

1 **Title:** Psychological distress after COVID-19 recovery and subsequent prolonged post-acute sequelae
2 of COVID-19: A longitudinal study with 1-year follow-up in Japan.

3
4 **Authors:**

5 Megumi Hazumi^{1,2}, Mayumi Kataoka^{1,3}, Zui Narita⁴, Kentaro Usuda¹, Emi Okazaki¹, and Daisuke
6 Nishi^{1,3*}

7 **Affiliation:**

8 ¹Department of Public Mental Health Research, National Institute of Mental Health, National Center
9 of Neurology and Psychiatry, 4-1-1 Ogawahigashicho, Kodaira, Tokyo 187-8553, Japan

10 ²Department of Sleep-Wake Disorder, National Institute of Mental Health, National Center of
11 Neurology and Psychiatry, 4-1-1 Ogawahigashicho, Kodaira, Tokyo 187-8553, Japan

12 ³Department of Mental Health, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo,
13 Bunkyo-ku, Tokyo 113-0033, Japan

14 ⁴Department of Behavioral Medicine, National Institute of Mental Health, National Center of
15 Neurology and Psychiatry, 4-1-1 Ogawahigashicho, Kodaira, Tokyo 187-8553, Japan

16
17 **Corresponding author:**

18 Daisuke Nishi, MD, PhD

19 Department of Public Mental Health Research, National Institute of Mental Health, National Center of
20 Neurology and Psychiatry, 4-1-1 Ogawahigashicho, Kodaira, Tokyo 187-8553, Japan

21 Tel: +81-42-341-2711 □ Fax: +81-42-346-1950

22 Email: d-nishi@m.u-tokyo.ac.jp

23
24 **Abstract:**

25 **Background:** This study investigated the longitudinal association between psychological distress in
26 the post-acute phase and the subsequent prolonged post-acute sequelae of COVID-19 (PASC) among
27 individuals with PASC. **Methods:** An online longitudinal survey with 1-year interval was conducted
28 from July to September 2021 (T1) and July to September 2022 (T2). Individuals who were 20-years-
29 old or older, had a positive Polymerase Chain Reaction test, were one month post-infection, and did
30 not select “Nothing” to a question regarding PASC presence were included. The primary outcome was
31 the presence of PASC at T2. The presence of general, respiratory, muscular, neurological,
32 gastrointestinal, dermatological, and cardiac symptoms at T2 was also used as an outcome among
33 patients with relevant symptoms at time 1 (T1). Exposure was measured using the Kessler distress
34 scale (K6) at T1, and those whose K6 was 13 or higher were identified as having psychological
35 distress. Marginal structure models with robust standard errors were used to examine the association
36 between psychological distress at T1 and any PASC symptoms at T2, and the associations between
37 psychological distress and each symptom at T2 among participants with relevant symptoms at T1.

1 **Results:** A total of 1674 patients were analyzed; 17% had psychological distress. ; In total, 818
2 (48.9%), 523 (31.2%), and 672 (40.1%) patients reported general, respiratory, and neurological
3 symptoms at T1, respectively. Individuals with psychological distress had higher odds of any
4 symptoms at T2 (Odds Ratio [OR] = 1.81, 95% Confidence Interval [CI] = 1.08 – 3.03) and general and
5 respiratory symptoms at T2 among participants with relevant symptoms at T1 (OR = 1.95, 95% CI =
6 1.02 – 3.76; OR = 2.44, 95% CI = 1.03 – 5.80). **Conclusion:** Psychological distress in the post-acute
7 phase may lead to prolonged PASC symptoms, mainly general and respiratory symptoms, at the 1-year
8 follow-up in individuals with PASC.
9 (294/300 words)

10

11

12 **Keywords**

13 Post-Acute COVID-19 Syndrome, Psychological Distress

14

15 **Key Messages**

16 Psychological distress before infection and during the acute phase predicts prolonged Post-Acute
17 Sequelae of COVID-19 (PASC); however, in individuals with PASC, it is unclear whether
18 psychological distress during the post-acute phase predicts prolonged PASC. This longitudinal survey
19 indicated that psychological distress in the post-acute phase led to prolonged any levels of PASC,
20 especially general and respiratory symptoms, at the 1-year follow-up. Therefore, mental health care
21 for individuals with PASC may help to improve or mitigate prolonged PASC.

