Post-acute sequelae of covid-19 six to 12 months after infection: population based study

Raphael S Peter,[1] Alexandra Nieters,[2] Hans-Georg Kräusslich,[3] Stefan O Brockmann,[4] Siri Göpel,[5] Gerhard Kindle,[2] Uta Merle,[6] Jürgen M Steinacker,[7] Dietrich Rothenbacher,[1] Winfried V Kern,[8] on behalf of the EPILOC Phase 1 Study Group

For numbered affiliations see end of the article

Correspondence to: W V Kern winfried.kern@uniklinik-freiburg.de (or @WinfriedKern on Twitter; ORCID 0000-0003-2550-358X)

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Abstract

OBJECTIVES

To describe symptoms and symptom clusters of post-covid syndrome six to 12 months after acute infection, describe risk factors, and examine the association of symptom clusters with general health and working capacity.

DESIGN

Population based, cross sectional study

SETTING

Adults aged 18-65 years with confirmed SARS-CoV-2 infection between October 2020 and March 2021 notified to health authorities in four geographically defined regions in southern Germany.

PARTICIPANTS

50 457 patients were invited to participate in the study, of whom 12 053 (24%) responded and 11 710 (58.8% (n=6881) female; mean age 44.1 years; 3.6% (412/11 602) previously admitted with covid-19; mean follow-up time 8.5 months) could be included in the analyses.

MAIN OUTCOME MEASURES

Symptom frequencies (six to 12 months after versus before acute infection), symptom severity and clustering, risk factors, and associations with general health recovery and working capacity.

RESULTS

The symptom clusters fatigue (37.2% (4213/11 312), 95% confidence interval 36.4% to 38.1%) and neurocognitive impairment (31.3% (3561/11 361), 30.5% to 32.2%) contributed most to reduced health recovery and working capacity, but chest symptoms, anxiety/depression, headache/dizziness, and pain syndromes were also prevalent and relevant for working capacity, with some differences according to sex and age. Considering new symptoms with at least moderate impairment of daily life and ≤80% recovered general health or working capacity, the overall estimate for post-covid syndrome was 28.5% (3289/11 536, 27.7% to 29.3%) among participants or at least 6.5% (3289/50 457) in the infected adult population (assuming that all non-responders had completely recovered). The true value is likely to be between these estimates.

CONCLUSIONS

Despite the limitation of a low response rate and possible selection and recall biases, this study suggests a considerable burden of self-reported post-acute symptom clusters and possible sequelae, notably fatigue and neurocognitive impairment, six to 12 months after acute SARS-CoV-2 infection, even among young and middle aged adults after mild infection, with a substantial impact on general health and working capacity.

TRIAL REGISTRATION

German registry of clinical studies DRKS 00027012.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies have shown that post-acute sequelae of covid-19 are common, particularly among patients who had been admitted to hospital for covid-19

Post-acute self-reported complaints and symptoms are often diverse and non-specific and sometimes of unknown severity and functional relevance

WHAT THIS STUDY ADDS

New symptom clusters such as fatigue, neurocognitive impairment, chest symptoms, smell or taste disorder, and anxiety/depression persist beyond six to 12 months after acute SARS-CoV-2 infection

The three most frequent clusters (fatigue, neurocognitive impairment, chest symptoms) often interfere with daily life and activities and often co-occur

Long term smell and taste disorders are reported relatively independently of other complaints

Introduction

SARS-CoV-2 has caused the covid-19 viral pandemic with far reaching consequences, including a worldwide health crisis. Although respiratory infection is the primary clinical manifestation, covid-19 is considered a multi-organ systemic disease that includes the lungs, heart, vascular system, brain, and other organ systems.[1 2] Most infections are mild or even asymptomatic, especially among children and adolescents, and the likelihood of severe disease and the need for hospital admission increase substantially with age and comorbidity.[3 4] The 30 day mortality among people in Germany admitted to hospital with covid-19 in a nationwide claims data cohort study (first wave) was 24% overall and 53% among patients needing ventilation.[5]

Besides the acute phase morbidity and mortality, post-acute health problems and sequelae have been reported in survivors of covid-19. According to a review, up to 80% of patients with covid-19 continue to complain about health problems after acute infection, and more than 50 adverse effects were reported.[6] The pathophysiology of many post-acute symptoms has remained unresolved. Symptoms can last for weeks and represent delayed reconvalescence or can persist or recur even three months or longer into the post-acute phase.[6-10]

Whereas "long covid" has been defined as ongoing symptoms beyond four weeks after acute infection, post-covid-19 condition or post-covid syndrome is

considered in patients with symptoms lasting for at least two months, being unexplained by an alternative diagnosis, and occurring three months from the acute infection.[11] So far, very few large scale studies have examined the symptomatology and prevalence of post-covid syndrome beyond six months after acute infection and its association with health related quality of life, wellbeing, and working capacity in a population based, non-clinical sample.

The primary aims of this study were to describe symptoms and symptom clusters of post-covid syndrome six to 12 months after acute infection, describe risk factors, and examine the association of symptom clusters with general health and working capacity. The data were generated in a large population based study in southern Germany involving 18-65 year old people with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) and notified to local health authorities.

