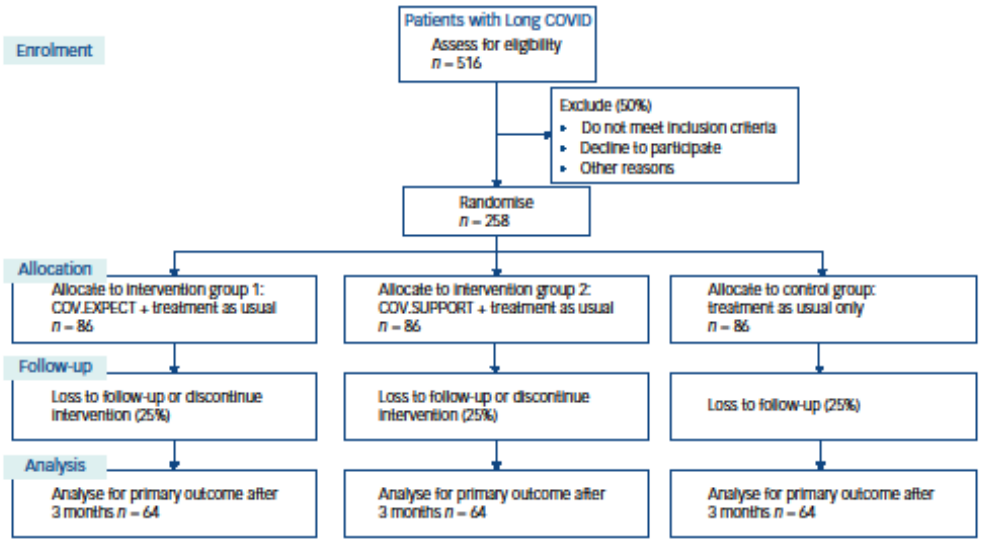

Fig. 2 Anticipated flow of participants through the course of the study. Outcomes after 6 months are secondary and were not included in the sample size estimation. COV.EXPECT, expectation management intervention; COV.SUPPORT, supportive intervention.

<0.05, the contrasts in change after 3 months for COV.EXPECT versus TAU, COV.SUPPORT versus TAU and COV.EXPECT versus COV.SUPPORT at the 5% level (two-sided hypothesis) will be considered. Because of the closed testing principle, an adjustment of the contrast *P*-values for multiplicity is not necessary.

Secondary end points will be analysed analogously to the primary end point, with the regression model corresponding to the measurement scale (mixed linear model for metric outcomes, mixed logistic model for binary outcomes, cumulative logit model for ordinal outcomes).

In subsidiary analyses, a potential effect of recruitment settings will be investigated by including the setting as a further fixed effect in the analysis. To analyse whether treatment effects on Long COVID resulted through changes in illness-related anxiety or symptom expectations, we will conduct mediation analyses.

To identify further risk factors involved in the persistence of Long COVID (objective 2), we will use longitudinal data from the control group and conduct multivariate regression analyses with symptom persistence as outcome, taking into account the number of predictors and sample size. Patients from the intervention groups will not be included in these analyses because the interventions could bias the results.

To compare risk factors and mechanisms of somatic symptom persistence in Long COVID exploratively with those identified in the other conditions investigated in the SOMACROSS Research Unit (objective 3), we will compare the results of the disease-specific regression analyses from the SOMACROSS Research Unit with the derived model from objective 2, and conduct further exploratory analyses.

Subgroup analyses will be conducted on differences in the primary outcome with respect to the following variables of interest: age, gender, education level, social support, duration and severity of Long COVID, any chronic physical disease, any mental health comorbidity, depression and anxiety. For safety analyses, adverse events will be compared between groups and analysed descriptively. Further details of statistical analyses will be described in detail in a statistical analysis plan, which will be finalised before breaking the treatment blind.

Methods against bias

A fixed randomisation list with variable block size and length, stratified by gender, will be generated by an independent member of the biostatistics unit and uploaded into REDCap version 13.7.7 for Windows (REDCap Consortium; see www.projectredcap.org), a software for building and managing online surveys and databases. Assignment will be performed automatically after inclusion in the database. Patient drop-out will be minimised by contacting patients according to a schedule of repeated contact attempts, and by allowing solely written or telephone data collection if electronic collection is not feasible. Because of the electronic collection of outcome variables and having the telephone interviews conducted by trained interviewers who are not involved in the treatment, the study is fully observer-blinded with respect to all treatment conditions. Treating physicians will not be informed about the group allocation or the type of intervention. As in most psychological intervention studies, full patient and therapist blinding is not feasible as their active involvement in the intervention is necessary. Still, patients in the active intervention groups will be blinded. Both interventions will be manualised and therapists and interviewers will be trained and supervised. As a manipulation check regarding potentially overlapping content, contamination and carry-over effects between the two interventions, patients will complete a rating scale on treatment content and on subjective treatment mechanisms after the post-intervention outcome assessment. Potential sampling bias will be avoided by recruiting patients both within and outside of psychotherapeutic care, and by aiming to include both patients with shorter and longer symptom duration in the study. Any questions regarding patient exclusions, serious adverse events and potential

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study termination will be reviewed by the study's Data Safety and Monitoring Board. Finally, report of the trial and results will follow the Consolidated Standards of Reporting Trials (CONSORT) 2010 recommendations.[39]

Feasibility of recruitment

In previous studies, we were able to successfully recruit patients within our network of cooperating general practitioners, e.g. in the three-arm GET.FEEDBACK.GP-RCT (depression screening using patient-targeted feedback in general practices).[40] In addition, resident pulmonologists, our pulmonary out-patient clinic and our psychosomatic out-patient clinic, three self-help groups and patient associations, and social media will support recruitment. The format as an online video consultation and the brevity of the intervention will also facilitate patient enrolment. We expect a high willingness to participate in a psychosocial intervention study for Long COVID symptoms, as patients express high needs in this direction and this area is considered to be massively undersupplied so far.

Ethics and dissemination

Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the Local Psychological Ethics Committee at the Center for Psychosocial Medicine of the University Medical Center Hamburg-Eppendorf on 14 February 2022 (approval number LPEK-0446). The trial will further be conducted in accordance with guidelines for Good Clinical Practice, and national and local laws. Before inclusion, eligible participants will provide written informed consent. Data will be stored in the REDCap database in pseudonymised form. A corresponding data management manual and a data review plan will be finalised before recruitment of the first patient. Any changes to the study protocol will be listed in the study registry and publications. The study is registered with the ISRCTN Registry (identifier ISRCTN15068418).

Data sharing

In accordance with the ethics committee approval and the DFG guidelines for the handling of research data adopted in 2015, de-identified individual patient data will be made publicly available. Data sharing will be in accordance with the FAIR data principles (Findable, Accessible, Interoperable, and Reusable) and international naming conventions (e.g. Systematised Nomenclature of Medicine) to maximise transparency and scientific reproducibility. According to the WHO Statement on Public Disclosure of Clinical Trials (https://www.who.int/ictrp/reporting-on-findings), the main findings will be submitted for publication in a peer-reviewed journal within 12 months of study completion.

Results

The results of this study will be published in peer-reviewed journals, presented at national and international conferences, and communicated in lay language to self-help groups and patient associations.

Discussion

Long COVID is associated with a high burden for those affected, and poses a growing challenge to healthcare systems worldwide. Given that a causal therapy and concrete treatment recommendations are missing so far,[3] effective and scientifically sound treatment options need to be developed for patients suffering from Long COVID. Study results suggest that illness-related anxiety[2–4] and dysfunctional symptom expectations[5,6] play a role in the development of PSS after COVID-19, thus representing a promising therapeutic target for a Long COVID intervention. Since a growing body of research provides evidence that targeted expectation management improves clinical outcomes,[24,27] we assume that enhancing realistic positive and reducing dysfunctional symptom expectations might also lead to improved clinical outcomes in patients with Long COVID.