22

23

1 **Introduction**

2 Post-acute sequelae of COVID-19 (PASC) are symptoms that persist or appear after the acute
3 phase, that is, after four weeks of COVID-19 infection[1]. PASC symptoms vary, but may include
4 dyspnea, cough, fatigue, fever, anosmia, ageusia, arthralgia, myalgia, hair loss, chest pain, palpitations,
5 throat pain, and others[2,3]. PASC can last more than several months and is as severe as other
6 infectious diseases. According to a systematic review, 54%, 55%, and 54% of COVID-19 survivors
7 had at least one PASC at one month, two to five months, and six or more months, respectively[1], and
8 50.1% continued to suffer from PASC for more than one year[4]. Abnormal pulmonary function
9 (45.6%), fatigue (28.7%), and neurological symptoms (18.7%) were mainly observed[4]. The
10 prevalence of symptoms was significantly higher in individuals infected with COVID-19 than in those
11 without after one year had passed[5], and such symptoms were not significantly reduced between one
12 year and two years after infection[6]. The prevalence of sequelae in patients with COVID-19 is
13 comparable to that in other respiratory infectious diseases[7]. Considering that persistent symptoms
14 not only affect these individuals' quality of life[8,9] but are also costly from an economic
15 perspective[10–12], it is important to identify factors that cause PASC to persist so that it can be
16 alleviated and prevented.

17 Having mental health problems before COVID-19 infection and in the acute phase is suggested to
18 be one factor that can cause prolonged PASC. The association between preexisting mental health
19 problems and PASC has been reported in several cross-sectional surveys[13–17]. According to several
20 longitudinal studies, preexisting mental health problems predict PASC at 3, 12, and 15 months after
21 infection[15,18–20]. An extensive cohort study reported that pre-existing depression predicted
22 prolonged PASC after 6, 12, and 18 months passed[21]. Mental health problems in the acute phase
23 have also been suggested to influence PASC. A prospective cohort study indicated that depressive
24 symptoms in the acute phase predicted the presence of PASC at one and three months after infection
25 [22]. Another prospective cohort study revealed that depression in the acute phase predicted prolonged
26 PASC at 12 months after infection[23]. Considering these factors, mental health problems before the
27 appearance of PASC may determine whether PASC will persist for more than 12 months.

28 However, it remains unclear whether mental health problems after the appearance of PASC
29 predict prolonged PASC. Several studies suggest that mental health problems may develop or continue
30 after the acute phase among those with PASC. Individuals who recover from COVID-19 are at risk of
31 developing new mental health problems[4,24–27]. COVID-19-related experiences, such as perceived
32 discrimination and negative thoughts about the infection, were reported to be associated with mental
33 health problems, independent of pre-existing mental health problems[28,29]. Several cross-sectional
34 studies also suggest that preceding PASC affects mental health after recovery[30–34], and longitudinal
35 studies have suggested that presence of PASC predicts mental health problems[35,36]. On the other
36 hand, mental health problems after acute illness are suspected to predict subsequent prolonged PASC,
37 considering that mental health problems generally exacerbate the severity or progression of various

1 physical diseases[37]. Psychological distress after the appearance of to contribute to prolonged PASC
2 as it is possible for mental health to develop after the acute phase of infection, and the possibility of
3 mental health problems exacerbating physical health problems. Various PASC symptoms, both general
4 symptoms, such as fatigue and fever, and respiratory symptoms, including dyspnea and shortness of
5 breath, may be influenced by mental health problems. The association between respiratory symptoms
6 and mental health problems is well known[38,39] because negative feelings generally promote the
7 perception of dyspnea, airway obstruction, and airway reactivity through the CNS and autonomic
8 pathways[40,41]. General symptoms, such as fatigue and fever, are generally affected by mental health
9 problems[42–44] through the elevation of interleukin-1 (IL-1) and IL-6, which induce fatigue and
10 fever[45,46].

11 Therefore, this study aimed to investigate whether psychological distress after the acute phase
12 predicts subsequent prolonged PASC at a one year follow-up afting forunder adjusted pre-existing
13 mental health problems in individuals with PASC. This study is believed to help elucidate the
14 significance of providing mental health care to individuals with PASC with the aim of alleviating their
15 symptoms.

16

17

18 **Materials and Methods**

19 *Participants and Setting*

20 The two-point longitudinal survey for COVID-19 was performed at 1-year intervals through the
21 Rakuten Insight Corporation, which is the company that delivering the most mass panels in Japan for
22 online surveys[47]. The panelists received information about study recruitment, and those interested in
23 the study accessed an online survey form. If the individuals agreed to participate in the study by
24 clicking the consent declaration button on the website after reading the informed consent document,
25 they were considered to have responded to the questionnaire. Those who completed the questionnaire
26 received rewards points that could can be used for online shopping. The data at Time 1 (T1) and Time
27 2 (T2) were collected from July to September 2021 and July to September 2022, respectively.