Methods

EPILOC (Epidemiology of Long Covid) is a non-interventional population based study conducted in four administratively and geographically defined regions in the Federal State of Baden-Württemberg in south-western Germany. The study included people aged 18 to 65 years who tested positive in a SARS-CoV-2 PCR test between 1 October 2020 and 1 April 2021 and whose infection was notified (according to the German Infection Protection Act) to the local public health authorities responsible for the following four regions: Freiburg (city of Freiburg, district of Breisgau-Hochschwarzwald, district of Emmendingen), Heidelberg (city of Heidelberg, Rhein-Neckar district), Tübingen (city of Tübingen, city of Reutlingen, Zollernalb district), and Ulm (city of Ulm, Alb-Donau district, district of Heidenheim, district of Biberach)—regions with a total population of 2.7 million combined.

Surviving people were directly contacted by the local public health authorities via postal mail between late August and September 2021. All study materials (that is, participant information, informed consent form, and a standardised questionnaire) were included in the letter. Participants were asked to provide written informed consent and send the study materials (postage paid) to the trustee office of the study centre at the Freiburg University Medical Centre. The trustee separated the declaration of informed consent from the completed questionnaire and forwarded the questionnaires to the data management centre at Ulm University. This analysis follows the STROBE recommendations.

Data sources and measurements

The standardised questionnaire included sociodemographic characteristics, lifestyle factors, and medically attended comorbidities already present before the acute SARS-CoV-2 infection. It questioned the presence of 30 specific symptoms before and during (and related to) the acute infection phase as well as at the time of filling out the questionnaire (that is, six to 12 months after acute infection) by yes/no responses. Further new or ongoing current symptoms could be added in a free text field. If any of the symptoms were present at the time of the survey, we asked for associated medical treatment (yes/no) and whether and to what extent each symptom impaired daily life and activities ("how much do you feel impaired by this at the moment?") using a four point Likert-type scale (none, light, moderate, or strong).

For the evaluation of fatigue (already included in the list of symptoms), we additionally used the 10 item Fatigue Assessment Scale.[12] A threshold score of ≥22 is used for determining the presence of substantial fatigue and a threshold score of ≥35 for extreme fatigue. To assess working capacity, we adapted questions from the short form of the work ability index.[13] Participants assessed their current general health recovery and current working capacity compared with the situation before the acute SARS-CoV-2 infection on a 10 point scale (10% steps from 0% to 100%). The wording of the question was "What percentage of your original work capacity (before your positive corona test) have you regained today?" The use of this single question has shown similar relations to sick leave and health related quality of life in occupational studies.[14] In a similar manner, we assessed the current general health condition compared with the situation before the acute SARS-CoV-2 infection with the question "What percentage of your general health (before your positive corona test) have you regained today?"

To evaluate the current health related quality of life, we used the SF-12 questionnaire assessing physical and mental health-related quality of life components (https://www.rand.org/health-care/surveys_tools/mos/12-item-short-form.html). Few data were missing in the analysis dataset (the highest number of missing values observed was 3.3% for cancer as a comorbidity), so we did not do any imputations.

Statistical methods

We evaluated the characteristics of the study population descriptively. We obtained the relative frequency of the individual symptoms before and during acute infection and at the time of the survey (that is, six to 12 months after the index infection) and calculated the differences in prevalence and the relative prevalence ratios (both current versus before acute infection), including a 95% confidence interval. We also provided sex and age stratified representations.

We used a two step approach to identify symptom clusters (not present before the SARS-CoV-2 infection). Firstly, we identified strongly correlated current symptoms (not present before the acute SARS-CoV-2 infection) by using exploratory polychoric factor analysis (using the oblimin rotation) based on symptom severity (not present, no impairment, light impairment, moderate impairment, or strong impairment). To identify the ideal number of factors, we used "parallel" analysis.[15] Secondly, we included each symptom into the cluster (identified in the first

step as factor) for which its factor loading was highest. We visualised the identified symptom clusters by means of a co-occurrence network using Gephi 0.9.2. In addition, as a sensitivity analysis, we visualised these clusters considering symptoms of moderate or strong grade only.

We calculated the prevalence ratios for symptom clusters (with 95% confidence intervals) by possible relevant characteristics (age, sex, education, smoking status, body mass index, time since positive PCR test, severity of acute infection, and pre-existing conditions), mutually adjusted. We used a linear model (adjusted for the presence of other symptom clusters) to estimate the association of each current symptom cluster with loss of general health and working capacity compared with pre-infection. We calculated the attributable loss as the associated loss multiplied by the symptom cluster's prevalence. We estimated corresponding 95% confidence intervals for the attributable impairment/loss by using a parametric bootstrap.

In addition, we calculated prevalence estimates (in percentages) of post-covid syndrome according to different criteria for possible case definitions as raw prevalence, age-sex standardised prevalence (according to the age-sex distribution of the invited population), and the minimum possible prevalence (under the extreme assumption that all non-responders fully recovered and were free of symptoms at the time of the survey).

We used Poisson models to estimate prevalence, prevalence ratios, and prevalence differences. All confidence intervals are based on robust standard errors, accounting for possible dispersion and the correlated nature of the data in case of comparing symptoms before and after acute infection. We did not do any imputation for missing values. We used the SAS statistical software package (release 9.4) or R version 4.1.2 for statistical analyses.

Patient and public involvement

This study was conducted in rapid response to the covid-19 pandemic, a public health emergency of national and international concern. Neither patients nor members of the public were directly involved in the design, conduct, or reporting of this research. We were aware from engagement of the general public and patient support groups that further information on the medium and long term prognosis of post-covid syndrome was desired.