To the best of our knowledge, this is the first study to investigate the modifiability of a specific psychological mechanism of symptom persistence in Long COVID. The results of our analyses for hypothesis 1 will allow us to draw conclusions regarding the applicability, potential efficacy and mechanisms of a targeted expectation management intervention for patients with Long COVID. If the effectiveness of the intervention via the proposed mode of action can be proven, it can be used stand-alone or in the context of a broader therapeutic approach, and might thus have an important clinical and potentially socioeconomic impact. The results regarding objective 2 will significantly contribute to a better understanding of symptom persistence in Long COVID, and will shed light on disease-specific risk factors and mechanisms in addition to illness-related anxiety and dysfunctional symptom expectations. Overall, this study will contribute to a better understanding of the contribution of psychological factors to Long COVID symptoms, and thereby advance the development of comprehensive care for patients. Data regarding mechanisms of symptom persistence from the control group will be pooled and compared with data from the SOMACROSS Research Unit.[9] The results of whether the mechanisms of symptom persistence are disease-specific or also effective across diseases will contribute to the further development of our aetiological model for PSS across diseases.

Although early data on the frequency of Long COVID came from hospitalised cohorts, Long COVID has been shown to occur at very similar rates in patients with mild acute symptoms treated in ambulatory care.[41] Because of different study designs and assessment times, use of unvalidated measures, lack of inclusion of control groups and focus on individual symptoms instead of Long COVID as a diagnostic entity, the exact prevalence of Long COVID and its natural course are currently difficult to estimate. Nevertheless, the high rate of infected people worldwide and significant number of PSS after a SARS-CoV-2 infection suggest that research into the mechanisms of symptom persistence, as well as treatment options, is of the highest clinical relevance.

One limitation of this study might be its particular focus on illness-related anxiety and dysfunctional symptom expectations as potential risk factors for Long COVID. However, it is inevitable to focus on selected promising constructs, as it is not feasible to investigate all potential risk factors simultaneously. The mere use of self-report instruments is another limitation. Medical aspects, including a history of COVID-19, will be collected from patient information only and will not additionally be verified by patient records or SARS-CoV-2 antibody tests. The fact that fewer people are getting tested for SARS-CoV-2 since the COVID-19 pandemic has progressed and containment measures have been relaxed could lead to a potential sampling bias, with predominantly more patients with longer symptom duration participating in the study.

A challenge in the conduction of the study could be that some patients might be reluctant to consider psychological factors in the pathophysiology of Long COVID, which could potentially result in a lower participation rate or a higher drop-out rate than expected. To counteract this issue, we will collaborate with patient

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associations and self-help organisations to jointly establish communication strategies. We will also involve affected patients in the development of our expectation management intervention, an aspect that we will include in our study materials (e.g. leaflets). During the intervention, multiple mechanisms in the emergence of Long COVID will be addressed in a sensitive manner, outlining psychological variables as being one of several relevant factors for the development of Long COVID. To enhance comprehensibility, illustrative examples of everyday life will be used carefully in the conveyance of a biopsychosocial model. Finally, as part of screening interviews, potential participants will receive conclusive information about the study before inclusion to prevent drop-outs.

Considering the scientific evidence, the clinical relevance of Long COVID and the high level of suffering of affected patients, the attempt to investigate whether a targeted modification of illness-related anxiety and dysfunctional symptom expectations has a beneficial effect on Long COVID symptoms seems to be a valuable endeavour. Evidence of an effect of modifying illness-related anxiety and dysfunctional symptom expectations on Long COVID symptoms would identify an important mechanism of action, as well as be a promising starting point for future treatments for Long COVID.

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Data availability

The data that support the findings of this study will be available from the corresponding author, P.E., on reasonable request.

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Author contributions

P.E., B.L. and A.Z. are principal investigators of the study. P.E. drafted the first version of the study protocol. All authors contributed to the refinement of the study protocol, and read and approved the final version.

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Declaration of interest

None.

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8.3. Study III

Psychological factors associated with Long COVID: a systematic review and meta-analysis

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Psychological factors associated with Long COVID: a systematic review and meta-analysis

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Summary

Background Despite the immense impact of Long COVID on public health and those affected, its aetiology remains poorly understood. Findings suggest that psychological factors such as depression contribute to symptom persistence alongside pathophysiological mechanisms, but knowledge of their relative importance is limited. This study aimed to synthesise the current evidence on psychological factors potentially associated with Long COVID and condition-relevant outcomes like quality of life.

Methods In this systematic review and meta-analysis, MEDLINE, PsycINFO, and the Cochrane Database of Systematic Reviews were searched for peer-reviewed studies published in English from 2019 to January 2, 2024. Studies providing cross-sectional or longitudinal data on the association between at least one psychological variable and the presence of Long COVID (primary outcome) or condition-relevant secondary outcomes (symptom severity, impairment, quality of life, and healthcare utilisation) were included. Psychological constructs with at least five comparisons were pooled as odds ratio (OR) for categorical data and standardised mean difference (SMD) for continuous data in random-effects meta-analyses of cross-sectional studies with control groups. This review is registered with PROSPERO, CRD42023408320.

Findings 113 studies (n = 312,831 patients with Long COVID) provided data on at least one psychological variable, 63 in cross-sectional group comparisons, 53 in cross-sectional associations, and 18 longitudinal. Most reported findings related to depression and anxiety, and — less frequently — to physical activity, posttraumatic stress disorder, stress, and history of mental illness. Depression (OR 2.35; 95% CI, 1.49–3.70) and anxiety (OR 2.53; 95% CI, 1.76–3.61) were significantly associated with Long COVID and higher in affected patients than controls (depression: SMD 0.88; 95% CI, 0.66–1.11; anxiety: SMD 0.74; 95% CI, 0.50–0.99), while results for physical activity and stress were non-significant. In most prospective studies, the investigated psychological constructs significantly predicted Long COVID.

Interpretation Evidence suggests depression and anxiety to be co-occurring phenomena and predictive factors of Long COVID. Future studies should prospectively investigate psychological constructs such as emotion regulation or dysfunctional symptom expectations, which are well-known risk factors and therapeutic targets of persistent somatic symptoms in other medical conditions, but are so far understudied in Long COVID.

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Keywords: Long COVID; Post COVID-19 condition; Persistent somatic symptoms; Biopsychosocial model; Psychological factors

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Research in context

Evidence before this study

Besides pathophysiological mechanisms, a growing number of studies indicate the potential role of psychological factors in the development and maintenance of Long COVID. Previous reviews of risk factors for Long COVID confirmed the importance of depression and anxiety; however, a broad spectrum of further psychological variables possibly involved in the persistence of somatic symptoms, such as emotion regulation or dysfunctional symptom expectations, has been relatively overlooked. To improve the understanding of Long COVID and inform research into much-needed treatments, aggregating the available evidence on psychological factors associated with Long COVID is of high relevance. We searched MEDLINE, PsycINFO, and the Cochrane Database of Systematic Reviews for peer-reviewed studies published in English from 2019 to January 2, 2024. Studies were required to report a) cross-sectional comparisons on psychological factors between patients with Long COVID and controls, b) cross-sectional associations with Long COVID or condition-relevant outcomes (symptom severity, impairment, quality of life, and healthcare utilisation), or c) prospective relations between psychological factors and Long COVID. 113 eligible studies of mostly fair quality included 312,831 patients with Long COVID and provided data for 58 psychological constructs in total.

Added value of this study

Of all psychological variables investigated, this systematic review could only confirm higher levels of depression and anxiety in individuals with Long COVID compared to controls in meta-analyses. Both factors were also predictive of Long COVID in longitudinal studies. The scarce evidence base for all other psychological variables hinders reliable conclusions.

Implications of all the available evidence

The results of this review, together with previous studies, support that depression and anxiety should be considered in multidisciplinary Long COVID treatments. Future studies should examine psychological constructs such as emotion regulation or expectations, which are well-known risk factors and therapeutic targets of persistent somatic symptoms in other medical conditions, but are so far understudied in Long COVID. Large methodological heterogeneity of the identified studies points to the need of guidelines for research on Long COVID.