28 Individuals who met the following criteria were included: 1) Over 20 years old, 2) answered “yes”
29 to the screening question “Have you been infected with COVID-19?”, 3) selected an option other than
30 “Nothing” to the question “What kind of PASC symptoms do you have now?”, and 4) more than a
31 month after infection, based on the definition of PASC[48]. In addition, data that met the following
32 criteria were excluded from the analysis: duplication, incorrect answers to the dummy question,
33 statement that they had not been infected, inconsistent answers, and outlier answers according to their
34 demographic information responses.

35

36 *Measurements*

37 *Outcome*

1 The answer options to the question “What kind of physical PASC symptoms do you have now?”
2 at T2 were used as the outcomes. Options were generated based on the symptoms list by the World
3 Health Organization[49] and the detailed answers of “Others” symptoms at T1: “Nothing,” “Fever,”
4 “Cough,” “Fatigue,” “muscle or body pain,” “Sore throat,” “Headache,” “Diarrhea,” “Red or irritated
5 eyes,” “Altered taste,” “Altered smell,” “A rash on skin, or discoloration of fingers or toes,”
6 “Difficulty breathing or shortness of breath,” “Chest pain or pressure,” “Loss of speech or mobility,”
7 “Menstrual problems,” “Blurred vision,” “Dizziness,” “Constipation or acid reflux” “Convulsion,”
8 “Neuralgia,” “Tachysystole and palpitation,” “Tinnitus and ear problems,” “New Allergy” and
9 “Others.” Unless the respondent selected the “nothing” option, they were able to select multiple
10 options. Those who selected “Others” were additionally asked to fill in the details in the free text field,
11 and authors categorized the described complaint by compiling similar symptoms. Furthermore, these
12 symptoms were classified into the following symptom groups based on a previous study[50]:
13 “General,” “Respiratory,” “Musculoskeletal,” “Neurologic,” “Gastrointestinal,” “Eye,”
14 “Dermatologic,” “Cardiac,” “Urinary,” and “Others.” Details regarding the symptoms and
15 classifications are provided in Appendix 1.

16 To confirm whether any physical PASC was maintained, the option “Nothing” at T2 was used as
17 a primary outcome. Those who selected “Nothing” were identified as having no PASC, and those who
18 didn’t were identified as having some PASC. The presence of each symptom group at T2 was also
19 used as an outcome measure.

20 These variables and classification procedures were also employed for the data at T1 in subgroup
21 analyses.

22

23 ***Exposure***

24 The Kessler Psychological Distress Scale (K6) at T1 was used to measure the severity of
25 psychological distress over the past 30 days at T1[51–53]. The K6 comprises six items with 5-point
26 Likert scales (0–4 points). A total score of 13 or higher indicates psychological distress[51].

27

28 ***Covariates***

29 The following variables reported at T1 were used as covariates: sex (male, female, others)[54,55],
30 age group (20–29, 30–39, 40–49, 50–59, ≥ 60)[54,55], income level (< Japanese yen [JPY] 3,000,000,
31 < JPY 10,000,000, \geq JPY 10,000,000, unknown or refuse to respond)[56,57], the presence of
32 psychiatric history (yes, no)[24,54,55], hospitalized (yes, no)[54,58], and the presence of acute
33 symptoms (yes, no)[55,58]. We also adjusted for BMI[48,54,59] and pre-existing comorbidities,
34 including respiratory diseases (COPD, asthma, bronchitis, and pneumonia)[54,55,60],
35 hypertension[55,61,62], diabetes[48,59,63], and cardiac diseases (angina and myocardial
36 infarction)[48,64]. These pre-existing comorbidities were identified as those who selected options
37 other than “Nothing before” or “Never,” “Yes, in the past,” “Yes, currently (in hospitals),” and “Yes,

1 currently (not in hospitals)” to the question about above comorbidities.

2

3 ***Patent and Public Involvement***

4 From inception, our research team included COVID-19 survivors to leverage their first-hand
5 experiences in developing the hypothesis and ensuring patient-centered perspectives were integral to
6 our study design.

7

8 ***Analyses***

9 After absolute risks and risk differences were calculated, marginal structure models with robust
10 standard errors were performed to examine the association between the presence of psychological
11 distress at T1 and the occurrence of PASC symptoms at T2[65]. Similar analyses were performed to
12 examine the association between the presence of psychological distress at T1 and the presence of each
13 symptom at T2, including “General,” “Respiratory,” and “Neurologic,” among those with relevant
14 symptoms at T1, given that sample size at T1 was sufficient. covariates were controlled to use inverse
15 probability weighting. Stabilized weights were calculated to determine the presence of psychological
16 distress. We further accounted for the loss to follow-up using stabilized weights. The stabilized
17 weights were multiplied to obtain the final stabilized weights.