Results

A total of 50 457 adults with confirmed SARS-CoV-2 infection were invited to participate in the study, of whom 12 053 (24%) responded and 11 710 provided at least information on age and sex (see study flowchart in supplementary figure A) and were included in the analysis. The mean time between the initial positive PCR test and the time of the survey was 8.5 (SD 1.6) months.

As shown in table 1, the mean age of the participants was 44.1 (SD 13.7) years and slightly more were female (58.8%; 6881/11 710) than male. Most participants were born in Germany (88.7%; 10 355/11 668), had German nationality (94.1%; 11 004/11 688), were from urban areas (84.2%; 9575/11 365), and had a university entrance qualification (51.9%; 6065/11 678). More than half of the participants reported pre-pandemic full time employment (56.8%; 6608/11 628). Reported chronic pre-existing health conditions included musculoskeletal disorders (28.9%; 3310/11 448), cardiovascular disorders (17.4%; 1992/11 477), neurological and sensory disorders (16.2%; 1855/11 480), and respiratory diseases (12.1%; 1385/11 467), besides others. Most participants (77.5%; 8988/11 602) did not need medical care for the previous acute SARS-CoV-2 infection, 19.0% (2202/11 602) reported outpatient care, and less than 4% (412/11 602) had needed hospital admission (table 1).

Symptoms and derived symptom clusters

The frequency of the reported symptom at the three time points differed greatly overall (supplementary figure B), according to age categories and sex (supplementary figure C), and also regarding the level of impairment, showing higher levels of impairment for women than men for most new symptoms, and regarding medical treatment (supplementary figure D). Some symptoms, such as vomiting, nausea, abdominal pain, diarrhoea, chills, fever, and skin rash, were rare and contributed little to the post-covid syndrome symptomatology, as was the case for post-acute symptoms added in free text (most common: abnormal heart beat and disturbed vision), which were mentioned by <1% of the respondents (free text data not shown).

Participants with two or more symptoms were, on average, slightly older (45.4 v 42.5 years), more often female (64.5% (3891/6030) v 52.6% (2889/5489)), more often obese (21.9% (1313/5984) v 14.9% (813/5446)), and needed medical care during the acute phase of the infection more often (32.6% (1948/5976) v 11.4% (622/5445)) compared with participants reporting one or no symptoms still present (supplementary table A).

In view of the relatively low response rate and the less reliable results for absolute prevalence rates, we further concentrated on how symptoms clustered. We found that several of the 30 post-acute new symptoms were strongly correlated and could be combined into 13 symptom clusters (fig 1). The individual symptoms rapid physical exhaustion and chronic fatigue, for example, were combined into the cluster "fatigue," which was the most common symptom cluster among participants (37.2%; 4213/11 312), followed by "neurocognitive impairment" with a prevalence of 31.3% (3561/11 361), "chest symptoms" (30.2%; 3443/11 403), "smell or taste disorder" (23.6%; 2661/11 254), and "anxiety/depression" (21.1%; 2422/11 485). This ranking remained similar when we included only symptoms with moderate or strong impairment, although the prevalence was lower (supplementary figure E). Self-reported fatigue as

Table 1 | Characteristics of study population. Values are numbers (percentages) unless stated otherwise

Characteristic	No	Value
Mean (SD) age, years	11 710	44.1 (13.7)
Age group, years:		
<30	11 710	2474 (21.1)
30-<40		2158 (18.4)
40-<50		2075 (17.7)
50-<60		3443 (29.4)
≥60		1560 (13.3)
Sex:		
Male	11 710	4829 (41.2)
Female		6881 (58.8)
Marital status:		
Single	11 492	3425 (29.8)
Married/living together		7563 (65.8)
Living apart		368 (3.2)
Widowed		136 (1.2)
University entrance qualification:		
Yes	11 678	6065 (51.9)
No		5613 (48.1)
Place of birth:		
Germany	11 668	10 355 (88.7)
Other		1313 (11.3)
Nationality:		
German	11 688	11 004 (94.1)
Other		684 (5.9)
Place of residence:		
Mostly urban	11 365	7246 (63.8)
Partly urban		2329 (20.5)
Mostly rural		1790 (15.8)
Pre-pandemic employment:		
Full time	11 628	6608 (56.8)
Part time		3220 (27.7)
Studying/vocational education		1143 (9.8)
None		657 (5.7)
Current employment:		
Full time	11 651	6335 (54.4)
Part time		3215 (27.6)
Studying/vocational education		1031 (8.8)
None		1070 (9.2)
Smoking status:		
Current smoker	11 678	1192 (10.2)
Former smoker		2882 (24.7)
Never smoked		7604 (65.1)
Mean (SD) body mass index	11 619	26.1 (5.3)
Obese (body mass index ≥30)	11 619	2171 (18.7)
Pre-existing conditions:		
Musculoskeletal disorders (including rheumatism)	11 448	3310 (28.9)
Cardiovascular disorders (including hypertension)	11 477	1992 (17.4)
Neurological or sensory disorders	11 480	1855 (16.2)
Metabolic disorders	11 554	2014 (17.4)
Mental disorders	11 479	1470 (12.8)
Respiratory diseases	11 467	1385 (12.1)
Dermatological diseases	11 547	1257 (10.9)
Cancer	11 323	386 (3.4)
Mean (SD) time since positive PCR test, months	11 521	8.5 (1.6)
Treatment of acute SARS-CoV-2 infection:		
No medical care	11 602	8988 (77.5)
Outpatient care		2202 (19.0)
Inpatient care (without intensive care)		315 (2.7)
Intensive care		97 (0.8)
Vaccinated (first shot) before positive PCR test:		
Yes	11 431	220 (1.9)
No		11 211 (98.1)

PCR=polymerase chain reaction; SD=standard deviation.

symptom cluster with its grades of interference with daily life correlated well with the standardised Fatigue Assessment Scale questionnaire scores (supplementary table B).