Introduction

Five years after the outbreak of the COVID-19 pandemic, the aetiology of Long COVID[1] is far from being clearly understood. Investigations into the pathophysiology of persistent somatic symptoms after SARS-CoV-2 infection have remained inconclusive so far, with no diagnostic markers known to fully explain them[2] and several reports of objective clinical examinations discrepant with subjective symptom burden.[3–5] While a growing body of research suggests that psychological factors like depression or anxiety contribute to the development and maintenance of Long COVID in addition to pathophysiological changes,[6–8] the discussion about the involvement of psychological processes in its aetiology also raises critics who fear a "psychologisation" of the condition.[6,9]

Persistent somatic symptoms remain after many infectious diseases[10] and are generally common in the general population.[11] Research into persistent somatic symptoms and chronic medical diseases indicates accompanying psychological features such as health anxiety or negative expectations to be more crucial for impairment in quality of life or increase in healthcare utilisation of affected patients than the severity of the somatic symptoms per se.[12] Accordingly, evidence-based etiological models clearly argue for the contribution of both biomedical and psychological mechanisms to the development and persistent course of somatic symptoms.[13–15] Besides depression and anxiety,[16,17] aggravating factors include cognitive-perceptual mechanisms such as selective attention, somatosensory amplification,[18] and catastrophising.[19,20] Additional assumed maintaining factors are unhelpful symptom-related behaviours like physical inactivity and dysfunctional healthcare use.[21,22] Emotion regulation deficits, adverse childhood experiences, negative affectivity, or life stressors[23,24–26] can predispose the development of persistent somatic symptoms. The same complex bio-psychosocial interactions including a broad spectrum of psychological mechanisms can also be assumed for processes of symptom development and persistence in Long COVID.

While not accounting for non-affected control groups, van der Feltz-Cornelis et al.[26] recently meta-analysed the all-time prevalence of any mental health condition in patients with Long COVID. They found a prevalence of 20.4%, with most studies on depression and anxiety, and the odds of mental health conditions significantly increasing over time after acute infection. Previous systematic reviews and meta-analyses of risk factors for Long COVID have largely neglected the role of psychological risk factors other than depression and anxiety.[7,27]

Regarding further potentially relevant psychological concepts, Hüsing et al.[28] developed the PSY-PSS framework for systematic reviews to support the aggregation of empirical evidence on psychological (risk) factors in persistent somatic symptoms and related

conditions. It provides the first comprehensive list of psychological variables to be considered in this field of research, which is constantly being expanded and has recently been applied in a systematic review of psychological risk factors for somatic symptom disorder.[29] Considering Long COVID as dominated by persistent somatic symptoms, it is likely that the psychological constructs compiled in the PSY-PSS framework are also relevant with regard to this condition.

This study aimed to systematically review literature providing original data on psychological constructs associated with Long COVID and Long COVID-relevant outcomes by applying the PSY-PSS framework[28] and, where possible, pool data using meta-analyses. For an individual psychological variable to be of relevance for Long COVID, it should either 1) be significantly higher in patients with Long COVID compared to controls, or 2) show a significant association with Long COVID or condition-relevant outcomes (symptom severity, impairment, quality of life, and healthcare utilisation), or 3) prove as a significant predictor of the development or maintenance of Long COVID. Consequently, three methodological approaches were followed and translated into the following three research questions (RQs):

1) In which psychological factors do patients with Long COVID report significantly higher values compared to control groups (cross-sectional group comparisons; RQ1)?
2) Which psychological factors are significantly associated with the presence of Long COVID or condition-relevant outcomes such as symptom severity, impairment, quality of life, and healthcare utilisation (cross-sectional associations; RQ2)?
3) Which psychological factors significantly predict the development or maintenance of Long COVID (longitudinal data; RQ3)?

Methods

This systematic review and meta-analysis was preregistered on PROSPERO (CRD42023408320) and was conducted and reported in accordance with the PRISMA guidelines as well as the MOOSE reporting guidelines for meta-analyses of observational studies.[30] It is the second review that emerged from a proposed framework of systematic reviews designed to facilitate research in the area of persistent somatic symptoms (PSY-PSS[28]) and follows the methodology outlined in the PROSPERO registration (CRD42022302014). Ethical approval was not sought or required, as the study involved no individual patient data.

Eligibility criteria

Articles were eligible if written in English and published in a peer-reviewed journal since 2019, i.e., since the COVID-19 outbreak. Studies were required to report original, quantitative data on at least one of the pre-defined psychological variables from the comprehensive list of the PSY-PSS framework by any tool of measure in patients of any age group who self-report to suffer from or have received a clinical diagnosis of Long COVID according to the NICE guideline (i.e., somatic symptoms that develop during or after SARS-CoV-2 infection, continue for at least 4 weeks, and are not explained by an alternative diagnosis).[1] Studies that referred to other conditions or used an unclear definition of Long COVID were excluded.

Studies needed to provide a) cross-sectional comparisons between patients with Long COVID and controls, b) cross-sectional associations, or c) longitudinal data on the relation between psychological variables and the presence of Long COVID (primary outcome) or condition-relevant secondary outcomes (i.e., symptom severity, impairment defined as impaired functioning in activities of daily living,[31] quality of life, or healthcare utilisation). Preprints, case reports, purely qualitative studies, reviews and meta-analyses with no new data, study protocols, editorials, comments, letters, conference abstracts, and grey literature such as dissertations were excluded. Studies using results from previous publications (secondary analyses) were not included to prevent bias.

Study selection

To ensure all relevant publications on Long COVID were found, an extensive list consisting of the 21 most commonly used terms for Long COVID in pertinent publications and guidelines[1,32] in a variation of spellings was compiled. For psychological factors, the comprehensive list of the PSY-PSS framework[28] was applied, which was generated to be used as search terms for literature reviews on persistent somatic symptoms. This list has a hierarchical structure, with seven overarching categories of psychological mechanisms (affective, cognitive, behavioural, psychophysiological, personality & interpersonal factors, prior experiences, and psychopathology) containing 120 psychological variables overall (e.g., emotion regulation, expectations, or illness behaviour; list and search terms can be found in the open science framework: https://osf.io/anbm6). All 120 terms from the list of potentially relevant psychological factors were crossed with all 21 Long COVID terms. The literature search was first run on 06/25/2023, and updated on 01/02/2024 using the bibliographic databases MEDLINE (via PubMed), PsycINFO (via OvidSP), and the Cochrane Database of Systematic Reviews (via Cochrane Library). The search syntax string including the precise search terms is available in eAppendix 1 in the Supplement. Due to the large number of hits, a manual search in the reference lists of obtained articles was not carried out.

Endnote[33] was used to combine identified studies from all databases. Three authors (CS, MR, PE) removed

duplicates and screened study titles and abstracts using the software Rayyan.[14] Conflicts were resolved following discussion between the three authors. Studies identified for full-text review were independently reviewed twice against eligibility criteria by initially blinded authors (PE, MR, CS, SS, AT, MSM). Disagreements during full-text review were cleared through consultation of other authors (PE, MR, CS, SS, AT, MSM).

Data extraction

Full-text data extraction was independently completed and summarised in one descriptive and three results tables (one for each RQ) by four authors (PE, MR, CS, AT). Descriptive data comprising study design and objectives, sample characteristics, diagnostic criteria used for Long COVID, and a short summary of key results were extracted for all studies. If control groups were described as individuals without prior SARS-CoV-2 infection and not explicitly labelled as diagnosed with another medical condition, they were categorised as "healthy controls without a history of COVID-19". For cross-sectional associations and longitudinal evidence (RQ2 and RQ3), condition-relevant outcomes and their assessment along with effect sizes (if reported) were compiled. Besides the operationalisation of the respective construct, the following data were retrieved regarding psychological variables: raw measures of central tendency, frequencies, significance statistics, and effect sizes for each group in cross-sectional comparisons (RQ1), correlations and proportions for cross-sectional associations (RQ2), and predictive testing for longitudinal studies (RQ3). When reported data were inconsistent or incomplete, corresponding authors were contacted for clarification during the data extraction process.