18

19 ***Ethics***

20 This study was performed in accordance with the Declaration of Helsinki and was approved by
21 the Research Ethics Committee of the National Center of Neurology and Psychiatry (A2021-034).

22

23

24 **Results**

25 ***Characteristics***

26 Figure 1 illustrates the data collection process. A total of 1674 eligible participants completed the
27 questionnaire at T1, and their data were analyzed. At T2, 673 participants completed the questionnaire.

28 Table 1 presents the demographic characteristics of the participants. Of all participants, 57.6%
29 were male, and the age group of 40–49 years was the largest (29.2%). The proportion of those whose
30 have psychological distress was 17%.

31

32 Table 1. Characteristics

	n=1674	
	n/ mean	%/ SD
Sex		
Male	964	57.6%

Female	699	41.8%
Other	11	0.7%
Age		
20 - 29	271	16.2%
30 - 39	407	24.3%
40 - 49	488	29.2%
50 - 59	371	22.2%
≥ 60	137	8.2%
Income		
< JPY3,000,000	247	14.8%
< JPY10,000,000	1031	61.6%
≥ JPY10,000,000	249	14.9%
Unknown or refuse to respond	147	
BMI	24.01	4.42
Physical comorbidity		
Hypertension	469	28.0%
Diabetes	238	14.2%
Respiratory diseases	651	38.9%
Cardiac diseases	155	9.3%
Psychiatric history	478	28.6%
Hospitalized	639	38.2%
Duration after infection (month)	5.12	4.25
Any acute symptoms	1665	99.5%
Psychological distress (K6 ≥ 13)	284	17.0%
PASC symptom groups		
General	818	48.9%
Respiratory	523	31.2%
Musculoskeletal	190	11.4%
Neurologic	672	40.1%
Gastrointestinal	72	4.3%
Eye	24	1.4%
Dermatologic	137	8.2%
Cardiac	143	8.5%
Urinary	2	0.1%
Other	23	1.4%

1 PASC, Post-acute sequelae of COVID-19; BMI, Body Mass Index; JPY, Japanese Yen; K6, Kessler
2 distress scale

1

2 **Relationships between psychological distress and subsequent prolonged PASC**

3 Table 2 shows the absolute risks and risk differences of the presence of prolonged PASC between
4 those with psychological distress and those without.

5 As table 3 shows, psychological distress at T1 was significantly associated with the presence of
6 any symptoms, general symptoms, and respiratory symptoms at T2 among those with the relevant
7 symptoms at T1 (OR=1.80 [1.08 – 3.01]; OR=1.92[1.002 – 3.67]; OR=2.44[1.03 – 5.80]).

8

9 Table 2. Absolute risks and risk differences of PASC at 1-year follow-up

	Psychological distress		Risk difference
	Yes	No	
Any symptoms	66.1%	50.7%	15.3%
General	55.9%	34.3%	21.5%
Respiratory	51.3%	32.4%	18.9%
Neurologic	47.3%	43.0%	4.3%

10

11 Table 3. Psychological distress as a predictor of prolonged PASC at 1-year follow-up

	OR	95% CI	
		Lwr	Upr
Any symptoms	1.81	1.08	3.03
General	1.95	1.02	3.76
Respiratory	2.44	1.03	5.80
Neurologic	1.14	0.58	2.26

12 OR = Odds Ratio; 95% CI = 95% confidence interval; Lwr, Lower; Upr, Upper

13

14

15 **Discussion**

16 This study investigated the association between psychological distress after recovery from
17 COVID-19 and PASC at one-year follow-up in individuals with PASC after COVID-19 infection.
18 Psychological distress after recovery was significantly associated with subsequent prolonged PASC,
19 both general and respiratory symptoms, at one year among those with relevant symptoms, independent
20 of pre-existing psychiatric problems.

21 These results suggested that psychological distress at the post-acute phase was associated with
22 prolonged PASC of any type. In addition to the mental health problems observed before the post-acute
23 phase[15,18–20,22,23,66], psychological distress after PASC becomes apparent may lead to prolonged
24 PASC. COVID-19 survivors often face discrimination, negative thoughts about COVID-19, and

1 experience unemployment after recovery, which can exacerbate mental health problems
2 [28,29][67][68]. These factors may, in turn, lead to prolonged PASC due to resultant mental health
3 problems.