We also looked at patterns of co-occurrence between clusters. Interestingly, we found that smell or taste disorder was the cluster with the weakest co-occurrence with any other symptom cluster (supplementary figure F). Fatigue, as the most prevalent symptom cluster, frequently co-occurred with neurocognitive impairment and chest symptoms.

Associations of sociodemographic and other variables with symptom clusters

We explored characteristics associated with the 13 symptom clusters (supplementary table C). The mutually adjusted models included demographic and lifestyle variables, the severity of acute infection, time since infection, and pre-existing comorbidities. Importantly, time since acute infection showed no association with symptom clusters (except for a weak association with an altered sense of smell/taste). The strongest consistent association was for initial outpatient or inpatient care versus no medical care during acute infection (as a proxy for severity of the initial infection), in particular for rash/paraesthesia, chills/fever, and hair loss. The second strongest consistent association was for female sex. Most of these associations became stronger when we restricted the analysis to symptom clusters with a level of impairment of moderate to strong (supplementary table D).

Body mass index and smoking (particularly current smoker status) also seemed to be risk factors for several symptom clusters. Increasing age was a risk factor for fatigue, neurocognitive impairment, and musculoskeletal pain (among others). Musculoskeletal and mental pre-existing disorders were associated with occurrence of reporting any symptom and with many different symptom clusters, whereas the associations of other pre-existing conditions with any or specific symptom clusters were variable and often weak.

Impaired recovery of general health and working capacity

We next examined the association between symptom clusters and general health and working capacity (percentage recovered compared with before the acute infection). The self-reported mean health recovery among respondents was 89.5% (corresponding to an overall loss of 11.5%, 95% confidence interval 11.2% to 11.7%), and the overall loss of working capacity was 10.7% (10.4% to 11.0%). The various symptom clusters differed with regard to the associated loss of health and working capacity (fig 2). In terms of population attributed loss, the fatigue cluster with the highest prevalence contributed most, with a 2.27% (2.07% to 2.47%) loss of general health and a 2.32% (2.09% to 2.56%) loss of working capacity; estimates of population attributable loss for all other clusters were below 2%. Neurocognitive impairment had a significantly stronger effect on loss of working capacity than on loss of health. The opposite was