Statistics

The study quality assessment tools of the National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) were employed to assess study quality and bias. Two authors (PE, AT) independently evaluated each study. Disparities were discussed between the two authors until reaching agreement.

To provide a concise overview of the available evidence for each psychological construct investigated so far in any of the included study designs, results were further summarised in a synthesis table. Meta-analyses were conducted if valid data was available for at least five studies per psychological variable, per type of data (psychological features in categorical vs. continuous format), and per outcome variable (for RQ2 and RQ3). The minimum number of studies for meta-analysis was increased from three to five compared to the predefined number stated in the PROSPERO registration (CRD42023408320) in favour of the robustness of findings given the heterogeneous assessment of psychological variables.

Meta-analyses were performed separately for psychological variables measured categorically (e.g., diagnosis of depression) and continuously (e.g., depression severity). If studies did not report the same central tendencies, corresponding authors were asked to provide mean values to integrate all continuous data. For studies that reported several follow-ups on persistent symptoms after SARS-CoV-2 infection, the first follow-up was used to be able to run analyses with the highest pooled sample size possible. Control groups of studies that examined both healthy controls without a history of SARS-CoV-2 infection and patients after SARS-CoV-2 infection without Long COVID were merged into one control group since no relevant differences between these two groups were assumed (i.e., healthy controls might have had a hidden infection).[15] Studies with other control groups were excluded from meta-analyses due to an insufficient number of studies.

Due to the presumed heterogeneity between studies, random-effects models with raw data were employed. Effect sizes were estimated as odds ratio (OR) for categorical data and standardised mean difference (SMD) for continuous data. Heterogeneity between studies was quantified using I^2. Risk for publication bias was assessed graphically through funnel plots and statistically with Egger's regression test. In case of significance, the trim-and-fill method was applied. Sensitivity analyses were conducted by first excluding studies with the greatest weight, then those with the smallest sample size ($n < 20$ per group), and again by excluding studies rated as poor in the quality assessment. All analyses were performed in RStudio version 4.2.3.[16]

Role of the funding source

There was no funding source for this study.

Results

A PRISMA flow diagram of study selection is displayed in Fig. 1. Descriptive information of all included studies is shown in eTable 1 in the Supplement. Three results tables split by RQs 1–3 can be found in the Supplement (eTables 2–4).

Study characteristics and overall results

A final of 113 studies (see eReferences) were included in the review, assessing 312,831 patients with Long COVID. Sixty-eight studies were conducted in Europe (most frequent: Germany), followed by Northern America (32; most frequent: USA), Asia (24; most frequent: China), Latin America (16; most frequent: Brazil), and Australia (1), with several studies involving multiple countries. 63 studies provided data on at least one psychological construct in cross-sectional group comparisons, 53 in cross-sectional associations, and 18 longitudinal format (eTable 1 in the Supplement). According to the categories of the PSY-PSS framework,[28]

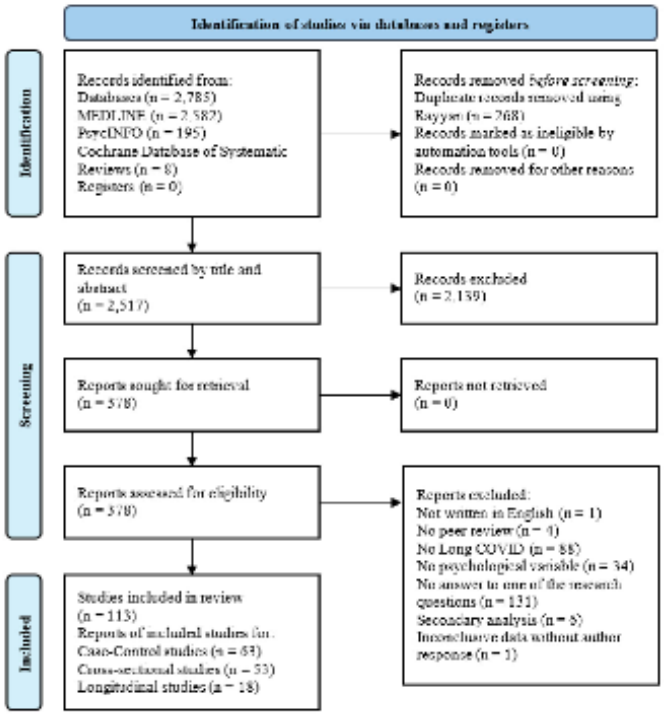

Fig. 1: PRISMA flow diagram. Note. Some studies give information for more than one research question.

most studies (20) investigated signs of psychopathology, followed by cognitive factors and personality & interpersonal factors (11 each), affective and behavioural factors (5 each), and psychophysiological factors (4). For an overview of all 58 psychological features examined in total, their respective category, and their number of investigations, separated by research question, see eTable 5 in the Supplement. The available evidence for each psychological concept assessed in patients with Long COVID in each included study design is synthesised in Table 1.

For RQ1, meta-analyses could be calculated for depression (17 categorical and 24 continuous comparisons), anxiety (15 categorical and 16 continuous comparisons), physical activity (6 continuous comparisons), and stress (5 continuous comparisons). The variable "depression/anxiety", which comprises measures of either "depression or anxiety" or "depression and anxiety" as reported in the included studies, was not meta-analysed due to the higher informative value of depression and anxiety alone. For RQ2 and RQ3, it was not possible to conduct meta-analyses for any psychological factor due to highly heterogeneous outcome variables and statistical coefficients for both categorical and continuous data. The diverse operationalisation of psychological variables can be viewed for those with at least five observations, along with the respective control groups (for RQ1) or outcomes of the studies (for RQ2 and RQ3), in eTables 6–17 in the Supplement.

Research question 1: In which psychological factors do patients with Long COVID report significantly higher values compared to control groups (cross-sectional group comparisons)?

Patients with Long COVID were compared to patients after SARS-CoV-2 infection but without Long COVID in 44 studies, to healthy controls without a history of COVID-19 in 24 studies, to patients with chronic fatigue syndrome in two studies, and to patients with fibromyalgia and post-concussion syndrome in one

