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SARS-CoV-2 infection is associated with physical but not mental fatigue – Findings from a longitudinal controlled population-based study

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A R T I C L E I N F O

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A B S T R A C T

Objective: Fatigue has been identified as the core symptom of long-Covid, however, putative pandemic-related influences remain largely unclear. We investigated trajectories of total, physical and mental fatigue and the factors associated with it in previously infected and non-infected individuals up to one year post- infection.

Methods: We used data from a longitudinal cohort study of German adults with two samples: A representative probability sample and a sample of individuals with proven SARS-CoV-2 infection. Surveys were conducted in spring 2020(T1), autumn 2020(T2) and summer 2021(T3). Fatigue was assessed using the FAS, distinguishes between physical and mental fatigue. Depression, anxiety and stress were assessed using PHQ-4 and PSQ.

Results: 1990 participants [mean age 47.2 (SD = 17.0), 30.5% previously infected] were included in the survey at T1 ($n = 1118$ at T2, $n = 692$ at T3). Total and physical fatigue, but not mental fatigue were significantly higher in the previously infected compared to the non-infected sample at T2, but this group difference disappeared at T3. We identified Covid-infection as a factor associated with transient total and physical fatigue at T2. Depression, anxiety and stress at T1 were associated with total, physical and mental fatigue at both follow-ups.

Conclusions: Our results highlight the importance of considering physical and mental fatigue as separate entities, while suggesting a greater relevance of the physical signs of fatigue in understanding long-Covid. The results further showed that baseline mental health symptoms were the most strongly associated with fatigue trajectories.

1. Introduction

A global pandemic followed the SARS-CoV-2 virus outbreak in late 2019. A substantial subgroup of individuals infected by SARS-CoV-2 reports persistent or newly emerging symptoms, even weeks or months after acute infection [1]. Up to now, a variety of physical, cognitive, and psychological post-acute symptoms have been identified [2–4]. If these symptoms are ongoing or develop four weeks beyond the acute infection, they are classified as 'long-Covid'; if these symptoms are persistent or newly develop in a timeframe of more than twelve weeks after infection, this is called 'post-Covid' according to current guidelines [5,6], however, the term 'long-Covid' is also commonly used for these longer persistent symptoms. The World Health Organization (WHO) defines post-COVID-19 disease as a condition that occurs in individuals who have previously had a confirmed or probable SARS-CoV-2 infection and suffer from symptoms that cannot be attributed to an alternative

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diagnosis, while the time period is defined as "usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months" [7]. The proportion of those developing post-COVID-19 is very heterogeneous, ranging from 13% [8] to 87% [9]. This heterogeneity can be attributed to several factors, including the severity of acute disease course, a wide range of symptoms [10], different virus variants [11], the use of different definitions for long-/Post-Covid, and the lack of control groups in many studies [12]. In a recent controlled study based on data of >200,000 individuals from England, 10.2% reported long-COVID symptoms and 7.5% reported post-COVID symptoms after COVID-19 infection [10].

The symptom which is consistently reported most frequently by patients affected by long-Covid is fatigue [2–4,13,14]. Fatigue is conceptualized as an overwhelming and prolonged feeling of tiredness or exhaustion with both a physical (e.g., difficulty performing physical activities) and mental (e.g., concentration problems and difficulty in carrying out cognitive task, diminished attention and concentration) dimension [15–18]. Research suggests that mental fatigue likely reflects a specific psychological response to prolonged pandemic conditions [19] which is associated with higher levels of depression and anxiety [20]. Calabria and colleagues examined overall, mental and physical fatigue in individuals reporting cognitive complaints after infection [21]. While higher levels of depression, anxiety as well as deficits in executive function and working memory were associated with mental fatigue, executive control deficits (e.g. switching abilities), anxiety and being female were associated with physical fatigue [21]. Overall fatigue is more commonly reported by females [22,23], and is common in the general population, especially due to psychosocial stressors in everyday life [24]. Previous evidence is inconclusive regarding the relationship between age and fatigue, with studies showing a positive correlation [25], a negative correlation [26], or no link between fatigue and age [27]. Generally, fatigue is frequently associated with a range of disorders, including infectious, physical, neurological, and mental health diseases (e.g., Eppstein-Bar virus, sarcoidosis, cancer, depression) [15,17,28,29]. Since fatigue is the most commonly reported symptom in almost all studies in patients with post-Covid, with a prevalence ranging from 28 to 87% [30], it is important to better understand the risk factors and the course of fatigue.

A challenge in defining the clinical picture of long-Covid are confounding general effects of the pandemic. The restrictions on public and private life during the pandemic, such as lockdown and social isolation, led to a deterioration of mental health in the general population [31–36]. Previous studies have shown that individuals with heightened stress levels and also prior mental health burden may be more likely to be affected by fatigue [34,35,37]. Longitudinal data from a controlled cohort study comparing trajectories and the associated factors with fatigue in previously infected versus non-infected individuals could provide more insight into the course of fatigue and its role in long-Covid. In previous controlled studies, higher fatigue scores and longer-lasting fatigue were found in individuals after infection as compared with controls, but also individuals who did not experience an infection were affected by fatigue [26,37–40]. These data suggest that there may be additive or synergistic effects of virus infection, individual (pre-pandemic) factors and the general pandemic circumstances on fatigue symptomatology and reporting. However, to date, there are few controlled studies examining Covid-related fatigue between previously infected and non-infected individuals over the long term. Longitudinal controlled cohort data is needed to disentangle mechanisms of fatigue and to contribute to a better understanding of the evolving clinical picture of long-Covid.

We report data collected within a controlled population-based longitudinal survey study assessing physical, mental and overall fatigue in a sample of the general population who have not been infected with SARS-CoV-2 as compared to a sample with a proven SARS-CoV-2 infection from the same area. Additionally, we aim to identify the factors associated with fatigue Data was assessed at three measurement time points, starting in spring 2020 (T1), and following up in autumn 2020 (T2) as well as in summer 2021 (T3). Anxiety, depression, and stress were assessed at T1, T2 and T3, fatigue was assessed at T2 and T3.