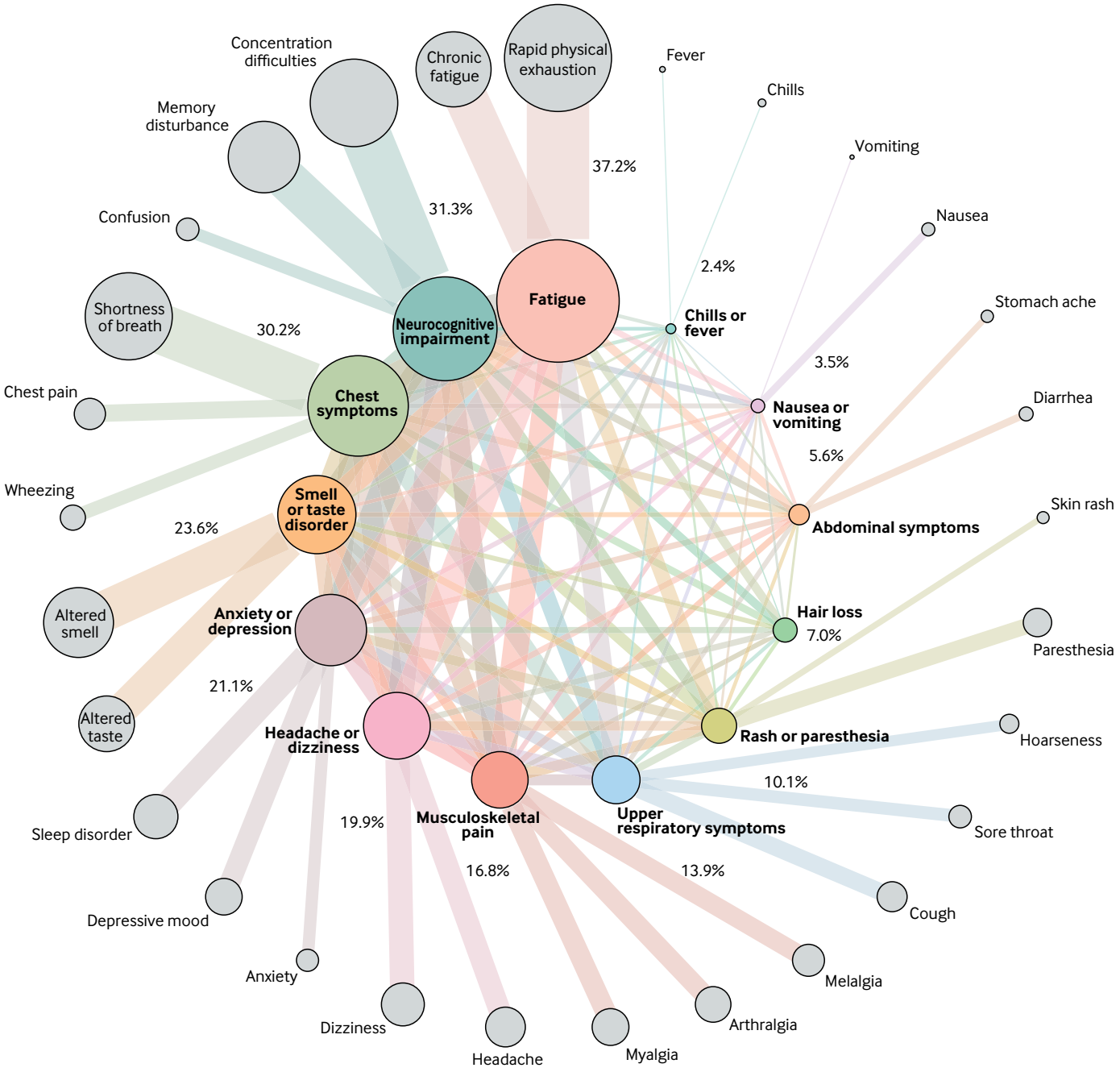

Fig 1 | Co-occurrence network of symptom clusters 6-12 months after acute infection. Outer circles represent individual symptoms. Circle area represents proportion of patients with that symptom. These are linked to inner circles, which represent symptom clusters. Width of link lines again represents proportion of patients with that symptom. Circle area for clusters represents proportion of patients with at least one symptom from that cluster. Central links between symptom clusters represent co-occurrence of symptom clusters. Link width represents degree of co-occurrence. Based on data from 11 536 participants. Only symptoms not present before acute SARS-CoV-2 infection were considered

true for chest symptoms and distorted sense of smell or taste, which both primarily affected general health recovery rather than working capacity (fig 2). Again, notable differences existed according to age and sex (supplementary figure G).

We finally examined how health related quality of life correlated with health recovery and working capacity. We found a good correlation between the SF-12 physical subscore (but less so between the SF-12 mental health subscore) and both health recovery (r=0.68) and working capacity (r=0.69) (supplementary figure H).

As functional consequences such as impaired health recovery or reduced working capacity might become key in estimating and discussing the prevalence and burden of post-covid syndrome among adults, we explored several scenarios for possible alternative case definitions. As shown in figure 3, almost a third of the respondents (30.4%; 3446/11 326) reported their health recovery to be ≤80%, and 26.6% (3028/11 397)