Psychological variable	RQ1 (cross-sectional group comparisons)	RQ2 (cross-sectional associations)		RQ3 (longitudinal data)	
		Sig. association	No sig. association	Sig. prediction	No sig. prediction
Depression	LC > CO (27)[37–48]/HC (17)[37,44–46,55,59,61,64,73] LC = CO (4)[37,39,74,75]/HC (4)[37,64,74,77]/FMS (1)[76]/CFS (1)[78]/PCS (1)[79] LC < ME/CFS (1)[80]	QoL (9),[43,81–88] fatigue (6),[43,51,69,90,91,93] impairment (5),[60,86,90–92] LC (4),[54,57,103,56] number of persistent symptoms (4),[40,64,65,94] cognitive deficits (4),[97–100] pain (2),[90,93] gastrointestinal symptoms (1)[95]	LC (3),[40,45,101] number of persistent symptoms (1),[52] cognitive deficits (1)[102]	LC (7),[4,6,47,103–106] impairment (2),[6,106] fatigue (2)[55,107]	LC (2),[50,108] fatigue (1),[105] pain (1),[109] respiratory symptoms (1)[109]
Anxiety	LC > CO (18)[37,39,40,43–45,47,49,53,54,55,57,59,61–63,110]/HC (13)[37,45,46,55,61,64–69,71–73] LC = CO (6)[37,39,57,74,75,111]/HC (4)[37,44,46,77]/ME/CFS (1)[80]/FMS (1)[76]/CFS (1)[78]/PCS (1)[79] LC < ME/CFS (1)[80]	QoL (5),[81,84,86–88] number of persistent symptoms (5),[40,52,64,65,94] fatigue (4),[69,90,91,93] cognitive deficits (4),[97–100] LC (3),[40,54,93] impairment (2),[91,92] pain (2),[90,93] gastrointestinal symptoms (1)[95]	QoL (4),[83,85,85,112] impairment (1),[90] fatigue (1),[30] pain (1)[90]	LC (3),[4,6,110] impairment (1),[6] cognitive deficits (1)[107]	LC (3),[50,67,108] fatigue (1),[105] pain (1),[109] respiratory symptoms (1)[109]
Physical activity	LC = CO (2)[55,113]/HC (1)[114] LC < CO (3)[45,59,115]/HC (4)[45,55,67,76]	LC (1),[116] symptom severity (1),[56] impairment (1),[56] QoL (1),[117] overall health (1)[56]	LC (3),[115,116,118] QoL (2)[86,117]	LC (1)[119]	–
Depression/ Anxiety	LC > CO (6)[44,49,120–123]/HC (2)[66,124] LC = CO (1)[125]/HC (1)[114]	LC (2),[126,127] fatigue (2),[53,128] impairment (1),[126] QoL (1)[127]	–	LC (1),[121] respiratory symptoms (1)[129]	LC (1)[125]
PTSD	LC > CO (4)[44,47,63,122]/HC (2)[46,73] LC = CO (2)[49,75]	LC (1),[53] number of persistent symptoms (1),[55] gastrointestinal symptoms (1)[95]	fatigue (1)[130]	–	–
Stress	LC > CO (2)[45,59]/HC (2)[45,64] LC = CO (3)[57,75,131]/HC (1)[77]/PCS (1)[79]	QoL (1)[81]	QoL (1)[81]	LC (2),[6,106] impairment (2)[6,106]	–
History of mental health disorders	LC > CO (3)[20,133,132] LC = CO (2)[20,74] LC < CO (1)[135]	LC (3)[133–135]	LC (1)[131]		fatigue (1)[53]
Alcohol abuse/ dependence	LC = CO (2)[49,134]/PCS (1)[79]	–	–	–	–
Suicidal ideation	LC > CO (1)[47] LC = PCS (1)[79] LC < ME/CFS (1)[80]	impairment (1),[80] fatigue (1),[90] pain (1)[80]	–	–	–
Mood disorders	LC > CO (1)[37]/HC (2)[37,76]	–	cognitive deficits (1)[135]	dizziness (1),[136] change in appetite (1)[136]	fatigue (1),[136] cognitive deficits (1),[136] sleep disturbance (1)[136]
Reaction to severe stress and adjustment disorders	LC > HC (1)[72] LC = CO (1)[110]	–	–	LC (1)[108]	LC (1)[110]
Mania	LC = PCS (1)[79]	–	–	–	–
Schizophrenia/ Psychosis/Paranoia	LC < PCS (1)[79]	–	–	LC (1)[105]	–
ADHD	–	–	–	–	cognitive deficits (1)[136]
Disorders of psychological development	LC = CO (1)[110]	–	–	–	LC (1)[110]
Nicotine abuse/ dependence	–	–	–	LC (1)[105]	LC (1)[108]
Drug problems/ substance abuse	LC = PCS (1)[79]	–	–	LC (1)[105]	–
Borderline features	LC = PCS (1)[79]	–	–	–	–
Antisocial features	LC = PCS (1)[79]	–	–	–	–
Thought disorder	LC > CO (1)[37]/HC (1)[37]	–	–	–	–
Depression medications	LC = HC (1)[76]	–	LC (1)[137]	–	–
Anxiety medications	–	LC (1)[137]	–	–	–
Loneliness	–	–	–	LC (2)[6,119]	impairment (1)[6]
Anger	LC = HC (1)[76]	–	–	–	–
Positive trait affect	–	–	–	LC (1),[106] impairment (1)[106]	–
Fear of COVID-19	LC > CO (1)[61] LC = CO (1)[138] LC < HC (1)[138]	LC (1)[139]	LC (1)[137]	LC (1),[106] impairment (1)[106]	–

(Table 1 continues on next page)

Psychological variable	RQ1 (cross-sectional group comparisons)	RQ2 (cross-sectional associations)		RQ3 (longitudinal data)	
		Sig. association	No sig. association	Sig. prediction	No sig. prediction
(Continued from previous page)					
Maternal health anxiety	LC > CO (1)[139]/HC (1)[139]	–	–	–	–
Worry about COVID-19	–	–	–	LC (1),[6] impairment (1)[6]	–
Catastrophising	LC > CO (1)[45]/HC (1)[45] LC = FMS (1)[74] LC < CFS (1)[74]	QoL (1)[83]	pain (1)[83]	–	–
Negative cognitions	LC = HC (1)[134]	–	–	–	–
Personal control	–	fatigue (1)[83]	QoL (1)[83]	–	–
Treatment control	–	fatigue (1)[83]	QoL (1)[83]	–	–
Treatment rejection	LC = PCS (1)[79]	–	–	–	–
Coherence	–	fatigue (1)[83]	QoL (1)[83]	–	–
Self-compassion	–	symptom severity (1),[140] psychosocial impact (1)[140]	–	–	–
Emotional representation	–	fatigue (1)[83]	QoL (1)[83]	–	–
Illness identity	–	QoL (1),[83] fatigue (1)[83]	–	–	–
Walking self-efficacy	LC = HC (1)[74]	–	–	–	–
Fear avoidance/ Kinesiophobia	LC > CO (1)[45]/HC (1)[45] LC = CFS (1)[74] LC < FMS (1)[74]	–	QoL (1),[83] pain (1)[76]	–	–
Avoidance	LC = HC (1)[134]	–	–	–	–
Connection with friends	LC = HC (1)[134]	–	LC (1),[114] impairment (1)[134]	–	–
Sedentary behaviour	–	LC (1),[114] fatigue (1)[114]	–	–	–
Neuroticism/ emotional instability	LC > CO (1)[148]/HC (1)[149]	–	fatigue (1)[149]	–	–
Extraversion	LC < HC (1)[149]	–	fatigue (1)[149]	–	–
Openness	LC = HC (1)[149]	–	fatigue (1)[149]	–	–
Conscientiousness	LC = HC (1)[149]	–	fatigue (1)[149]	–	–
Agreeableness	LC < HC (1)[149]	–	fatigue (1)[149]	–	–
Resilience	LC = CO (1)[75] LC < CO (1)[148]	–	LC (2)[150,149]	–	–
Psychological flexibility	–	symptom severity (1),[140] psychosocial impact (1)[140]	–	–	–
Aggression	LC = PCS (1)[79]	–	–	–	–
Dominance	LC = PCS (1)[79]	–	–	–	–
Warmth	LC = PCS (1)[79]	–	–	–	–
Stigma	LC > CO (1)[146]	–	–	–	–
Life events	LC > CO (1)[148] LC = CO (1)[148]	–	–	fatigue (1)[139]	–
Nonsupport	LC = PCS (1)[79]	–	–	–	–
Psychological distress	LC > CO (1)[151] LC = HC (1)[149]	cognitive deficits (1)[146]	–	–	–
Central sensitisation	LC > CO (1)[45]/HC (1)[45]	QoL (2),[76,83] pain (1)[76]	–	–	–
Multisensory sensitivity/ somatosensory amplification	LC = CFS (1)[74] LC < FMS (1)[74]	–	–	–	–

Note: Numbers in parentheses refer to the frequency of studies. For RQ1, directions of effect are shown. Some studies provide results for more than one comparison group or outcome. RQ, research question; LC, patients with Long COVID; CO, patients after COVID-19 without Long COVID; HC, healthy controls without a history of COVID-19; ME/CFS, patients with myalgic encephalomyelitis/chronic fatigue syndrome; FMS, patients with fibromyalgia syndrome; PCS, patients with post-concussion syndrome; QoL, quality of life; sig., significant; threshold for statistical significance $p < 0.05$.