We hypothesize that on average, we will find (a) higher total fatigue levels at T2 and T3 among those who have been infected as compared to those who have been not, and (b) that we will be able to identify factors that are associated with higher fatigue at T2 and T3 and these will include younger age, female gender, higher baseline depression, anxiety and stress at T1. Additionally, we investigate putative differential trajectories and associated factors of mental versus physical fatigue on an exploratory level.

2. Method

2.1. Study design and participants

Data stems from a longitudinal cohort study in the adult general population living in Stuttgart, Germany with around $n = 630.000$ inhabitants. Data on the non-infected general population (sample A) is derived from a probability sample, which was drawn by the residents' registration office. The sample was representative of the adult population living in Stuttgart, based on age and sex distribution. Persons with a previous infection were excluded.

Data on individuals who have been infected (sample B) was derived from the database on infected adults officially registered at the Stuttgart Public Health Department by May 2020.

For sample A, adult members of 4400 households were invited for study participation via postal letters. For sample B, all $N = 1267$ adult registered individuals with proven SARS-CoV-2 infection were invited to participate in the study by the Stuttgart public health authority. Survey assessments took place in May 2020 (T1), November 2020 (T2), and July 2021 (T3). At each measurement point, participants were asked if they had previously been infected with Covid-19. In sample A, the infection with Covid-19 was based on self-declaration.

Participants could fill out the questionnaire either online or on a paper. 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 subjects were approved by the ethics committee of the Medical Faculty Tuebingen and the University Hospital Tuebingen (271/2020BO1). Written informed consent was obtained from all subjects.

2.2. Measures

Fatigue was assessed at T2 and T3 using the 10-item Fatigue Assessment Scale (FAS) which comprises, the two subscales *mental fatigue* and *physical fatigue* [41]. The total score and the subscale scores were calculated. The total score ranges from 10 to 50 [41]. A previous study on fatigue in sarcoidosis indicated that FAS scores $\geq 22 \leq 34$ represent mild to moderate fatigue and scores ≥ 35 represent severe fatigue [42]. The FAS was validated in a working population in the Netherlands, among others [43]. In the absence of more generally validated cut-off scores, we have relied on this previously reported classification. Mental burden was assessed at all measurement time points relying on core symptoms of anxiety and depression as assessed by the PHQ-4 [44], a widely used screening instrument consisting of two items assessing anxiety (GAD-2) and two items assessing depressive symptoms (PHQ-2) [44]. Subjective stress experience was measured using the Perceived Stress Questionnaire (PSQ) with 20 items and mean values were transformed linearly between 0 and 100 [45]. In addition, sociodemographic variables (e.g., age, gender) were collected.

2.3. Statistical analyses

The primary outcome of the study was the Fatigue total scale (FAS), secondary outcomes were physical and mental subscales of the FAS. Multiple imputation was applied to allow an analysis of fatigue data in all subjects with FAS data at T2. We excluded subjects from the control group which had an infection between T2 and T3 ($n = 1118$, $n = 722$ not infected, $n = 396$ previously infected). These subjects were not imputed. In the imputation model, age and gender and PHQ at T1, T2, and T3, and FAS at T2 were used to simulate the distribution of missing FAS at T3. Five hundred imputation samples were drawn. The imputation module of SPSS for Windows release 26 was used. The missing structure was non-hierarchical. Comparisons between groups were done using the chi-square test for nominal and the *t*-test for independent samples of normally distributed data. For non-normally distributed measurements and ordinal variables Mann-Whitneys rank sum test was used. In linear regression analyses with FAS at T2 and T3 a priori defined potentially associated characteristics (gender, age, PHQ-4 baseline and PSQ-20 baseline) were included as covariates (continuous, except for gender) additionally to infection (yes/no). We have calculated further analyses, adjusting for smoking, coronary heart disease, respiratory disease and previous mental disorders. No variable selection was applied. The level of significance was 0.05 (two-sided) in all statistical tests. All analyses were done using SPSS for Windows release 26.

3. Results

3.1. Sample characteristics at baseline

$N = 5667$ adults living in Stuttgart were invited to participate in our study, resulting in a final sample of 1990 participants at T1 after dropout and exclusion (Fig. 1). A total of $n = 5667$ adults living in Stuttgart were invited to participate, resulting in a final sample of $n = 1990$ who participated at T1 after dropout and exclusion.

In the previously infected sample, from which data is missing for $n = 20$ participants, $n = 509$ (86.9%) were treated at home, $n = 78$ (13.3%) were hospitalized, among them $n = 26$ (4.4%) required admission to intensive care (ICU) and $n = 10$ (1.7%) required artificial respiration. Patients could require both ICU treatment and artificial respiration. In the total sample, the most common underlying chronic conditions were cardiovascular disease (16.8%), metabolic disease (11.8%), and musculoskeletal disease (11.5%). A history of mental illness was reported by $n = 83$ participants (4.2%).

There were no differences between groups in underlying chronic conditions. Patients who have been infected were younger than those with no infection. Table 1 shows demographic and clinical characteristics of both study samples.

3.2. Attrition of survey participants

We included a total of 1118 (56.2% of the baseline-sample) at T2, with 722 (52.2%) from the non-infected sample and 396 (65.3%) from the previously infected sample. We were still able to include 692 subjects (34.8% of the baseline-sample) at T3, with 462 (33.4%) from the non-infected sample and 230 (38.0%) from the previously infected sample. Dropout analysis showed a difference in the frequency of missing data between samples regarding fatigue, with more responders in the previously infected sample than in the non-infected sample (chi^2 ($df = 2$) $= 29.366$, $p < .001$) at both follow-ups. Responders in the non-infected sample were younger and more often female.

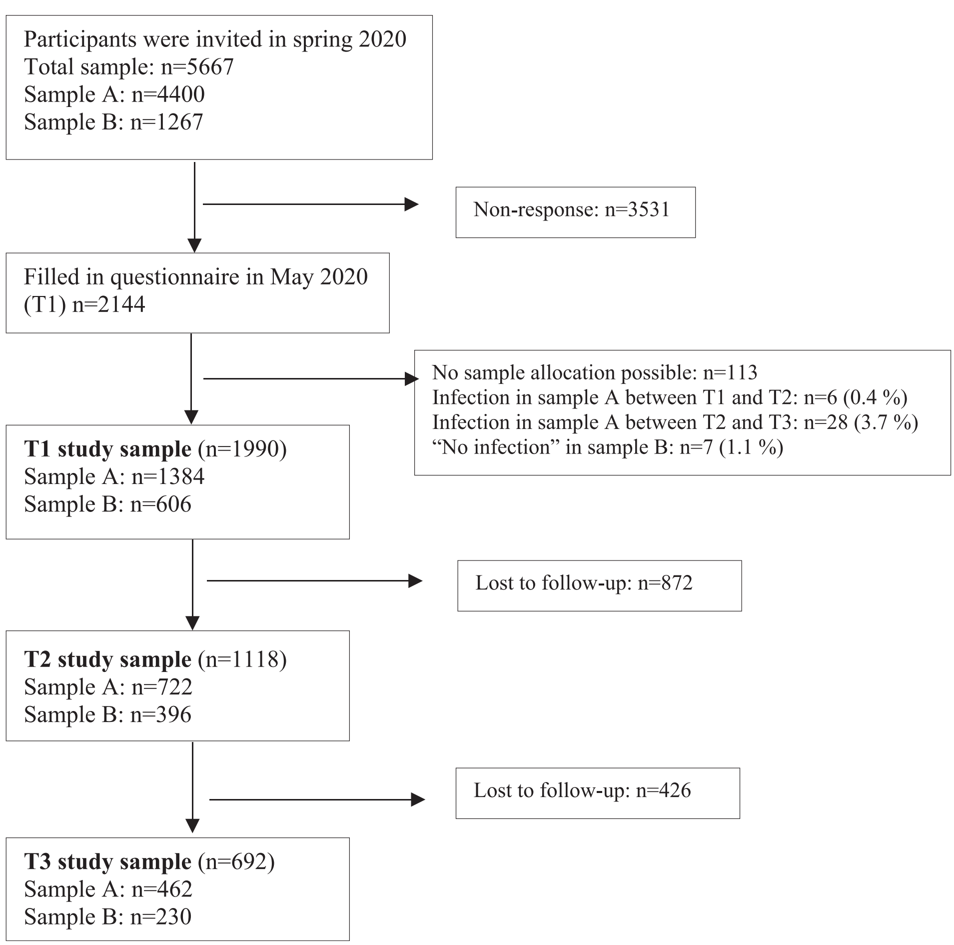

Fig. 1. Flowchart of sample recruitment and response. Sample A = non-infected sample, Sample B = previously infected sample.

Table 1
Demographic and clinical characteristics of study participants at baseline (T1, May 2020).

	control group	previously infected group	overall	p value
	n = 1384	n = 606	n = 1990	
Gender				
Female, n (%)	713 (51.5)	308 (50.8)	1021 (51.3)	chi^2 (df = 1) = 0.081, p = .78
Male, n (%)	671 (48.5)	298 (49.2)	969 (48.7)	
Age (years) M ± SD	48.0 ± 17.4	45.5 ± 15.9	47.2 ± 17.0	t (df = 1188.8) = 3.004, p = .003
missing, n (%)	6 (0.4)	25 (4.1)	32 (1.6)	
BMI M ± SD	25.2 ± 4.7	24.9 ± 4.1	25.1 ± 4.5	U = 402,859.50, Z = −0.489, p = .63
missing, n (%)	20 (1.4)	7 (1.2)	27 (1.4)	
persons in housholds M ± SD	2.4 ± 1.1	2.6 ± 1.2	2.5 ± 1.1	U = 391,569.00, Z = −2.089, p = .04
missing, n (%)	4 (0.3)	5 (0.8)	9 (0.5)	
smoking				
yes, n (%)	222 (16.0)	52 (8.6)	274 (13,8)	chi^2 (df = 1) = 19.891, p < .001
no, n (%)	1157 (83.6)	553 (91.3)	1710 (85,9)	
missing, n (%)	5 (0.4)	1 (0,1)	6 (0,3)	
Chronic disease				
present, n (%)	569 (41.1)	235 (38.8)	804 (40.4)	chi^2 (df = 1) = 0.924, p = .37
absent, n (%)	814 (58.8)	370 (61.0)	1184 (59.5)	
missing, n (%)	1 (0.1)	1 (0.2)	2 (0.1)	
PHQ baseline M ± SD	2.2 (2.2)	2.3 (2.6)	2.3 (2.3)	U = 397,509.00, Z = −0.937, p = .35
missing, n (%)	12 (0.9)	11 (1.8)	23 (1.2)	
PSQ baseline M ± SD	32.5 (18.8)	33.2 (18.8)	32.7 (18.8)	U = 364,618.00, Z = −0.782, p = .43
missing, n (%)	61 (4.4)	42 (6.9)	103 (5.2)	

Notes. M = Mean, SD = Standard deviation.

3.3. Longitudinal trajectories of fatigue and associated factors

At T2, fatigue-scores were higher in the participants after infection (M = 21.69, SD = 7.45) as compared to the participants with no infection (M = 20.68, SD = 6.60; t (df = 1116) = −2.33, p = .02, Cohen's d = −0.15). There were no differences in reported fatigue between these groups at T3 (M = 21.81, SD = 7.56 in those who have been infected and M = 21.26, SD = 7.02, t (df = 690) = −0.95, in those who have been not, p = .342, Cohen's d = −0.08). Women reported more fatigue than men at both, T2 and T3 (T2: female M = 22.04, SD = 7.19; male M = 20.01, SD = 6.49; t (df = 1163) = −5.10, p < .001, Cohen's d = −0.30; T3: female M = 22.59, SD = 7.42 and male M = 20.17, SD = 6.77, t (df = 770) = −4.71, p < .001, Cohen's d = −0.30). Fig. 2 displays categorized fatigue severity at both follow-up measurements. Participants who have had SARS-CoV-2 infections experienced more severe fatigue at T2 compared to the control group (chi^2 (df = 1) = 12.335, p < .001).

Fig. 3 shows the course of physical and mental fatigue in both samples over both measurement time points. The samples differ with respects to physical fatigue, with those who have been infected reporting higher scores as to those non-infected at T2 (M = 12.00, SD = 4.30 vs. M = 11.12, SD = 3.70, t (df = 1116) = −3.50, p < .001, Cohen's d = −0.22). However, there was no difference in physical fatigue at T3 (M = 11.96, SD = 4.35 vs. M = 11.36, SD = 3.86, t (df = 691) = −1.85, p = .06, Cohen's d = −0.15). Our results show no difference in mental fatigue at both time points. At T2, previously infected participants reported mental fatigue of M = 9.71, SD = 3.73, the non-infected of M = 9.56, SD = 3.42 (t (df = 1117) = −0.68, p = .50, Cohen's d = −0.04) and at T3, the previously infected reported mental fatigue of M = 9.86, SD = 3.78 and the non-infected of M = 9.89, SD = 3.69 (t (df = 693) = 0.113, p = .91, Cohen's d = 0.01).

3.4. Factors associated with fatigue after six months and one year

The results of our regression analysis showed that Covid-infection, female sex, younger age, higher baseline PHQ-4 and PSQ scores were associated with total fatigue at T2, while female sex, higher baseline PHQ-4, and PSQ scores were associated with total fatigue at T3 (Table 2).

For the fatigue subscales, factors associated with physical fatigue at T2 were female sex, Covid-infection, higher baseline PHQ-4 and PSQ scores. In addition, female sex, higher baseline PSQ scores were also

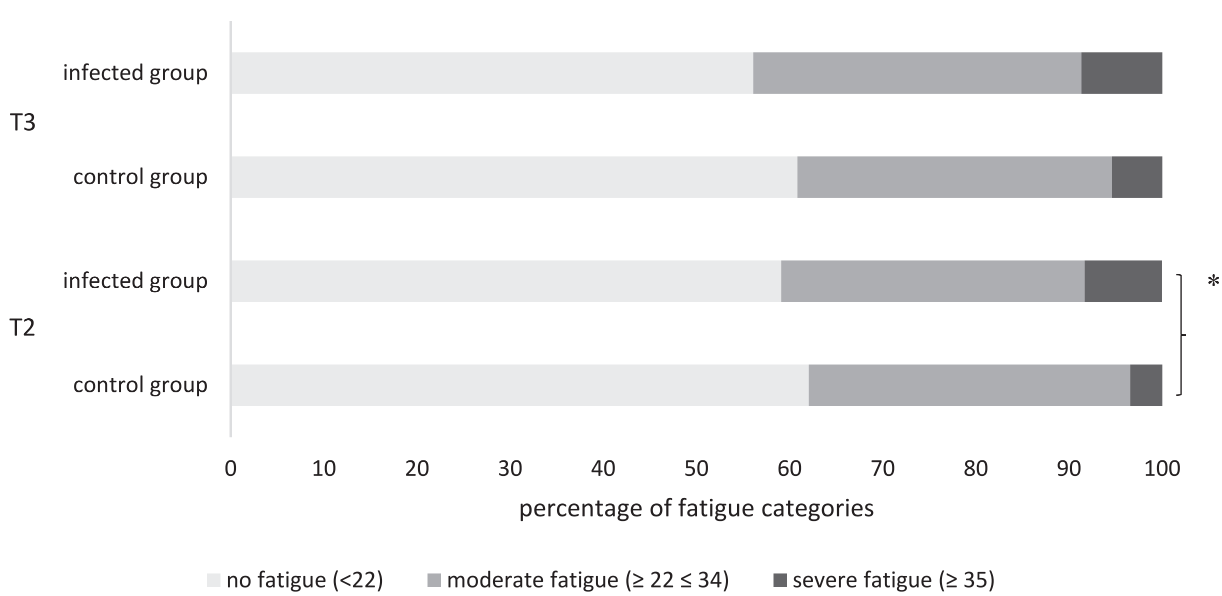

Fig. 2. Categorical fatigue severity in the previously infected and control group at T2 (November 2020) and T3 (July 2021) according to a classification by Hendriks et al. [42] * p < .05.

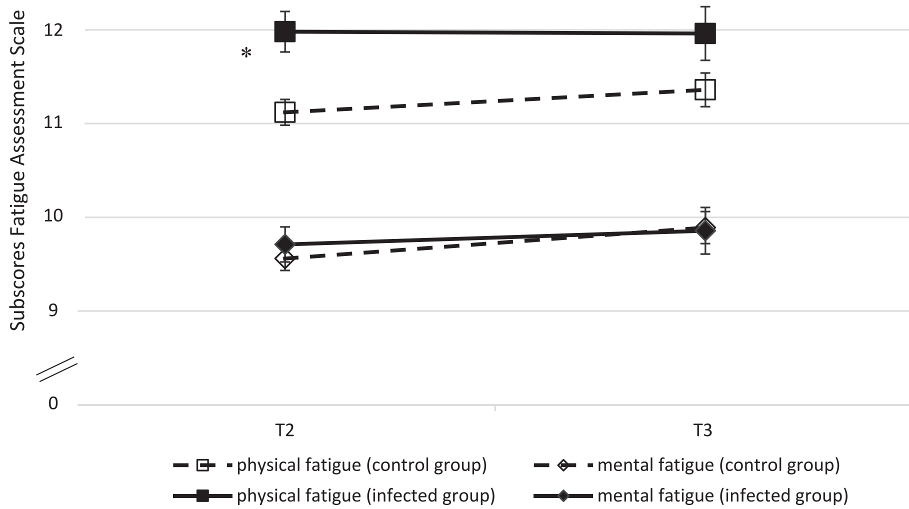

Fig. 3. Trajectories in physical and mental fatigue in previously infected versus non-infected samples. * $p < .05$ at T2 for physical fatigue.

associated with physical fatigue at T3. Younger age, higher scores on the baseline PHQ-4 and PSQ were found to be associated with mental fatigue at T2, as well as higher baseline PHQ-4 and PSQ scores, were found to be associated with mental fatigue at T3. For the adjusted models, coronary heart disease and respiratory disease were not associated with any of the fatigue variables (total, somatic, mental, T2, T3, difference). Smoking and mental disorders were associated with most of the outcomes if analyzed separately. Only previous mental disorders were associated with the outcomes in the multiple regression models as presented in Table 2. However, results for the covariates did not change after inclusion of smoking and mental disease. Results are presented in the supplement (Appendix B).

4. Discussion

The present study is one of the first controlled population-based studies investigating trajectories of fatigue in previously infected as compared to non-infected adults during the Covid-19 pandemic. Starting shortly after the Covid-19 outbreak in May 2020, we completed follow-up analyses with our study sample for more than one year in July 2021 after the initial data collection.

While at T2, i.e., six months post-acute infection, the previously infected group reported higher total fatigue than the control group, reported fatigue scores did not differ between both groups after one year at T3. Meanwhile, we found similar scores in mental fatigue in both groups during T2 and T3. Covid-infection therefore was associated with total and physical fatigue at 6 months-follow-up, but not with mental fatigue at any time point. Depression, anxiety or stress at baseline, were associated with most fatigue trajectory data regarding total, physical and mental fatigue. Younger age was associated with total and mental fatigue at T2, and female sex was associated with total and physical fatigue at T2 and T3. When adjusting for smoking and chronic disease including respiratory disease, coronary heart diseases and previous mental disorders, it turned out that respiratory disease and coronary heart diseases were not associated with any of the fatigue outcomes, while smoking and previous mental disorders were associated with most of the outcomes separately.

Our trajectory data of fatigue within the first year post-acute infection suggests that higher fatigue levels among individuals infected with Covid-19 could be present in a period closer to the infection. A recently published matched controlled study showed more general tiredness in those previously infected than in controls after 90–150 days, which is in line with our findings at the first follow-up (T2) [46]. However, our findings differ from those of a large Norwegian cohort study, in which the increased risk of fatigue was higher in infected than in non-infected individuals at 12-months follow-up (T3) [38]. In this study, fatigue was measured by only one item [38]. It should be mentioned that total fatigue scores increased in both of our samples between T2 and T3. Specifically, the non-infected sample showed a larger increase between T2 and T3 in physical and total fatigue, while the previously infected sample already reported a relatively high total and physical fatigue level at T2. This pattern of fatigue development might therefore merely reflect general pandemic-related influences on overall well-being and mental distress [31–33]. By contrast, non-infected individuals might have experienced a more constant increase of fatigue which could be associated with reactions to recurrent lockdown circumstances and other pandemic-related stressors. The tendency for increasing fatigue scores, not only in the previously infected but also in the non-infected individuals, has also been reported in studies examining general population samples without prior infection [34,35,37]. This effect might be explained by so-called *pandemic fatigue* [47], a general tiredness as a result of the ongoing pandemic. Our surveys were conducted within the first 1.5 years of the pandemic, when people in Germany had to restrict themselves, especially in terms of social contacts, travel activities and the work environment. Previous studies completed at the beginning of the pandemic have shown that these restrictions and lockdowns led to higher stress levels [32,48], depressive symptomatology [49] as well as generalized anxiety [48] in the general population. When interpreting longitudinal development of fatigue in both groups, it is important to consider the effect sizes which show that the effect at T3 still reaches approximately 2/3 of the effect at T2.

Taking a closer look at the dimensions of fatigue, previously infected individuals reported higher physical fatigue at the first follow-up (T2). These results could indicate that physical fatigue represents a larger part of the long-Covid syndrome than mental fatigue, at least for a short period of time. Our results highlight the need for distinguishing between physical and mental fatigue when defining the clinical picture of long-Covid. At the same time, the high levels of total and predominantly mental fatigue among both previously infected and non-infected individuals suggests that fatigue may be overestimated as the core symptom of long-Covid, or at least that this should not exclusively be attributed to the post-acute symptoms etiology.

Younger age was associated with total and mental fatigue at the first follow-up in autumn 2020. This age effect is in line with previous data on mental health burden in the general population during the pandemic, showing a stronger mental health deterioration in young people [34,50]. Previous studies have reported that people with younger age experienced more depression, anxiety and stress at the beginning of the pandemic [51,52]. Female gender, depression and anxiety, as well as high perceived stress at baseline were strongly associated with fatigue at

Table 2
Linear Regression Analysis.

	Sample (previously infected)			Gender (female)			Age (in years)			PHQ-4 baseline			PSQ baseline			
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	R Square
Total fatigue																
FAS T2	1.04	1.006; 1.066	0.003	0.91	0.881; 0.938	0.006	−0.03	−0.034; −0.032	0.002	1.06	1.050; 1.067	0	0.12	0.115; 0.117	0	0.42
FAS T3	0.23	0.201; 0.260	0.52	1.05	1.022; 1.108	0.002	−0.01	−0.015; −0.013	0.21	0.36	0.354; 0.371	<0.001	0.08	0.076; 0.078	<0.001	0.165
difference	−0.81	−0.838; −0.772	0.04	0.14	0.109; 0.173	0.71	0.02	0.018; 0.020	0.12	−0.7	−0.706; −0.686	<0.001	−0.04	−0.040; −0.038	0.007	0.131
Physical fatigue																
FAS physical T2	0.91	0.888; 0.923	<0.001	0.86	0.868; 0.902	<0.001	−0.01	−0.006; −0.005	0.37	0.42	0.412; 0.422	<0.001	0.08	0.079; 0.080	0	0.382
FAS physical T3	0.34	0.324; 0.359	0.12	0.76	0.746; 0.779	<0.001	0	0.001; 0.002	0.8	0.1	0.097; 0.108	0.12	0.05	0.049; 0.050	<0.001	0.139
difference	−0.56	−0.584; −0.544	0.02	−0.12	−0.142; −0.104	0.6	0.01	0.007; 0.008	0.333	−0.31	−0.320; −0.308	<0.001	−0.03	−0.030; −0.029	<0.001	0.111
Mental fatigue																
FAS mental T2	0.13	0.114; 0.146	0.48	0.03	0.009; 0.040	0.89	−0.03	−0.028; −0.027	<0.001	0.64	0.637; 0.647	0	0.04	0.036; 0.037	<0.001	0.361
FAS mental T3	−0.11	−0.130; −0.092	0.67	0.29	0.270; 0.307	0.25	−0.02	−0.016; −0.015	0.06	0.26	0.254; 0.265	<0.001	0.03	0.027; 0.028	0.003	0.102
difference	−0.24	−0.262; 0.220	0.38	0.26	0.244; 0.284	0.32	0.01	0.011; 0.013	0.16	−0.38	−0.388; −0.376	<0.001	−0.01	−0.010; −0.009	0.35	0.076

Notes. B = unstandardized regression coefficient, FAS = Fatigue Assessment Scale, PHQ-4 = Patient Health Questionnaire-4, PSQ = Perceived Stress Questionnaire, T2: November 2020, T3: July 2021.

both follow-ups. These findings are consistent with previous studies showing that females [4,23,53], people with higher depression [23,53,54] or anxiety, and physically inactive or lonely persons [55] were more strongly affected by fatigue.

Although many studies have found that females report more fatigue, it is important to exercise caution when interpreting these results due to various factors. These factors include self-report bias, traditional gender roles, socialization processes, and the tendency of women to internalize and men to externalize distress [56].

Covid-infection was associated with total and physical fatigue after six months, but not after one year. Overall, evidence from the pattern of factors associated with fatigue suggests that, in addition to previous Covid-infection, perceived stress and psychological distress may play an important role in predicting the long-term course of fatigue. Presumably those individuals with a higher vulnerability to mental health issues at the beginning of the pandemic (i.e., higher perceived stress, depression, anxiety) were more strongly affected by fatigue during the course of the pandemic, compared to people without mental health issues. This is also supported by results from our regression models when adjusting for previous mental disorders.

4.1. Strengths and limitations

The major strength of this study is that we conducted a population-based study including Covid infected and non-infected individuals from the same population. We rely on widely used and validated self-report instruments. The first assessment was completed early on in the pandemic, allowing us to conduct a longitudinal design with a one-year follow-up following a Covid-infection. Moreover, we used the fatigue assessment scale as an instrument assessing physical and mental components of fatigue. A recent review supports the applicability of the FAS with good psychometric properties in a range of different conditions and populations [42]. However, the thresholds used were originally derived from a study population with sarcoidosis [57]. This is a chronic disease that can affect patients undergoing immunosuppressive treatment. Therefore, the classification should be interpreted with caution for the present population. Furthermore, it should be noted that the FAS has not yet been validated in the German population.

Several limitations should nevertheless be noted. We had an attrition rate of appr. 65% at T3 assessment. The dropout should be considered when interpreting T3 data. We were unable to assess baseline fatigue values at the beginning of our study, as fatigue was only identified as a potentially relevant long-term symptom of Covid-infections later in the pandemic. However, fatigue might have been associated with baseline mental health symptoms. [58]. Furthermore, we did not assess cognitive function in our survey. However, cognitive impairment is a commonly reported symptom after COVID and is associated with mental health symptoms [58,59]. Our study was conducted with the prevailing SARS-CoV-2 variant Alpha. The impact of infection with other variants on fatigue might differ from these findings. We were unable to obtain data related to the period of time before the pandemic. Therefore, we have no information on pre-Covid fatigue values. We have assessed a history of mental health disorder in the sample, however, as a broad category, and therefore cannot report on specific diagnoses. Our study included subjects from a large city in southern Germany, these results might not be generalizable to other locations, and especially rural areas. We had a small number of reported infections between T1 and T3 in sample A. This might partly be due to self-selection of sample A participants, resulting infected people not taking part in the follow-up assessments as the study invitation explicitly outlined that we were looking for non-infected controls.

Conclusion

Our findings suggest that psychological stress at the onset of the pandemic is more strongly associated with fatigue than the infection itself, and that individuals one year after Covid-infection have fatigue levels comparable to non-infected controls. Furthermore, differentiating between physical and mental fatigue within the post-Covid context could aid in the clarification of long-term Covid syndrome. The present results suggest that treatment of mental health problems (e.g. depression, anxiety, stress) may be important treatment targets for people suffering from fatigue and post-Covid.

Author contributions

KEG, GP, JSJ, PM, SE & FJ designed the study and implemented core study procedures. AGG supported survey conduction and data handling. PM is the responsible biostatistician. PM and MS conducted the data analysis and prepared the figs. PM, KEG, and MS interpreted the data. MS and KEG drafted the manuscript. MB, HW and SZ contributed intellectual content to drafting the manuscript. CA, FJ and RM aquired funding. All co-authors critically revised the manuscript and approved the final version.

Ethical statement

The present research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All participants provided written informed consent. The study protocol was approved by the ethics committee of the Medical Faculty and the University Hospital Tübingen.

CRediT authorship contribution statement

Marisa Schurr: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Florian Junne:** Writing – review & editing, Project administration, Conceptualization. **Peter Martus:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Gregor Paul:** Conceptualization. **Jan Steffen Jürgensen:** Conceptualization. **Christine Allwang:** Writing – review & editing, Funding acquisition. **Marius Binneböse:** Writing – review & editing. **Hannah Wallis:** Writing – review & editing. **Rafael Mikolajczyk:** Writing – review & editing, Funding acquisition. **Annette Galante-Gottschalk:** Project administration. **Stephan Zipfel:** Conceptualization. **Stefan Ehehalt:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Katrin Elisabeth Giel:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2024.111598.

References

[1] H.E. Davis, et al., Characterizing long COVID in an international cohort: 7 months of symptoms and their impact, EClinicalMedicine 38 (2021) 101019.
[2] S. Lopez-Leon, et al., More than 50 long-term effects of COVID-19: a systematic review and Meta-analysis, Res. Sq. 9 (11) (2021).
[3] A. Nalbandian, et al., Post-acute COVID-19 syndrome, Nat. Med. 27 (4) (2021) 601–615.
[4] C. Forster, et al., Persisting symptoms after COVID-19, Dtsch. Arztebl. Int. 119 (10) (2022) 167–174.
[5] (NICE), N.I.f.H.a.C.E, COVID-19 rapid guideline: managing the long-term effects of COVID-19, 2022 [cited 2022 30.11.22]; Available from: https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742.
[6] A.R. Koczulla, et al., S1 guideline post-COVID/long-COVID, Pneumologie 75 (11) (2021) 869–900.
[7] J.B. Soriano, et al., A clinical case definition of post-COVID-19 condition by a Delphi consensus, Lancet Infect. Dis. 22 (4) (2022) e102–e107.
[8] C.H. Sudre, et al., Attributes and predictors of long COVID, Nat. Med. 27 (4) (2021) 626–631.
[9] A. Carfi, et al., Persistent symptoms in patients after acute COVID-19, JAMA 324 (6) (2020) 603–605.
[10] C.J. Atchison, et al., Long-term health impacts of COVID-19 among 242,712 adults in England, Nat. Commun. 14 (1) (2023).
[11] S. Diexer, et al., Association between virus variants, vaccination, previous infections, and post-COVID-19 risk, Int. J. Infect. Dis. 136 (2023) 14–21.
[12] T.B. Hoeg, S. Ladhani, V. Prasad, How methodological pitfalls have created widespread misunderstanding about long COVID, Bmj. Evid. Based Med. 25 (2023).
[13] B. Blomberg, et al., Long COVID in a prospective cohort of home-isolated patients, Nat. Med. 27 (9) (2021) 1607–1613.
[14] R.S. Peter, et al., Post-acute sequelae of covid-19 six to 12 months after infection: population based study, BMJ 379 (2022) e071050.
[15] A.J. Dittner, S.C. Wessely, R.G. Brown, The assessment of fatigue: a practical guide for clinicians and researchers, J. Psychosom. Res. 56 (2) (2004) 157–170.
[16] B. Karshikoff, T. Sundelin, J. Lasselin, Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms, Front. Immunol. 8 (2017) 21.
[17] M.C. Campos, et al., Post-viral fatigue in COVID-19: a review of symptom assessment methods, mental, cognitive, and physical impairment, Neurosci. Biobehav. Rev. 142 (2022) 104902.
[18] M.A. Boksem, T.F. Meijman, M.M. Lorist, Effects of mental fatigue on attention: an ERP study, Brain Res. Cogn. Brain Res. 25 (1) (2005) 107–116.
[19] E. Morgul, et al., COVID-19 pandemic and psychological fatigue in Turkey, Int. J. Soc. Psychiatry 67 (2) (2021) 128–135.
[20] F. Torrente, et al., Psychological symptoms, mental fatigue and behavioural adherence after 72 continuous days of strict lockdown during the COVID-19 pandemic in Argentina, BJPsych Open. 8 (1) (2022) e10.
[21] M. Calabria, et al., Post-COVID-19 fatigue: the contribution of cognitive and neuropsychiatric symptoms, J. Neurol. 269 (8) (2022) 3990–3999.
[22] W.M. Vanderlind, et al., A systematic review of neuropsychological and psychiatric sequalae of COVID-19: implications for treatment, Curr. Opin. Psychiatry 34 (4) (2021) 420–433.
[23] A.M. Ruiter, J. Verschuuren, M.R. Tannemaat, Prevalence and associated factors of fatigue in autoimmune myasthenia gravis, Neuromuscul. Disord. 31 (7) (2021) 612–621.
[24] I. Engberg, et al., Fatigue in the general population- associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014, BMC Public Health 17 (1) (2017) 654.
[25] X. Zhang, et al., Symptoms and health outcomes among survivors of COVID-19 infection 1 year after discharge from hospitals in Wuhan, China, JAMA Netw. Open 4 (9) (2021) e2127403.
[26] T.J. Hartung, et al., Fatigue and cognitive impairment after COVID-19: a prospective multicentre study, EClinicalMedicine 53 (2022) 101651.
[27] J.C. Ferreira, et al., Clinical, sociodemographic and environmental factors impact post-COVID-19 syndrome, J. Glob. Health 12 (2022) 05029.
[28] M. Roeder, et al., The prevalence of obstructive sleep apnea in sarcoidosis and its impact on sleepiness, fatigue, and sleep-associated quality of life. A cross-sectional study with matched controls (the OSASA study), J. Clin. Sleep Med. 18 (10) (2022).
[29] P. Servaes, C. Verhagen, G. Bleijenberg, Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions, Eur. J. Cancer 38 (1) (2002) 27–43.
[30] H. Heesakkers, et al., Clinical outcomes among patients with 1-year survival following intensive care unit treatment for COVID-19, J. Am. Med. Assoc. 327 (6) (2022) 559–565.
[31] E. Iob, et al., Levels of severity of depressive symptoms among at-risk groups in the UK during the COVID-19 pandemic, JAMA Netw. Open 3 (10) (2020) e2026064.
[32] N. Vindegaard, M.E. Benros, COVID-19 pandemic and mental health consequences: systematic review of the current evidence, Brain Behav. Immun. 89 (2020) 531–542.
[33] K. Patel, et al., Psychological distress before and during the COVID-19 pandemic among adults in the United Kingdom based on coordinated analyses of 11 longitudinal studies, JAMA Netw. Open 5 (4) (2022).
[34] L.J. Labrague, C.A. Ballad, Lockdown fatigue among college students during the COVID-19 pandemic: predictive role of personal resilience, coping behaviors, and health, Perspect. Psychiatr. Care 57 (4) (2021) 1905–1912.
[35] Y.X. Zhan, et al., Prevalence and influencing factors on fatigue of first-line nurses combating with COVID-19 in China: a descriptive cross-sectional study, Curr. Med. Sci. 40 (4) (2020) 625–635.
[36] K.E. Giel, et al., Longitudinal development of depression and anxiety during COVID-19 pandemic in Germany: findings from a population-based probability sample survey, Front. Psychol. 13 (2022) 1000722.

[37] K.M. Abel, et al., Association of SARS-CoV-2 infection with psychological distress, psychotropic prescribing, fatigue, and sleep problems among UK primary care patients, JAMA Netw. Open 4 (11) (2021) e2134803.

[38] I.H. Caspersen, P. Magnus, L. Trogstad, Excess risk and clusters of symptoms after COVID-19 in a large Norwegian cohort, Eur. J. Epidemiol. 37 (5) (2022).

[39] B. Lapin, I.L. Katzan, Health-related quality of life mildly affected following COVID-19: a retrospective pre-post cohort study with a propensity score-matched control group, J. Gen. Intern. Med. 37 (4) (2022) 862–869.

[40] T. Stephenson, et al., Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study, Lancet Child. Adolesc. Health 6 (4) (2022) 230–239.

[41] H.J. Michielsen, et al., Examination of the dimensionality of fatigue - the construction of the fatigue assessment scale (FAS), Eur. J. Psychol. Assess. 20 (1) (2004) 39–48.

[42] C. Hendriks, et al., The fatigue assessment scale: quality and availability in sarcoidosis and other diseases, Curr. Opin. Pulm. Med. 24 (5) (2018) 495–503.

[43] J. De Vries, H.J. Michielsen, G.L. Van Heck, Assessment of fatigue among working people: a comparison of six questionnaires, Occup. Environ. Med. 60 (2003) 10–15.

[44] B. Lowe, et al., A 4-item measure of depression and anxiety: validation and standardization of the patient health Questionnaire-4 (PHQ-4) in the general population, J. Affect. Disord. 122 (1–2) (2010) 86–95.

[45] H. Fliege, et al., The Perceived Stress Questionnaire (PSQ) reconsidered: validation and reference values from different clinical and healthy adult samples, Psychosom. Med. 67 (1) (2005) 78–88.

[46] A.V. Ballering, et al., Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study, Lancet 400 (10350) (2022) 452–461.

[47] J.B. Krakowczyk, et al., Pandemic fatigue, psychopathological risk factors, and vaccination attitudes during the COVID-19 pandemic in 2021-a network analysis, J. Affect. Disord. Rep. 8 (2022) 100345.

[48] A. Bauerle, et al., Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany, J. Public Health (Oxf.) 42 (4) (2020) 672–678.

[49] A. Bendau, et al., Longitudinal changes in anxiety and psychological distress, and associated risk and protective factors during the first three months of the COVID-19 pandemic in Germany, Brain Behav. 11 (2) (2021) e01964.

[50] F. Moulin, et al., Longitudinal impact of the COVID19 pandemic on mental health in a general population sample in France: evidence from the COMET study, J. Affect. Disord. 320 (2023) 275–283.

[51] I. Nwachukwu, et al., COVID-19 pandemic: age-related differences in measures of stress, anxiety and depression in Canada, Int. J. Environ. Res. Public Health 17 (17) (2020).

[52] C. Gonzalez-Sanguino, et al., Mental health consequences during the initial stage of the 2020 coronavirus pandemic (COVID-19) in Spain, Brain Behav. Immun. 87 (2020) 172–176.

[53] Y. Ma, et al., Prevalence and risk factors of cancer-related fatigue: a systematic review and meta-analysis, Int. J. Nurs. Stud. 111 (2020) 103707.

[54] J.E. Bower, The role of neuro-immune interactions in cancer-related fatigue: biobehavioral risk factors and mechanisms, Cancer 125 (3) (2019) 353–364.

[55] J. Theorell-Haglow, E. Lindberg, C. Janson, What are the important risk factors for daytime sleepiness and fatigue in women? Sleep 29 (6) (2006) 751–757.

[56] K.E. Giel, B. Derntl, The weaker sex? What we can learn from sex differences in population mental health during and beyond the COVID-19 pandemic, Eur. Arch. Psychiatry Clin. Neurosci. 272 (1) (2022) 165–166.

[57] J. De Vries, et al., Measuring fatigue in sarcoidosis: the fatigue assessment scale (FAS), Br. J. Health Psychol. 9 (Pt 3) (2004) 279–291.

[58] M. Gasnier, et al., Comorbidity of long COVID and psychiatric disorders after a hospitalisation for COVID-19: a cross-sectional study, J. Neurol. Neurosurg. Psychiatry 37 (5) (2022).

[59] M. Taquet, et al., Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19, PLoS Med. 18 (9) (2021) e1003773.