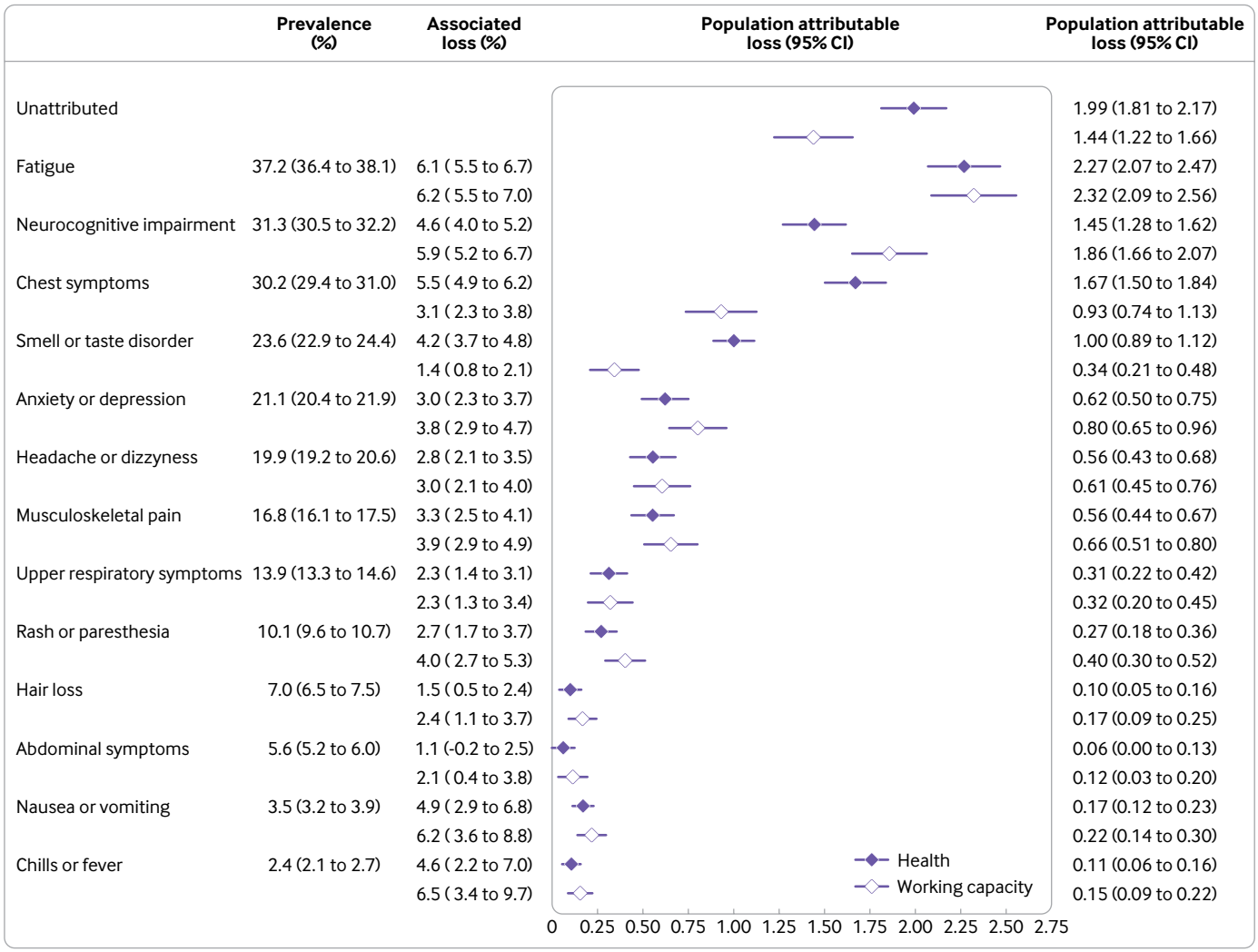

Fig 2 | Prevalence of symptom clusters 6-12 months after acute infection (only symptoms not present before acute SARS-CoV-2 infection) and associated loss (%) and population attributable loss (%) of general health (n=10 268; average loss 11.5%, 95% CI 11.2% to 11.7%) and working capacity (n=10 324; average loss 10.7%, 10.4% to 11.0%)

of the respondents reported ≤80% working capacity recovered in comparison with the situation before the acute infection. If such reduced health or working capacity was combined with reporting (any) new symptom of moderate or strong impairment of daily life, we estimated a prevalence of 28.5% (3289/11 536) among respondents (corresponding to an age and sex standardised prevalence of 26.5%). Given the response rate of 24% (12 053/50 457) and potential selection and recall bias, the absolute prevalence numbers should be interpreted with caution. Under the assumption of all non-responders having completely recovered, the overall prevalence of post-covid syndrome according the definition above would be 6.5% (3289/50 457), or 4.6% (1145/24 959) among men and 8.4% (2144/25 483) among women.

Discussion

This large population based study found a considerable burden of symptom clusters with possible sequelae six to 12 months after SARS-CoV-2 infection affecting both general health and working capacity. Although a variety of long lasting complaints was reported, few symptom clusters drove this burden, and fatigue, neurocognitive impairment, and chest symptoms (for example, shortness of breath) seemed to be the key health problems. A novel and important finding was that specific symptom clusters differed in their impact on health recovery and working capacity. Fatigue and neurocognitive impairment, as well as being the most prevalent health problems in this study, seemed to be most relevant for both impaired health recovery and reduced working capacity. A second important finding already observed by others was that most symptoms and symptom clusters were more frequent among women than men and among people with more severe acute infection, and post-covid syndrome also affected younger participants. We note that our study cohort was infected mainly with the wild type of SARS-CoV-2 as the first variants of concern appeared in January 2021 in Germany. On the basis of national data on the spread of variants of concern,[16] we estimated that less

		No	Prevalence (%)	Standardised prevalence (95% CI)	Minimum possible (%)
Any (new) symptom	Total	11536	63.7 (62.8 to 64.6)	61.8 (60.9 to 62.7)	14.6
	Men	4747	56.8 (55.4 to 58.2)	55.3 (53.9 to 56.8)	10.8
	Women	6789	68.5 (67.4 to 69.6)	67.9 (66.8 to 69.0)	18.3
Any (new) symptom moderate to strong	Total	11536	41.5 (40.6 to 42.4)	39.2 (38.3 to 40.1)	9.5
	Men	4747	34.0 (32.7 to 35.4)	32.3 (31.0 to 33.7)	6.5
	Women	6789	46.8 (45.6 to 48.0)	45.7 (44.5 to 46.9)	12.5
Any (new) symptom treated	Total	11536	11.4 (10.8 to 12.0)	10.4 (9.9 to 11.0)	2.6
	Men	4747	9.0 (8.2 to 9.9)	8.2 (7.5 to 9.0)	1.7
	Women	6789	13.0 (12.2 to 13.8)	12.5 (11.7 to 13.3)	3.5
Health recovered <100%	Total	11326	55.4 (54.5 to 56.4)	53.3 (52.3 to 54.2)	12.4
	Men	4672	50.9 (49.5 to 52.4)	49.0 (47.5 to 50.5)	9.5
	Women	6654	58.6 (57.4 to 59.8)	57.3 (56.1 to 58.6)	15.3
Working capacity recovered <100%	Total	11397	47.1 (46.2 to 48.0)	44.3 (43.4 to 45.3)	10.6
	Men	4700	43.5 (42.1 to 44.9)	40.9 (39.5 to 42.4)	8.2
	Women	6697	49.6 (48.5 to 50.8)	47.6 (46.4 to 48.8)	13.0
Health recovered ≤80%	Total	11326	30.4 (29.6 to 31.3)	28.4 (27.6 to 29.3)	6.8
	Men	4672	27.1 (25.9 to 28.4)	25.4 (24.2 to 26.7)	5.1
	Women	6654	32.7 (31.6 to 33.9)	31.2 (30.1 to 32.4)	8.6
Working capacity recovered ≤80%	Total	11397	26.6 (25.8 to 27.4)	24.4 (23.6 to 25.2)	6.0
	Men	4700	24.1 (22.9 to 25.3)	22.1 (21.0 to 23.3)	4.5
	Women	6697	28.3 (27.3 to 29.4)	26.6 (25.5 to 27.7)	7.4
Health or working capacity recovered ≤80%	Total	11512	34.6 (33.7 to 35.5)	32.5 (31.7 to 33.4)	7.9
	Men	4740	31.0 (29.7 to 32.4)	29.2 (28.0 to 30.6)	5.9
	Women	6772	37.1 (36.0 to 38.3)	35.6 (34.5 to 36.8)	9.9
Health or working capacity recovered ≤80% and any (new) symptom, moderate to strong	Total	11536	28.5 (27.7 to 29.3)	26.5 (25.7 to 27.4)	6.5
	Men	4747	24.1 (22.9 to 25.4)	22.6 (21.4 to 23.8)	4.6
	Women	6789	31.6 (30.5 to 32.7)	30.3 (29.2 to 31.4)	8.4
Substantial fatigue (FAS>21)	Total	11141	41.9 (41.0 to 42.8)	39.6 (38.7 to 40.5)	9.3
	Men	4579	33.4 (32.1 to 34.8)	32.0 (30.7 to 33.4)	6.1
	Women	6562	47.8 (46.6 to 49.0)	46.8 (45.6 to 48.1)	12.3
Extreme fatigue (FAS>34)	Total	11141	11.2 (10.6 to 11.8)	10.4 (9.8 to 11.0)	2.5
	Men	4579	8.5 (7.7 to 9.4)	10.4 (9.8 to 11.0)	1.6
	Women	6562	13.1 (12.3 to 13.9)	12.7 (11.9 to 13.5)	3.4

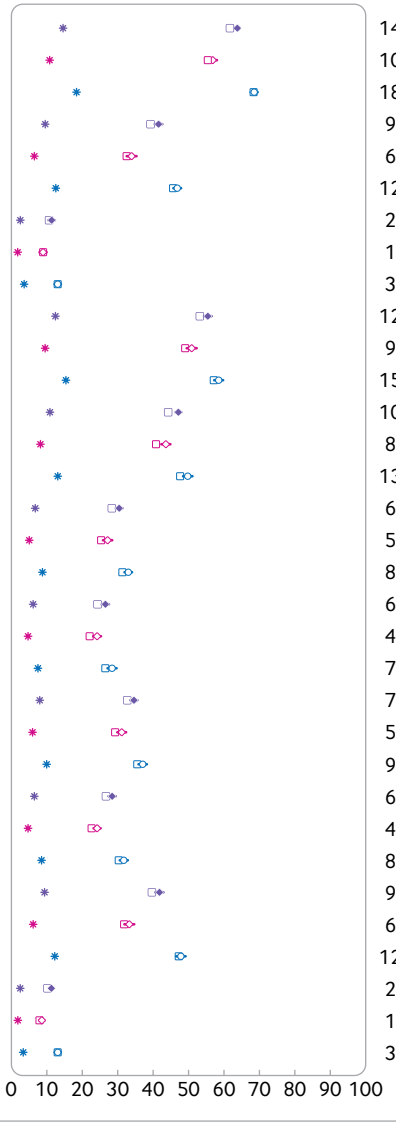

Fig 3 | Prevalence (%) of post-covid syndrome according to different criteria for possible case definitions based on self-reported (new) symptoms, Fatigue Assessment Score (FAS), and recovered general health and working capacity

than 15% of the cohort had been infected with B.1.1.7 (alpha) and less than 1% with B.1.351 (beta).

Comparison with other studies

The relevance in particular of fatigue and neurocognitive impairment, in this and earlier work,[17 18] is noteworthy for three reasons. Firstly, fatigue or tiredness and exercise intolerance and similar problems are definitely more frequent in survivors of covid-19 than in control populations,[19-26] and they have been the main complaints in many studies of long covid, although few of them (12 of 43 evaluable studies in a recent review) used standardised instruments to quantify or validate self-reported symptoms of fatigue.[9] The Fatigue Assessment Scale instrument, used by us and in a population based Swiss study,[20] assesses fatigue largely distinct from depressive symptoms, anxiety, and neuroticism, and seemed to support the validity of self-reported symptoms of fatigue with different grades of impairment in our study. Whether alternative fatigue assessment instruments provide better sensitivity and specificity in the current pandemic setting is unknown but merits further study. Secondly, fatigue was frequently accompanied by other prevalent symptom clusters, such as chest pain and neurocognitive impairment, but also co-occurred with anxiety/depression as a symptom cluster including sleep disorders and with many other complaints such as pain syndromes—similar to observations elsewhere.[19 27-30] This may indicate some overlap of post-covid syndrome with myalgic encephalomyelitis/chronic fatigue syndrome, which may include similar

sometimes relapsing symptoms and usually persists for years rather than for months. Further studies are needed to investigate this overlap.[31 32] A third aspect is that not only has neurocognitive impairment frequently been self-reported after acute SARS-CoV-2 infection, as in this study, but it has already been validated in several studies as measurable deficiencies in reasoning, problem solving, spatial planning, target detection, and diverse memory functions.[33-38] At least some of the studies suggested lack of improvement of cognitive performance measures after covid-19 over time,[29 34] and we also had no evidence of decreasing prevalence of neurocognitive symptoms within our observation period six to 12 months after acute infection. This may indicate that, similarly to fatigue, this disorder might develop into a chronic health problem in an unknown proportion of patients.

Previous epidemiological studies of post-covid syndrome have been challenging, with results being difficult to interpret given the variety and heterogeneity of methods used, including the differences in selection of patient populations and response rates, availability of comparison groups, different follow-up periods, and inconsistent terms used to describe symptoms and adverse health conditions. The prevalence of post-acute symptoms has varied widely across these studies also because often any symptom has been included in interviews and questionnaires, irrespective of whether it already existed before covid-19 or whether it was considered severe and functionally relevant. In a large survey from the UK (with 76 155 participants after confirmed acute SARS-CoV-2 infection), for example, self-reported tiredness and fatigue were quite frequent among the 37.7% of participants having (any) persistent symptoms 12 weeks or more after acute infection.[30] However, only a third of the respondents considered their symptoms to be "severe," the questionnaire did not include cognitive impairment items, and the number of respondents reporting one versus more than one symptom differed greatly, making a valid overall prevalence estimate of post-covid syndrome difficult.

Strengths and limitations of study

Strengths of this work are the large number of participants, the defined period between six and 12 months after PCR confirmed SARS-CoV-2 infection, and the population based approach with inclusion of all infected people who were subject to the statutory reporting requirement within defined geographic regions. Furthermore, we used a within participant comparison considering the symptom frequency before acute infection. Besides general health and working capacity, we included other measures assessing symptom severity and their individual consequences as well as potential societal consequences such as work ability.

Limitations include a lack of medical validation of the self-reported nature of symptoms and sequelae. Also, recall bias has to be considered when reporting symptoms from the past, especially in participants with neurocognitive sequelae. Furthermore, we had a limited response with the possibility for selection bias (for example, potential for overestimation of prevalence measures) and some overrepresentation of older people and women (supplementary table E). Thus, we cannot provide valid and reliable prevalence estimates in the affected population. However, our study shows how different working definitions for post-covid syndrome can yield widely ranging prevalence estimates, between 64% (any post-acute symptom not present before acute infection included) and 11% (counting only extreme fatigue based on a correspondingly high Fatigue Assessment Scale score), and we can only speculate that whatever definition of post-covid syndrome is being used the true prevalence probably lies between the minimum possible estimates shown in figure 3 and the raw estimates for the participant population.

Our study regions were located around medium sized university cities, and respondents had higher education than the general population, which may limit generalisability. Also, our study focused on the working age population and should not be generalised to populations older than 65 or to children and adolescents. In addition, 5.5% of the postal invitations could not be delivered, probably because people were seasonal workers or recent immigrants who had already moved to another place without a postal forwarding request. This small group might have been enriched by non-white ethnicities, which are now not well represented in our data. As we have only a before-after comparison within infected participants (which is an advantage in limiting confounding as every participant is their own control), we cannot differentiate between the impact of the pandemic itself and its consequences such as non-pharmaceutical and public health interventions on symptoms and symptom reporting from direct consequences of the virus infection. Unfortunately, in Germany, test negative controls were not available within the sampling frame of our cases as a comparison group (as negative tests were not reported by name and address to the public health authorities owing to lack of a legal basis). Finally, we used only one specific method for symptom clustering and cannot exclude the possibility that other methods would define different and presumably larger clusters. Symptom frequency and clustering may be different with more recent virus variants.

Conclusions

As one of the largest population based studies, with a follow-up of six to 12 months after acute SARS-CoV-2 infection, we show a considerable burden of symptom clusters with possible individually and societally relevant sequelae also affecting younger adults with a history of mild acute infection. Fatigue and neurocognitive impairment were common in the post-acute phase and considerably impaired general health and working capacity. Given the individual and societal burden of post-covid sequelae, the underlying biological abnormalities and causes need urgent

clarification to define adequate treatment options and develop effective rehabilitation measures.

AUTHOR AFFILIATIONS

[1]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

[2]Institute for Immunodeficiency, Medical Centre and Faculty of Medicine, Albert-Ludwigs-University, Freiburg, Germany

[3]Institute of Virology, Department of Infectious Diseases, University Hospital Heidelberg, Heidelberg, Germany

[4]Department of Health Protection, Infection Control and Epidemiology, Baden-Wuerttemberg Federal State Health Office, Ministry of Social Affairs, Health and Integration Stuttgart, Germany

[5]Division of Infectious Diseases, Department of Internal Medicine I, University Hospital Tübingen, Tübingen, Germany

[6]Department of Internal Medicine IV, University Hospital Heidelberg, Heidelberg, Germany

[7]Division of Sports and Rehabilitation Medicine, Department of Medicine, Ulm University Hospital, Ulm, Germany

[8]Division of Infectious Diseases, Department of Medicine II, Medical Centre and Faculty of Medicine, Albert-Ludwigs-University, Freiburg, Germany

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Data sharing: Data from EPILOC phase 1 are available for research purposes upon request from the corresponding author at winfried.kern@uniklinik-freiburg.de.

The study guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: At the time of writing, results from this study have been shared with Federal State public health officials, with the Baden-Württemberg state university hospitals, and with the global community by posting on a preprint server. Findings have helped to inform the short term state health planning for long covid units and are also informing the state ministry of science, research and art planning. We will distribute the publication and main results via different social media and via the press offices of the contributing universities. We also plan a central press conference with the Federal State ministry of science, research and art and the state Health Office to present data and allow official press inquiries. In addition, we will contact patient advocacy groups and inform them about our results in lay terms. The data will further be presented at national scientific conferences such as the coming congress of the German Epidemiological Association (DGEpi) congress in Greifswald (Germany) at the end of September 2022.

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Web appendix: Supplementary materials