Table 1: Synthesis of evidence for all psychological variables by research question.

study respectively. The most studied psychological factors within any control group were depression and anxiety, followed by physical activity, a combination of depression and/or anxiety, posttraumatic stress disorder, stress, and history of mental health disorders. For all other searched psychological constructs, evidence was very limited, with a maximum of three studies per variable (eTable 2 in the Supplement). The majority of studies found almost all maladaptive psychological factors to be significantly higher and more frequent in patients with Long COVID than in both patients after SARS-CoV-2 infection who did not develop Long COVID and in healthy controls without a history of COVID-19, with no study reporting the opposite direction. Lower scores for depression, anxiety, history of mental health disorders, paranoia, catastrophising, kinesiophobia, somatosensory amplification, and suicidal ideation were reported in patients with Long COVID compared to controls in one study each, all but one of which referred to comparisons to a control group with other persistent somatic symptoms (chronic fatigue, fibromyalgia, post-concussion syndrome). Solely no significant differences between patients with Long COVID and controls were found for alcohol abuse, drug problems, disorders of psychological development, mania, borderline features, depression medications, walking self-efficacy (confidence in the ability to walk at a certain pace for a certain time without stopping), openness, conscientiousness, connection with friends, warmth, antisocial features, anger, aggression, dominance, negative cognitions, avoidance, nonsupport, and treatment rejection. However, it should be noted that, with the exception of alcohol abuse, all of these factors were only examined in one study each. Some studies reported both significant and non-significant differences between groups for the same psychological variable depending on measures (psychometric questionnaire data vs. clinical diagnosis of depression and anxiety[97,84]; adverse life events in the past year vs. earlier),[141] follow-up time point on symptoms after SARS-CoV-2 infection,[85,179] and different aspects of a construct (trait vs. state anxiety; Table 1: RQ1).[85]

Meta-analysis of cross-sectional studies with control groups

Meeting the required criteria (≥5 studies with valid data in the same format) allowed meta-analyses to be calculated for depression, anxiety (both categorical and continuous comparisons), physical activity, and stress (continuous comparisons). Pooled meta-analytic evidence for each construct is presented in Fig. 2. Sensitivity analyses led to almost identical results for all the meta-analyses executed, demonstrating model robustness (see eTable 18 in the Supplement). For all forest and funnel plots, see eFigures 1–12 in the Supplement.

Depression

Meta-analysis of continuous data revealed depression to be significantly higher in patients with Long COVID compared to controls ($z = 7.73$; $p < 0.001$; eFigure 1 in the Supplement). High between-study heterogeneity ($I^2 = 93\%$, $p < 0.001$) and a significant risk for publication bias were found ($p < 0.01$). After applying the trim-and-fill method, the model remained significant with a SMD of 0.37 (95% CI, 0.07–0.67). Meta-analysis of categorical data indicated a significant association between Long COVID and depression ($z = 3.69$; $p < 0.001$; eFigure 2 in the Supplement). Again, heterogeneity between studies was high ($I^2 = 87\%$, $p < 0.001$). Publication bias risk was not significant ($p > 0.05$).

Anxiety

Meta-analysis of continuous data showed significantly higher anxiety in patients with Long COVID compared to controls ($z = 5.98$; $p < 0.001$; eFigure 3 in the Supplement). Heterogeneity testing yielded high between-study variability ($I^2 = 92\%$, $p < 0.001$). Risk for publication bias was significant ($p < 0.01$) and the model remained significant after the trim-and-fill method (SMD = 0.32; 95% CI, 0.002–0.63). Meta-analysis of categorical data resulted in a significant association between Long COVID and anxiety ($z = 5.07$; $p < 0.001$; eFigure 4 in the Supplement). High heterogeneity between studies ($I^2 = 88\%$, $p < 0.001$) was found. Risk for publication bias was not significant ($p > 0.05$).

Physical activity

The model's overall effect was not significant ($p = 0.07$; eFigure 5 in the Supplement). Heterogeneity between studies was high ($I^2 = 97\%$, $p < 0.001$). No risk for publication bias was found ($p > 0.05$).

Stress

The model's overall effect was not significant ($p = 0.10$; eFigure 6 in the Supplement). Heterogeneity between studies was high ($I^2 = 84\%$, $p < 0.001$). No risk for publication bias was found ($p > 0.05$).

Research question 2: Which psychological factors are significantly associated with the presence of Long COVID or condition-relevant outcomes such as symptom severity, impairment, quality of life, and healthcare utilisation (cross-sectional associations)?

Cross-sectional associations with psychological variables were investigated in 16 studies for presence of Long COVID, in 11 for quality of life, in 8 for impairment, in 4 for number of persistent somatic symptoms, and 2 for symptom severity. In other studies, single Long COVID symptoms such as fatigue were used as outcomes. No study examined healthcare utilisation. Depression and anxiety were by far the most frequently investigated factors, followed by physical activity and a

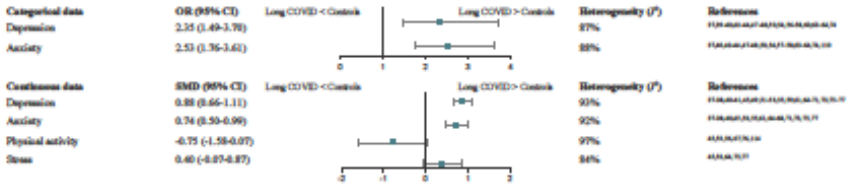

Fig. 2: Pooled data from random-effects meta-analyses of cross-sectional studies with control groups. Note. OR, odds ratio; SMD, standardised mean difference; CI, confidence interval.

combination of depression and/or anxiety. All other constructs were examined in no more than three studies each (eTable 3 in the Supplement). In general, most studies demonstrated significant associations between maladaptive psychological factors and Long COVID or condition-relevant outcomes. Significant negative associations between psychological factors and condition-relevant outcomes were found in only three studies in total, with these relating to depression, anxiety, suicidal ideation, and illness identity. Solely no significant associations were reported in two studies for resilience and in one study each for the personality factors extraversion, openness, conscientiousness, agreeableness, and neuroticism as well as for connection with friends, kinesiophobia, depression medications, and mood disorders. Some studies reported both significant and non-significant results depending on measures (depression reported as mean vs. cut-off),[40] outcomes (mental vs. physical quality of life),[38,137] acute COVID-19 severity,[111] and aspects of a construct (state vs. trait anxiety[40]; physical activity vs. inactivity; Table 1: RQ2).[116]

Research question 3: Which psychological factors significantly predict the development or maintenance of Long COVID (longitudinal data)?

Prospective relations with psychological factors were assessed in 16 studies for Long COVID and in two for impairment. Other outcomes were individual Long COVID symptoms. No study investigated symptom severity, quality of life, or healthcare utilisation. Again, depression and anxiety were assessed most frequently. A maximum of three longitudinal studies each were conducted on other variables (eTable 4 in the Supplement). The majority of studies showed maladaptive psychological factors to be significant predictors of Long COVID or impairment. The only exception was one study in which psychosis, tobacco smoking, and substance abuse significantly predicted a lower risk of Long COVID. For disorders of psychological development and Attention-Deficit Hyperactivity Disorder (ADHD), only non-significant results were reported (in one study each). Results for all psychological factors can be found in Table 1, RQ3.

Risk of bias of included studies

Twelve studies providing psychological data for cross-sectional group comparisons (e.g., in case-control studies) were of good quality, 44 were fair, and seven were poor. For data on cross-sectional associations, 11 studies were of good quality, 41 were fair, and one was poor. Regarding longitudinal data, 13 studies were of good quality, five were fair, and none was poor. For individual quality ratings by study design, see eAppendix 2 in the Supplement.