4 Psychological distress after the acute phase is associated with prolonged general symptoms, such
5 as fatigue and fever, in individuals with PASC. This result is consistent with general symptoms not
6 induced by COVID-19 infection[42–44]. The depressive conditions are known to elevate IL-1 β and
7 IL-6, which cause fever and fatigue[45,46]. Mental health problems related to PASC and COVID-19
8 are believed to activate inflammatory cytokines such as IL-1 β and IL-6 that can prolong general
9 symptoms.

10 Psychological distress after the acute phase is associated with prolonged respiratory symptoms,
11 such as dyspnea and shortness of breath. As respiratory symptoms are unrelated to COVID-19
12 infection[38,39], respiratory symptoms, such as PASC, may be affected by mental health problems.
13 Respiratory symptoms, such as dyspnea, obstruction, and airway sensations, are sensitive to negative
14 emotions[40,41]. Therefore, mental health problems may promote the perception of respiratory
15 symptoms and delay improvements in PASC.

16 Psychological distress was not associated with prolong neurological symptoms, supporting
17 previous findings that the presence of psychological distress did not differ significantly between
18 those with edalting smell or taste after COVID-19 infection and those without [13].

19 These findings underscore the need to routinely assess mental health as a critical aspect of PASC
20 care. Early identification and support for psychological distress may reduce the risk of prolonged
21 PASC. These implications are not limited to the clinical realm for medical professionals but also
22 extended to larger scales, such as regional and societal levels, indicating significant public health
23 implications.

24 This study had some limitations. PASC symptoms were self-reported by the participants. Thus,
25 they were not as subtle as diagnoses made by physicians or determined using validated measurements.
26 Instead, our findings reflect individuals with PASC who are not connected to medical care. We failed
27 to follow-up with over half of the participants, although missing values were complemented by a
28 statistical procedure to minimize missing bias. It cannot be denied that the mental health problems
29 measured in this study emerged prior to the PASC, although mental health problems before the
30 infection were adjusted. The results for several symptoms derived from the small sample size should
31 be interpreted carefully.

32 There are also some strengths to this study. Our data included individuals who were and were not
33 seeing doctors. As some individuals with PASC find it challenging to access healthcare[69,70],
34 collecting participants from both groups is believed to reflect comprehensive PASC characteristics.

35 In conclusion, this study revealed the relationship between mental health problems in the post-
36 acute phase and subsequent prolonged PASC at the 1-year follow-up in individuals with PASC.
37 General and respiratory symptoms were associated with mental health problems. Mental care may

1 reduce the incidence of PASC, especially general and respiratory symptoms. Future intervention
2 studies targeting mental health problems related to PASC should be conducted.

4 **Funding**

5 This work was supported by an Intramural Research Grant for Neurological and Psychiatric Disorders
6 of the National Center of Neurology and Psychiatry (grant number 1-6 and 4-3).

8 **Contributorship statement**

9 Conceptualization: all. Data collection: MH, MK, KU, EO, and DN. Formal analysis: MH.
10 Interpretation of data: MH, MK, ZN and DN. Original Draft preparation; MH. Review and editing: all.
11 Super vision: ZN and DN.

13 **Competing interests statement**

14 DN reports personal fees from Startia, Inc., en-Power, Inc., MD.net, and Takeda Pharmaceutical
15 Company, Ltd. outside of the submitted work. MH, MK, ZN, EO, and KU have no financial conflicts
16 of interest to disclose concerning the study.

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Appendix 1. The symptom classification

Symptom group	Classified symptoms
General	Fever, Fatigue, Loss of speech or mobility, Rigor*, Sweat*, Edma and swell*
Respiratory	Cough, Sore throat, Difficulty breathing or shortness of breath, Other throat problems*
Musculoskeletal	Muscle or body pain
Neurologic	Headache, Altered taste, Altered smell, Dizziness, Convulsion, Neuralgia, Tinnitus and ear problems
Gastrointestinal	Diarrhea, Constipation or acid reflux, Anorexia*
Eye	Red or irritated eyes, Blurred vision
Dermatologic	A rash on skin, or discoloration of fingers or toes, Hair loss*
Cardiac	Chest pain or pressure, Tachysystole and palpitation
Urinary	Urinary*
Others	Menstrual problems, New allergy, other complaints

*categories generated based on the detailed description of the alternative “Others”

The categories “Ear,” ”Metabolic,” and “Reproductive” were not developed because the responses equivalent to these categories were not collected.

1 **Figure Captions**

2 Figure 1. Flow chart

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