Discussion

This is the first systematic review and meta-analysis of a comprehensive range of pre-defined psychological factors with potential relevance for the development and/or maintenance of Long COVID and associated symptom severity, impairment, quality of life, and healthcare utilisation. Consequently, this study aimed to identify modifiable variables that could improve the understanding of Long COVID and have therapeutic relevance for affected patients. Overall, 113 studies of varying methodology provided original data for 58 psychological constructs in total (eTable 1 in the Supplement). Findings highlight above all the importance of depression and anxiety, which could be confirmed by meta-analyses of cross-sectional studies providing comparisons between patients with Long COVID and controls. Meta-analyses of physical activity and stress with only a small number of studies yielded no mean difference between patients with Long COVID and controls. The sound evidence found for depression and anxiety is in line with earlier systematic reviews and meta-analyses on Long COVID[37,38] and also corroborates a bio-psychosocial model of persistent somatic symptoms in general which proposes both to be important maintaining and aggravating factors.[13–15] However, the evidence base for psychological features other than depression and anxiety is scarce, which hinders conclusions to be drawn regarding their relevance for Long COVID.

A narrative synthesis across all study designs indicates the investigated psychological constructs to be associated with and predictive of Long COVID, with

only seven studies reporting contrary results.[43,58–60,85,103,111] The latter mainly concern mental health differences between patients with Long COVID and those with other persistent somatic symptoms (chronic fatigue,[59,103] fibromyalgia,[58] and post-concussion syndrome).[179] Considering the phenotypic resemblance between Long COVID and chronic fatigue syndrome in particular,[147] studies with control groups should include individuals with fatigue but no history of COVID-19 to shed further light on the role of SARS-CoV-2 infection.[13,180] Due to the high infection rates worldwide, such comparisons are becoming increasingly difficult though.

The vast majority of the evidence available to date relates to the role of depression and anxiety in Long COVID. However, the spectrum of psychological criteria known to be involved in chronic somatic symptoms is broader.[149] Also with regard to other post-acute infection syndromes, findings point to the importance of various psychological constructs like neuroticism or attributional styles.[150,151] In the course of this review, no studies were found on potentially relevant psychological variables such as alexithymia, emotion regulation, illness behaviour, symptom perception, and expectations.[28,152] In contrast to biomedical and sociodemographic risk factors for Long COVID,[7] psychological factors offer the advantage of being modifiable through interventions. Therefore, diversity of assessed constructs should be increased in Long COVID research, as is already the case with other forms of persistent somatic symptoms,[153] to establish further evidence-based treatment targets and inform guidelines.[1] A more solid foundation of robust research findings leading to thorough explanation models could help alleviate skepticism about the importance of psychological processes and disputes about their legitimacy in the context of Long COVID.[4,9]

In this review, high heterogeneity between publications and, in some cases, methodological shortcomings (e.g., insufficient reporting of statistical parameters such as sum scores or mean values) were observed. In addition to the monthly volume of new publications on the topic, widely varying methodologies (e.g., measures of psychological variables and outcomes such as impairment, methods of analysis, and reported statistical parameters) complicate the consolidation of evidence in this rapidly growing field of research and question the validity of results. Guidelines for research in the field of long COVID, including harmonisation of data collection, could improve methodological quality and comparability of future studies and pooling of data. A core battery of instruments to standardise the assessment of psychological aspects in Long COVID, for instance, would not only facilitate conclusions on their contribution to symptom persistence in the interplay between biomedical, psychological, and social factors, but also on the effectiveness of therapies.[154] Beyond that, more prospective analyses of representative cohorts are greatly needed to determine the predictive value of psychological features for trajectories of somatic symptoms after COVID-19, thereby improving our etiological understanding of Long COVID and the long-term impact of psychological burden on symptom severity. Fortunately, an increasing number of studies that strengthen our findings are currently being published.[155,156]

In contrast to previous reviews on Long COVID, we included a wide range of psychological factors in our literature search by applying the PSY-PSS framework,[28] which provides the first comprehensive list of potentially relevant psychological features in persistent somatic symptoms and related conditions such as Long COVID. One limitation concerns the scarcity of studies on Long COVID investigating psychological constructs other than depression and anxiety. While there is no doubt about their relevance in mental health research,[156] exclusively focusing on depression and anxiety prevents informed conclusions about the relative importance of other psychological risk factors for Long COVID. This disparity may also be due to the fact that valid self-report measures are widely available for depression and anxiety,[157,158] whereas clear recommendations on which other psychological variables should be assessed are still lacking for Long COVID.[11] Great methodological heterogeneity between studies further hindered the meta-analytical synthesis of existing data. In some studies, only significant effects were reported. Such publication bias was discovered in two of our meta-analyses. Individual studies employed innovative methods, for instance allowing for intra-individual trajectories over time, which unfortunately could not be meta-analysed.[159] Based on the results of our meta-analyses, no inferences can be made as to causal relations between maladaptive psychological factors and Long COVID. This requires further prospective studies. In this review, it was also not possible to investigate any interactions between psychological constructs — such as depression and anxiety — and biological factors in the aetiology of Long COVID, e.g., via inflammatory processes,[160,161] which could inform the further development of a bio-psychosocial explanatory model for Long COVID. Severity of SARS-Cov-2 infection, virus variant, vaccination status, pre-existing or comorbid somatic and/or mental diseases, and duration of Long COVID are important factors to be considered in the interpretation of our results. However, many studies did not provide any information on these factors. Accounting for these parameters also exceeded the scope of our study where we defined Long COVID as per NICE guideline, i.e., purely symptom-based, which does not take any of the above listed factors into account.[1] Females have a higher risk of developing Long COVID[7]; however, we did not consider sex and gender-specific differences regarding psychological variables in this review. Overall, the ratio of female and male patients was relatively

balanced across all included studies (58% females). In addition, we did not account for race or ethnicity of patients in the interpretation of our results and therefore cannot draw any conclusions regarding the racial or ethnic representativeness of study populations. We extracted data reported in manuscripts or supplements. If values were inconsistent or incorrect and we did not receive an author response, the corresponding studies were excluded. It should also be noted that we only included English-language studies and only studies up to January 2024, but new studies on Long COVID are constantly being published. We extracted additional psychological constructs that were examined in the identified studies but are not included in the PSY-PSS framework list (e.g., anger, self-compassion). Our database search, however, was based on the original list of psychological variables[28] and did not cover features such as psychodynamic factors added in a newer version.[140] Regarding the definition of Long COVID, we used the NICE guideline,[1] i.e., symptom duration of at least 4 weeks, instead of the stricter WHO criteria of post-COVID-19 condition,[12] i.e., symptom duration of at least 2 months, to take more findings into account. In the majority of identified studies, the time criterion of the WHO criteria was met (eTable 1 in the Supplement). However, no distinction was made in our interpretation of the results.

This review summarises the current evidence for psychological factors of importance for the understanding and tailored treatment of Long COVID. There is sufficient evidence for depression and anxiety to consider these variables in interventions; however, many other relevant features either miss empirical investigation or have hardly been tested in prospective designs. Psychological factors, even depression and anxiety, have insufficiently been addressed in the current mechanistic understanding of Long COVID pathophysiology.[30,31] While this review does not allow causal inferences regarding the role of psychological factors for Long COVID, it provides a starting point for further research. More longitudinal studies and experimental research using harmonised methods are needed to advance etiologic models of Long COVID and help differentiate between patient subtypes.[140] In light of the great burden on affected patients,[30,4] driving forward multidisciplinary treatment for Long COVID based on a biopsychosocial perspective is of high clinical and societal relevance.

Contributors

MSM and AT conceptualised and supervised the study. PE ran the database search. PE, MR, and CS screened titles and abstracts. Full texts were reviewed by PE, MR, CS, SS, AT, and MSM. PE, MR, CS, and AT extracted the data. PE and AT assessed study quality and bias. PE performed the meta-analysis and drafted the manuscript. AT, MSM, BL, SS, MR, CS, and PE revised and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary materials.

Declaration of interests

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Appendix A. Supplementary data

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9. ABSTRACT / ZUSAMMENFASSUNG

9.1. Abstract

This dissertation focuses on psychological factors in patients with burdensome persistent somatic symptoms lasting at least four weeks after an infection with SARS-CoV-2 that cannot be explained by another diagnosis, for which patients coined the term Long COVID (LC). The condition, which emerges in around 10% of infected individuals and potentially comprises a variety of symptoms, can lead to severe impairment in everyday life, increased health care utilization, and reduced quality of life. Due to the novelty of LC, its heterogeneous clinical presentation, and limited knowledge on its etiology, patients often experience a delay in diagnosis. Moreover, research into effective treatment approaches for LC is still in its infancy and there is no causal therapy available. Next to general risk factors, studies suggest the involvement of psychosocial factors in the maintenance of somatic symptoms after COVID-19 and preliminary evidence indicates cognitive behavioral therapy might be effective. In view of the detrimental effects on society and public health, supporting individuals with LC in dealing with their symptoms is crucial. However, structured diagnostic and therapeutic algorithms are still lacking.

The objectives of this dissertation project were to investigate psychological risk factors for somatic symptoms during the COVID-19 pandemic, to present a new treatment approach for LC based on the identified psychological factors, and to identify further psychological factors potentially related to LC by synthesizing the available evidence in the literature. Study I is a prospective observational cohort study that assessed specific risk factors for somatic symptom deterioration during the COVID-19 pandemic in adults with and without prior SARS-CoV-2 infection empirically. Study II is the study protocol of an observer-blinded, three-arm randomized controlled trial, which aims to evaluate a brief, low-threshold expectation management intervention developed together with patients suffering from LC. Study III is a systematic review and meta-analysis synthesizing published evidence on psychological factors associated with LC.

The results support the relevance of psychological factors for the persistence of somatic symptoms after COVID-19. Study I showed that, as opposed to actual SARS-CoV-2 infection, illness-related anxiety or psychological symptom burden, symptom expectations associated with COVID-19, and the belief of having been infected with SARS-CoV-2 were significant predictors of somatic symptom deterioration after almost two years of the COVID-

19 pandemic. Therefore, the RCT described in study II investigates the effects of a mechanism-based psychological intervention aimed at the targeted modification of both illness-related anxiety and dysfunctional symptom expectations about the clinical symptoms of LC in comparison to a non-specific supportive intervention and treatment as usual. Study III found, among others, that anxiety and depression are both co-occurring phenomena and predictive factors of LC.

By confirming psychological factors to be of relevance, this dissertation contributes to a better understanding of the etiology of LC and thereby provides clear indications of possible therapeutic starting points in the multimodal treatment of LC in accordance with a biopsychosocial model. This is especially important given the fact that evidence-based treatment recommendations for LC are still missing. Taking into account a broad spectrum of psychological factors such as emotion regulation, alexithymia or attributional styles, future studies should continue to advance a comprehensive understanding of LC and a scientifically sound multimodal treatment of those affected.

9.2. Zusammenfassung

Diese Dissertation befasst sich mit psychologischen Faktoren bei Menschen mit belastenden anhaltenden somatischen Symptomen, die mindestens vier Wochen nach einer Infektion mit SARS-CoV-2 anhalten und nicht durch eine andere Diagnose erklärbar sind, wofür Betroffene den Begriff Long COVID (LC) geprägt haben. Das Beschwerdebild, das bei etwa 10 % der Infizierten auftritt und potentiell eine Vielzahl von Symptomen umfasst, kann zu schweren Beeinträchtigungen im Alltag, einer erhöhten Inanspruchnahme von Gesundheitsleistungen und einer verminderten Lebensqualität führen. Aufgrund der Neuartigkeit des Krankheitsbildes, seiner heterogenen klinischen Erscheinung und des begrenzten Wissens über seine Ätiologie wird die Diagnose häufig erst mit Verzögerung gestellt. Darüber hinaus steht die Erforschung wirksamer Behandlungsansätze für LC noch am Anfang und es gibt keine kausale Therapie. Neben allgemeinen Risikofaktoren deuten Studien darauf hin, dass psychosoziale Faktoren an der Aufrechterhaltung somatischer Symptome nach COVID-19 beteiligt sind und erste Ergebnisse legen nahe, dass kognitive Verhaltenstherapie wirksam sein könnte. Angesichts der massiven Auswirkungen auf die Gesellschaft und die öffentliche Gesundheit ist die Unterstützung von Personen mit LC bei der Bewältigung ihrer Symptome von entscheidender Bedeutung. Strukturierte diagnostische und therapeutische Algorithmen fehlen jedoch bislang.

Ziele dieser Dissertation waren die Untersuchung psychologischer Risikofaktoren für somatische Symptome während der COVID-19-Pandemie, die Präsentation eines neuen Behandlungsansatzes für LC auf der Grundlage der gefundenen psychologischen Faktoren und die Ermittlung weiterer potentiell relevanter psychologischer Faktoren im Zusammenhang mit LC durch die Synthese der in der Literatur verfügbaren Evidenz. Studie I ist eine prospektive Kohortenstudie, in der spezifische Risikofaktoren für die Verschlechterung somatischer Symptome während der COVID-19-Pandemie bei Erwachsenen mit und ohne vorherige SARS-CoV-2-Infektion empirisch untersucht wurden. Studie II ist das Studienprotokoll einer Beobachter-verblindeten, dreiarmigen randomisierten kontrollierten Studie, in der eine kurze, niedrigschwellige Erwartungsmanagement-Intervention evaluiert werden soll, die gemeinsam mit von LC Betroffenen entwickelt wurde. Bei Studie III handelt es sich um eine systematische Übersichtsarbeit und Meta-Analyse, in der die bisher publizierte Evidenz zu psychologischen Faktoren im Zusammenhang mit LC zusammengefasst wurde.

Die Ergebnisse untermauern die Relevanz psychologischer Faktoren für die Persistenz somatischer Symptome nach COVID-19. Studie I zeigte, dass im Gegensatz zu einer tatsächlichen SARS-CoV-2-Infektion krankheitsbezogene Ängste bzw. die psychologische Symptombelastung, mit COVID-19 assoziierte Symptomerwartungen und der Glaube, mit SARS-CoV-2 infiziert gewesen zu sein, signifikante Prädiktoren für die Verschlechterung somatischer Symptome nach fast zwei Jahren COVID-19-Pandemie waren. Daher untersucht der in Studie II beschriebene RCT die Auswirkungen einer mechanismusbasierten psychologischen Intervention, die auf die gezielte Modifikation sowohl krankheitsbezogener Ängste als auch dysfunktionaler Symptomerwartungen abzielt, auf die klinischen Symptome von LC im Vergleich zu einer unspezifischen supportiven Intervention und einer alleinigen Behandlung wie üblich. Studie III ergab unter anderem, dass Angst und Depression sowohl Begleitphänomene als auch prädiktive Faktoren von LC sind.

Durch die Bestätigung der Relevanz psychologischer Faktoren trägt diese Dissertation zu einem besseren Verständnis der Ätiologie von LC bei und liefert damit klare Hinweise auf mögliche therapeutische Ansatzpunkte in der multimodalen Behandlung von LC in Übereinstimmung mit einem biopsychosozialen Modell. Dies ist insbesondere vor dem Hintergrund wichtig, dass es noch immer keine evidenzbasierten Behandlungsempfehlungen für LC gibt. Unter Berücksichtigung eines breiten Spektrums psychologischer Faktoren wie zum Beispiel Emotionsregulation, Alexithymie oder Attributionsstile sollten künftige Studien

ein umfassendes Verständnis von LC und eine wissenschaftlich fundierte multimodale Behandlung der Betroffenen weiter vorantreiben.

10. AUTHOR CONTRIBUTION STATEMENT

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12. EIDESSTATTLICHE VERSICHERUNG

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: