Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) in press
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article

https://doi.org/10.1631/jzus.B2300831

Association between post-COVID-19 sleep disturbance and neurocognitive function: A comparative study based on propensity score matching

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Abstract: Despite that sleep disturbance and poor neurocognitive performance are common complaints among coronavirus disease 2019 (COVID-19) survivors, few studies have focused on the effect of post-COVID-19 sleep disturbance (PCSD) on cognitive function.This study aimed to identify the impact of PCSD on neurocognitive function and explore the associated risk factors for the worsening of this condition.This cross-sectional study was conducted via the web-based assessment in mainland China. Neurocognitive function was evaluated by the modified online Integrated Cognitive Assessment (ICA) and the Number Ordering Test (NOT). Propensity score matching (PSM) was utilized to match the confounding factors between individuals with and without PCSD. Univariate analyses were performed to evaluate the effect of PCSD on neurocognitive function. The risk factors associated with worsened neurocognitive performance in PCSD individuals were explored using binary logistic regression.A total of 8692 individuals with COVID-19 diagnosis were selected for this study. Nearly half (48.80%) of the COVID-19 survivors reported sleep disturbance. After matching by PSM, a total of 3977 pairs (7954 individuals in total) were obtained. Univariate analyses revealed that PCSD was related to worse ICA and NOT performance (P<0.050). Underlying disease, upper respiratory infection, loss of smell or taste, severe pneumonia, and self-reported cognitive complaints were associated with worsened neurocognitive performance among PCSD individuals (p <0.050). Furthermore, aging, ethnicity (minority), and lower education level were found to be independent risk factors for worsened neurocognitive performance in PCSD individuals (P<0.050). PCSD was related to impaired neurocognitive performance. Therefore, appropriate prevention and intervention measures should be taken to minimize or prevent PCSD and eliminate its potential adverse effect on neurocognitive function.

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Key words: Post-COVID-19; Sleep disturbance; Neurocognitive function; Digital assessment

1 Introduction

The global incidence of COVID-19 has exceeded 750 million cases (World Health Organization, 2023). Remarkably, even though a substantial proportion of patients avoid severe complications, most of them may experience post-COVID-19 conditions during the recovery phase (i.e., fatigue, physical discomfort, impaired taste and smell) and neurocognitive impairment (i.e., attention deficit and memory decline) (World Health Organization, 2023). Additionally, a wide range of mental and psychological issues have been reported, such as

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Received Nov. 16, 2023; Revision accepted Mar. 19, 2024;
Crosschecked xxx. xx, 20xx; Published online xxx. xx, 20xx

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insomnia, depression, anxiety, posttraumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD) (Salfi et al., 2023). Post-COVID-19 conditions significantly diminish the quality of life (QoL) of COVID-19 survivors (Amdal et al., 2021; Ceban et al., 2022).

Sleep disturbance and worsened neurocognitive performance are common and distressing problems among COVID-19 survivors (Iqbal et al., 2021; Crivelli et al., 2022). A previous study revealed that 78.60% of post-COVID-19 individuals experienced sleep disturbance (Jahrami et al., 2022). According to Davis et al. (2021), the overall incidence rate of post-COVID-19 sleep disturbance (PCSD) was 28.98%. During the post-COVID-19 recovery period, sleep disturbance negatively impacted QoL (Linh et al., 2023). One study suggested that abnormalities in neurocognitive function can persist even 11 months after COVID-19 infection (Tedjasukmana et al., 2023). Another study conducted comprehensive neuropsychological assessments among COVID-19 patients and revealed widespread deficits in attention, processing speed, memory, executive function, language, and visuospatial abilities (Díez-Cirarda et al., 2023). A longitudinal study revealed that the worsened neurocognitive performance persisted in 12% to 34% of patients during one-year follow-up (Oliver et al., 2023).Neurocognitive function includes attention, working and episodic memory, and executive function, which are all vulnerable to sleep disturbance (Pearson et al., 2023; Zaheed et al., 2023). The COVID-19 infection-associated decline in neurocognitive performance has been described, but the literature has yet to document any evidence of worsened neurocognitive performance associated with PCSD.

Early post-COVID-19 neurocognitive studies were limited by their accessibility, particularly because they relied on traditional cognitive assessment methods, which are inherently restricted by the need for physical patient presence and excessive time and space requirements. Moreover, traditional methods are inadequate and insensitive in evaluating subtle neurocognitive functional changes in post-COVID-19 cognitions (Ceban et al., 2022). Due to the rapid spread of SaRS-CoV-2 and the large scale of infection, the challenges associated with traditional methods have become more prominent. Consequently, the need for high-quality digital cognitive assessments that can be conducted remotely and asynchronously has become increasingly evident. These assessments are crucial for addressing the growing demand for neuropsychological evaluation (Becker et al., 2023).

This study aimed to elucidate the association between PCSD and neurocognitive function using digital neurocognitive tasks. We hypothesized that COVID-19 survivors with sleep disturbance would exhibit worse neurocognitive performance than survivors without sleep disturbance.

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2 Methods

2.1 Participants and procedures

This cross-sectional study was conducted between January 15 and 29, 2023 at the Nanfang Hospital, Southern Medical University (Guangzhou, China), to assess neurocognitive function via a digital questionnaire and digital neurocognitive tasks in COVID-19 survivors. The snowball sampling method was used. All inclusion and exclusion criteria were based on self-reported information. Eligible individuals were required to meet the following criteria: 1) a history of COVID-19 infection; 2) ≥18 years of age; 3) residence in mainland China; 4) no presence of severe upper limb joint issues or movement disorders; and 5) no existing visual impairment.

Individuals excluded from this study included those with 1) dementia; 2) current mental disorders (i.e., schizophrenia, bipolar disorder, or major depression) or brain diseases (i.e., cerebrovascular or cardiovascular accidents, or epilepsy) that might affect the assessment result; and 3) taking medications that could bias the results (i.e., sedative-hypnotic drugs, antipsychotic drugs, or nonsteroidal anti-inflammatory drugs). A self-reported questionnaire was used to assess the inclusion and exclusion criteria. We obtained ethical approval from the ethics committee of Nanfang Hospital, Southern Medical University (No. NFEC-2022-307). The flowchart of this investigation is presented in **Fig. 1**.

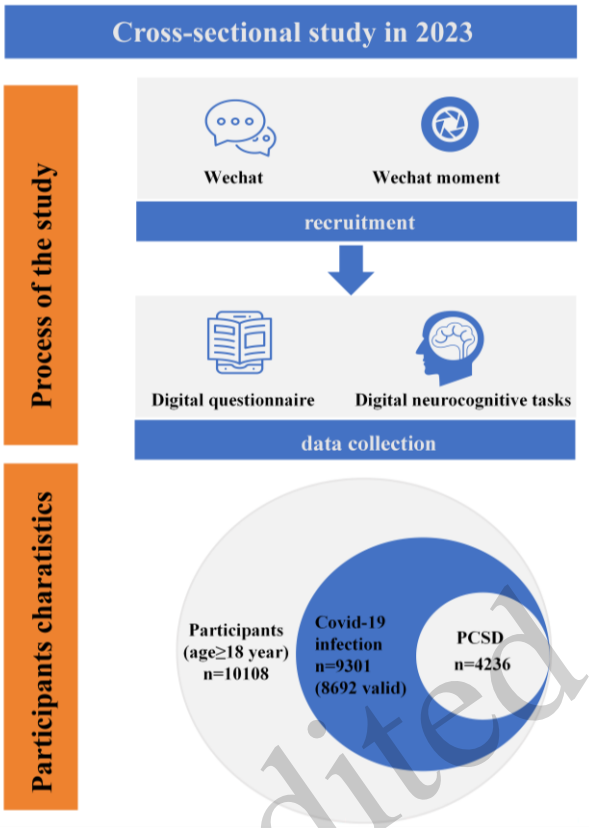

Fig. 1 Flowchart of the study.
Abbreviations: PCSD, post-COVID-19 sleep disturbance.

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2.2 Measurements

2.2.1 Clinical data

We used a digital self-assessment questionnaire to collect information on sociodemographic characteristics, including gender, age, height, weight, ethnicity, marital status, and education level. COVID-19 related factors, including history of SARS-CoV-2 infection, date of infection and recovery, presence of underlying disease, and presence of the conditions (asymptomatic infection, upper respiratory infection, loss of smell or taste, and severe pneumonia) during the epidemic of COVID-19, were also recorded. In addition, post-COVID-19 cognitive complaints (inflexible thinking and slowed information processing speed) and sleep disturbance were also investigated. Inflexible thinking was self-reported using the question “Did you feel thinking becomes inflexible after recovering from COVID-19?” with the options “Yes” or “No.” Slowed information processing speed was self-reported using the question “Did you feel a slowdown in information processing speed after recovering from COVID-19?” with the options “Yes” or “No.” Sleep disturbance was self-reported using the question “Did you suffer sleep disturbance after recovering from COVID-19?” with the options “Yes” or “No.”

2.2.2 Digital neurocognitive tasks

Each individual was required to finish the digital neurocognitive tasks on a mobile phone based on the Integrated Cognitive Assessment (ICA) and the Number Ordering Test (NOT).

The ICA is a 5-min computerized neurocognitive assessment tool focusing on a rapid visual categorization

task. The ICA evaluates the information processing speed and semantic processing by measuring accuracy and response reaction time (RT) (Khaligh-Razavi et al., 2019). In the test, one hundred grayscale natural images (50 animals and 50 nonanimals) of varying difficulty were presented in the center of the smartphone screen. Each image was shown for 100 ms followed by a 20 ms interstimulus interval (ISI) and a 250 ms dynamic noisy mask. Then, the participants were asked to click on the screen as quickly as possible following the rules for categorizing animals vs nonanimals (Kalafatis et al., 2021). The ICA is strongly correlated with the Montreal Cognitive Assessment (MoCA) and Addenbrooke's Cognitive Examination-Revised (ACE-R) scores. It is a dominant standard cognitive assessment tool in both primary care and memory clinic settings (Khaligh-Razavi et al., 2019; Shore et al., 2023).

NOT is a combination and adaptation of the Digital Ordering Test (DOT) and Trail Making Test-A (TMT-A) (Werheid et al., 2002; Bowie and Harvey, 2006), which was adapted to a mobile-friendly platform. It evaluates executive functioning, working memory, visual scanning, and information processing speed. If the participant clicks incorrectly, the trial will immediately progress to the next trial. Participants were asked to connect a series of 3 to 7 digits in ascending order. The total time for the NOT was limited to 1 min. The primary variables of interest were the total score and accuracy of the completed trials in NOT. The total score was calculated by multiplying the number of correctly clicked digits by the accuracy of the completed trials. We selected this task based on its sensitivity in detecting cognitive impairment in individuals, as observed in previous studies, or its proven ability to detect even subtle cognitive impairments in studies conducted with other clinical populations (Unsal et al., 2021; Chen et al., 2022). The testing processes of the online ICA and NOT are presented in **Fig. 2.**

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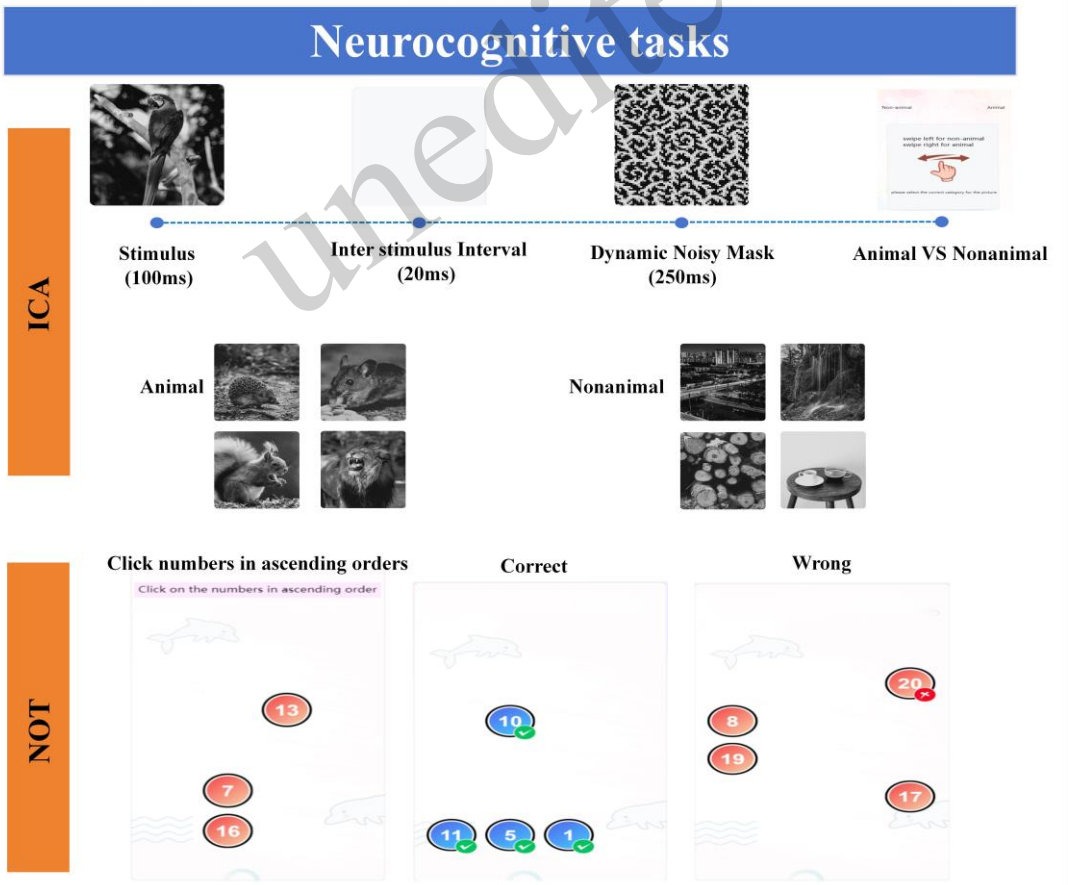

Fig. 2 Processes of the ICA and the NOT (Note for ICA: before the ICA task was started, we set up a practice mode that included ten test images (five animals, five nonanimals) to familiarize the participants with the task. The practice mode

was not included in data analysis.

Note for ICA and NOT: participants were instructed to conduct the test in a quiet environment, ensuring that incoming calls were forwarded and the internet connection was smooth.

Abbreviations: ICA, Integrated Cognitive Assessment; NOT, Number Ordering Test.

2.3 Statistical analysis

We excluded data from questionnaires with incorrect or missing answers and abnormal data from digital neurocognitive function tasks. We removed data that exceeded three standard deviations (SDs) above the normative mean for RTs. In addition, we also excluded participants with an accuracy rate lower than 50% in the ICA and an accuracy rate or a total score lower than three SDs below the normative mean in the NOT. We reported categorical variables as frequency (percentages), and continuous variables that were considered normally distributed as the mean±SDs. Otherwise, data were reported as median (interquartile range) (IQR). The chi-square test, t-test, or rank sum test was used in univariate analyses.

In order to minimize the impact of potential confounding factors, we utilized propensity score matching (PSM), a statistical technique aimed to balance the covariates between groups. PSM ensures that any disparities in the observed outcomes are ascribed to sleep disturbance rather than the impact of confounding factors. PSM typically requires a large sample size to achieve high-quality matching, which may not be feasible in some studies. The propensity scores were calculated by logistic regression. We performed 1:1 greedy nearest neighbour matching with a caliper of 0.03, relying on the R package "MatchIt." After matching, we conducted appropriate statistical tests to compare the clinical outcomes between the two groups. Furthermore, we used the chi-square test to compare differences in neurocognitive task scores between COVID-19 survivors with sleep disturbance and those without. We defined survivors in the worsened neurocognitive performance group as those whose reaction time, accuracy of ICA, and total score of NOT were the lowest at 27%. We used binary logistic regression to explore the risk factors for worsened neurocognitive performance among survivors with sleep disturbance. All statistical analyses were performed by using R software version 4.3.1. P values < 0.050 were considered to indicate statistical significance.

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3 Results

3.1 Participant information

A total of 10108 participants were recruited—9301 individuals with a recorded diagnosis of COVID-19 during the breakout pandemic. We extracted valid data for 8692 COVID-19 survivors. Altogether, 4236 individuals with PCSD and 4456 individuals without PCSD were enrolled in this survey and completed the assessment. There were statistically significant differences in age, gender, body mass index (BMI), education level, and marital status between COVID-19 survivors with and without sleep disturbance.

3.2 Propensity score matching

We employed the propensity score matching method to match the sociodemographic characteristics of COVID-19 survivors with and without sleep disturbance. A total of 3977 PCSD individuals were adequately matched to an equal number of Non-PCSD individuals. After matching, the baseline characteristics of the two groups were balanced and comparable. **Table 1** validates the comparability of the two matched groups in terms of age, gender, BMI, ethnicity, education level, and marital status ($P>0.050$). The distribution of propensity scores before and after matching (**Fig. 3**) revealed that the absolute standardized mean differences

(SMDs) in age, gender, BMI, ethnicity, education level, and marital status were all less than 0.1.

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Table 1 Sociodemographic characteristics between PCSD and Non-PCSD individuals

	Unmatched					Matched			
	Total sample n = 8692	**PCSD n = 4236**	**Non-PCSD n = 4456**	***Z*/χ^2**	***P* value**	**PCSD n = 3977**	**Non-PCSD n = 3977**	***Z*/χ^2**	***P* value**
Gender (female)	6263 (72.10)	3261 (77.00)	3002 (67.40)	99.67	**<0.001**[a]	3003 (75.50)	2995 (75.30)	0.04	0.835[a]
Age (years)	33.84 (27.22, 41.92)	34.76 (27.76, 42.47)	33.09 (26.94, 41.21)	-5.22	**<0.001**[b]	33.85 (27.32, 42.10)	33.36 (27.00, 41.53)	-1.91	0.056[b]
BMI (kg/m2)	22.19 (20.20, 24.65)	22.04 (20.08, 24.46)	22.27 (20.28, 24.80)	-2.92	**0.004**[b]	22.04 (20.06, 24.46)	22.04 (20.08, 24.54)	-0.29	0.771[b]
Ethnicity (Han)	8039 (92.50)	3909 (92.30)		0.51	0.476[a]	3665 (92.20)	3689 (92.80)	1.04	0.308[a]
Education level				6.40	**0.041**[a]			1.80	0.407[a]
Secondary or below	677 (7.80)	361 (8.50)	316 (7.10)			326 (8.20)	296 (7.40)		
Junior college or Undergraduate	5764 (66.30)	2796 (66.00)	2968 (66.60)			2626 (66.00)	2629 (66.10)		
Master’s or high	2251 (25.90)	1079 (25.50)	1172 (26.30)			1025 (25.80)	1052 (26.50)		
Marital status				14.45	**0.002**[a]			1.22	0.748[a]
Unmarried	3208 (36.90)	1483 (35.00)	1725 (38.70)			1458 (36.70)	1494 (37.60)		
Married	5154 (59.30)	2576 (60.80)	2578 (57.90)			2364 (59.40)	2341 (58.90)		
Divorced	280 (3.20)	150 (3.50)	130 (2.90)			130 (3.30)	121 (3.00)		
Widowed	50 (0.60)	27 (0.60)	23 (0.50)			25 (0.60)	21 (0.50)		

P value in bold indicate statistical significance. [a]χ^2 test. [b]Mann-Whitney U test. Abbreviations: PCSD: post-COVID-19 sleep disturbance; BMI: body mass index.

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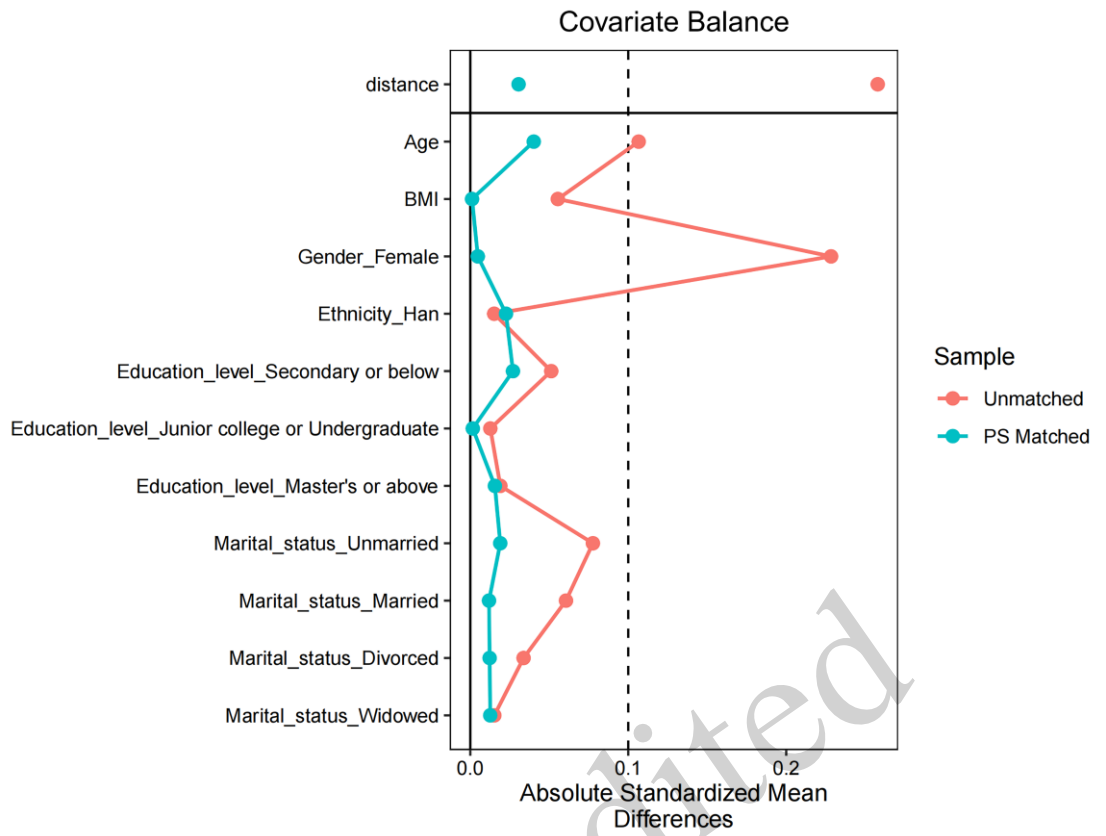

Fig. 3 Absolute standardized mean differences (SMDs) before and after matching.
Abbreviations: BMI, body mass index.

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3.3 Comparison of neurocognitive function between the PCSD group and non-PCSD group

After propensity score matching, we conducted univariate analyses. The violin plot (**Fig.4**) well illustrates the statistically significant differences in ICA-RT, ICA-Accuracy, NOT total score and NOT trial accuracy between PCSD and Non-PCSD individuals.

Specifically, statistically significant differences were observed in most neurocognitive tasks between COVID-19 survivors with and without sleep disturbance **(Table 2**). In the ICA, compared to those in the non-PCSD group, those in the PCSD group had longer RTs (RT [ms]: 947.88 [871.34~1045.12], *P*=0.003). Specifically, the PCSD group exhibited longer RTs in both the animal and nonanimal picture recognition tasks (RT-animal [ms]: 940.58 [864.34~1032.91], *P*=0.002; RT-nonanimal [ms]: 958.28[876.44~1057.30], *P*=0.005). In addition, survivors with sleep disturbance achieved lower accuracy in all picture recognition tasks and animal picture recognition (Accuracy [%]: 92.00 [87.00~95.00]; Accuracy-animal [%]: 90.00 [84.00~94.00], *P*<0.001 for both). Moreover, there were no significant differences between two groups in terms of the ICA-Accuracy in nonanimal pictures.

Similarly, in the NOT, compared to those in the non-PCSD group, participants in the PCSD group had lower total score and trial accuracy (total score: 52.80 [44.37~60.35], *P*<0.001, trial accuracy [%]: 88.00 [81.00~94.00], *P*=0.002); longer RTs (RT [ms]: 3250.71 [2973.00~3580.71], P=0.003); fewer completed trials and produced correct trials (*P*<0.050 for both).

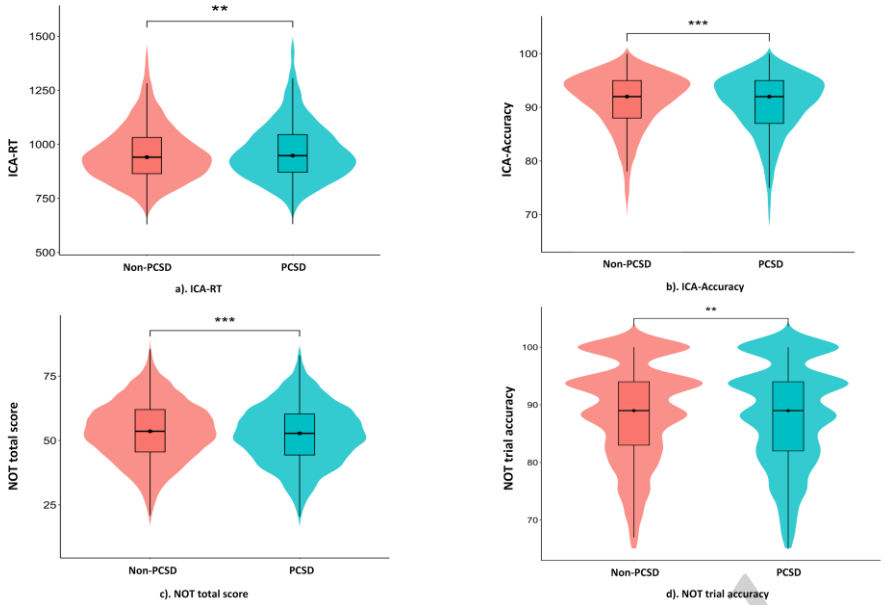

Fig. 4 Violin plot analysis comparing the levels and distributions of neurocognitive function among the PCSD and non-PCSD groups. A total of 7954 participants were used for analysis. **P*<0.050; ***P*<0.010; ****P*<0.001.
Abbreviations: PCSD, post-COVID-19 sleep disturbance; ICA, Integrated Cognitive Assessment; NOT, Number Ordering Test; RT, reaction time.

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Table 2 Comparison of neurocognitive function between PCSD and Non-PCSD individuals

	Total sample n = 8692	Unmatched				Matched			
		PCSD n =4236	**Non-PCSD n = 4456**	***Z***	***P* value**	**PCSD n =3977**	**Non-PCSD n = 3977**	***Z***	***P* value**
Integrated Cognitive Assessment									
RT (ms)	944.65 (867.98, 1039.37)	951.30 (873.22, 1048.25)	939.15 (862.88, 1028.49)	-4.74	**<0.001**	947.88 (871.34, 1045.12)	940.74 (864.49, 1032.17)	-3.01	**0.003**
RT-animal (ms)	936.13 (860.72, 1027.84)	943.53 (866.21, 1036.75)	930.38 (856.72, 1017.63)	-4.79	**<0.001**	940.58 (864.34, 1032.91)	932.30 (857.70, 1019.76)	-3.05	**0.002**
RT-nonanimal (ms)	954.25 (872.25, 1053.01)	960.98 (877.42, 1061.61)	948.69 (867.20, 1043.06)	-4.51	**<0.001**	958.28 (876.44, 1057.30)	950.49 (868.15, 1046.70)	-2.83	**0.005**
Accuracy (%)	92.00 (88.00, 95.00)	91.00 (87.00, 95.00)	93.00 (89.00, 95.00)	-8.32	**<0.001**	92.00 (87.00, 95.00)	92.00 (88.00, 95.00)	-5.72	**<0.001**
Accuracy-animal (%)	92.00 (86.00, 96.00)	90.00 (84.00, 94.00)	92.00 (86.00, 96.00)	-8.22	**<0.001**	90.00 (84.00, 94.00)	92.00 (86.00, 96.00)	-6.18	**<0.001**
Accuracy-nonanimal (%)	94.00 (90.00, 96.00)	94.00 (90.00, 96.00)	94.00 (90.00, 96.00)	-3.88	**<0.001**	94.00 (90.00, 96.00)	94.00 (90.00, 96.00)	-1.68	0.093
Number Ordering Test									
Total score	53.00 (45.13, 61.10)	52.80 (44.18, 60.16)	53.68 (45.57, 62.04)	-5.98	**<0.001**	52.80 (44.37, 60.35)	53.60 (45.57, 62.04)	-4.35	**<0.001**
RT (ms)	3229.93 (2956.25, 3567.47)	3260.95 (2980.26, 3588.62)	3203.77(2930.16, 3537.27)	-5.27	**<0.001**	3250.71(2973.00, 3580.71)	3217.50 (2946.67, 3556.70)	-2.93	**0.003**

P value in bold indicate statistical significance. Abbreviations: PCSD: post-COVID-19 sleep disturbance; RT: reaction time.

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3.4 Neurocognitive function among different subgroups of PCSD individuals

We next conducted a comprehensive stratification of the population based on COVID-19-related factors to further investigate the neurocognitive function of COVID-19 survivors with sleep disturbance across different subgroups (**Table 3)**.

Regarding the COVID-19-related symptoms and post-COVID-19 cognitive complaints, survivors with upper respiratory tract infection and loss of smell or taste had worse performance in terms of ICA-Accuracy and NOT total score ($P < 0.05$ for both). Severe pneumonia and inflexible thinking after recovery were significantly different only in terms of ICA-Accuracy ($P<0.050$). Slower processing speed after recovery was significantly lower in the ICA tasks ($P<0.050$). Having an underlying disease was associated with worse performance in most of the ICA and NOT results ($P< 0.001$).

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Table 3 Comparison of neurocognitive function in PCSD individuals in different subgroups

	PCSD n = 4236	**ICA-RT (ms)**		**ICA-Accuracy (%)**		**NOT total score**		**NOT trial accuracy (%)**	
		Median(IQR)	***P* value**	**Median(IQR)**	***P* value**	**Median(IQR)**	***P* value**	**Median(IQR)**	***P* value**
COVID-19 related symptoms									
Asymptomatic infection			0.784		0.266		0.144		0.121
No	4086 (96.50)	950.70 (873.47, 1048.29)		92.00 (87.00, 95.00)		52.80 (44.37, 60.16)		88.00 (81.00, 94.00)	
Yes	150 (3.50)	960.00 (864.39, 1047.63)		91.00 (86.00, 94.75)		51.08 (40.56, 58.55)		88.00 (79.00, 94.00)	
Upper respiratory infection			0.160		**0.002**		**0.007**		0.947
No	356 (8.40)	962.64 (877.18, 1064.16)		91.00 (86.00, 94.00)		50.59 (41.00, 59.34)		89.00 (81.00, 94.00)	
Yes	3880 (91.60)	950.09 (872.48, 1047.70)		92.00 (87.00, 95.00)		52.80 (44.37, 60.35)		88.00(81.00, 94.00)	
Loss of smell or taste			0.053		**0.002**		**0.013**		0.551
No	2370 (55.90)	947.97 (869.44, 1045.03)		92.00 (87.00, 95.00)		52.80 (44.55, 61.10)		88.00 (81.00, 94.00)	
Yes	1866 (44.10)	955.16 (877.78, 1052.63)		91.00 (87.00, 94.00)		52.08 (43.50, 60.16)		88.00 (81.00, 94.00)	
Underlying disease			**<0.001**		**<0.001**		**<0.001**		0.641
No	3665 (86.50)	944.83 (869.74, 1038.95)		92.00 (88.00, 95.00)		52.80 (44.46, 60.52)		88.00 (81.00, 94.00)	
Yes	571 (13.50)	999.19 (897.49, 1095.25)		90.00 (85.00, 93.00)		50.22 (41.04, 58.00)		89.00 (80.00, 94.00)	
Severe pneumonia			0.201		**0.002**		0.054		0.729
No	4168 (98.40)	951.03 (872.48, 1047.68)		92.00 (87.00, 95.00)		52.80 (44.37, 60.16)		88.00 (81.00, 94.00)	
Yes	68 (1.60)	972.92 (886.33, 1080.23)		89.00 (86.00, 92.25)		50.22 (39.06, 58.00)		89.00 (82.80, 94.00)	
Post-COVID-19 cognitive complaints									
Inflexible thinking after recovery			0.297		**<0.001**		0.332		0.315
No	1002 (23.70)	944.36 (868.83, 1044.23)		92.00 (88.00, 95.00)		52.90 (45.00, 61.10)		89.00 (82.00, 94.00)	

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Yes	3234 (76.30)	953.93 (874.74, 1049.73)		91.00 (87.00, 94.00)		52.29 (43.74, 60.16)		88.00 (81.00, 94.00)	
Slowed processing speed after recovery			**0.030**		**<0.001**		0.478		0.514
No	1169 (27.60)	942.49 (869.36, 1039.14)		92.00 (88.00, 95.00)		52.80 (44.46, 61.10)		89.00 (81.00, 94.00)	
Yes	3067 (72.40)	955.72 (874.90, 1051.76)		91.00 (87.00, 94.00)		52.29 (43.74, 60.16)		88.00 (81.00, 94.00)	

P value in bold indicate statistical significance. Abbreviations: PCSD: post-COVID-19 sleep disturbance; ICA: Integrated Cognitive Assessment; NOT: Number Ordering Test; RT: reaction time.

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3.5 Binary logistic regression analysis

Fig. 5 depicts the results of binary logistic regression analysis to explore the risk factors for worsened neurocognitive performance among individuals with PCSD. Age was considered as a risk factor for worsened neurocognitive performance (OR=1.10, 95% CI:1.08~1.12, *P*<0.001). Regarding the education level, a master's degree or above was a protective factor for neurocognitive function (OR=0.24, 95% CI:0.15-0.38, *P*<0.001), followed by a junior college education or undergraduate education (OR=0.43, 95% CI:0.31-0.62, *P*<0.001). Ethnic minority survivors had significantly worse neurocognitive function than Han survivors (OR=2.02, 95% CI:1.28-3.08, *P*<0.050). In general, age, ethnicity (minority) and lower education level were found to be independent risk factors for worse neurocognitive performance among individuals with PCSD.

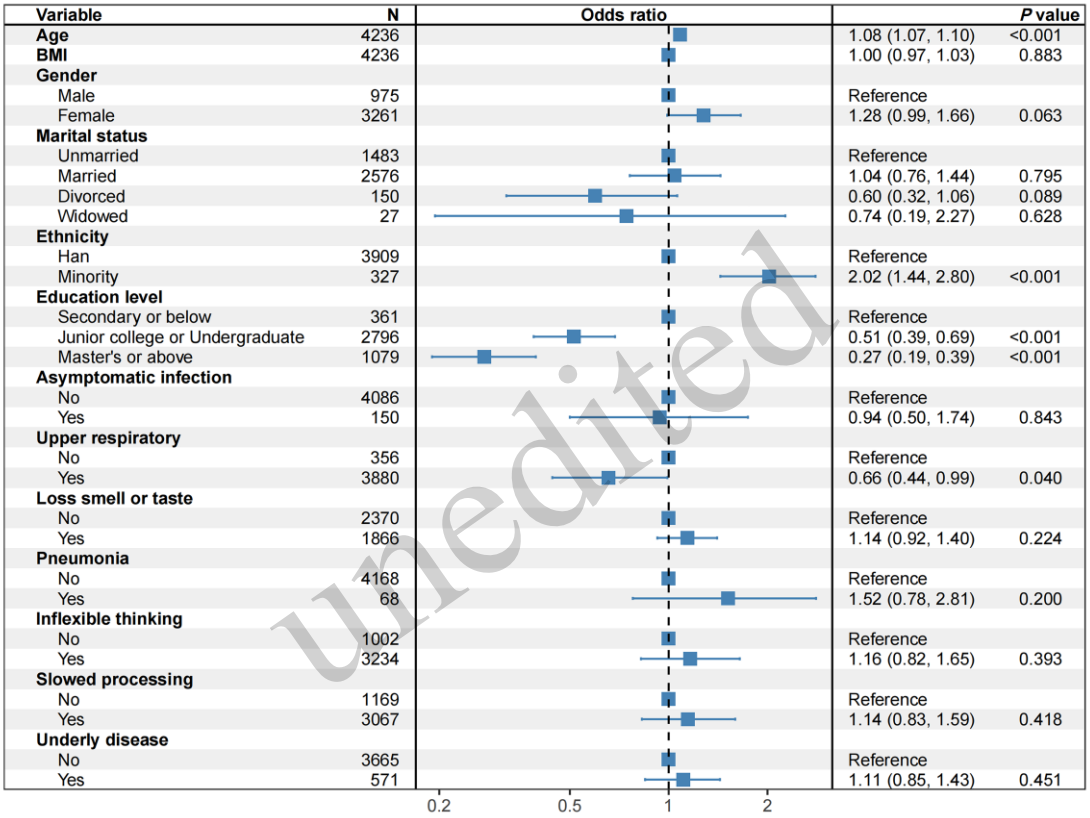

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Fig. 5 Forest plots of binary logistic regression model of PCSD.
Abbreviations: PCSD, post-COVID-19 sleep disturbance; BMI, body mass index; CI, confidence interval; OR, odds ratio.

4 Discussion

The present study is the first of its kind to investigate the association between neurocognitive function and PCSD in a large Chinese population. The results show that nearly 48.80% of COVID-19 survivors reported PCSD, which was associated with worsened neurocognitive performance. Underlying disease, COVID-19-related symptoms (upper respiratory infection, loss of smell or taste, severe pneumonia), and self-reported cognitive complaints (inflexible thinking, slowed processing speed) after recovery were associated with worsened neurocognitive performance among individuals with PCSD. Furthermore, age, ethnicity (minority) and lower education levels were found to be independent risk factors for worsened neurocognitive performance.

We found that individuals with PCSD exhibited worsened neurocognitive performance, indicating mild

deficits in executive functioning and information processing. Although the differences between the two groups were relatively minor, they may be considered clinically significant. According to our results, PCSD individuals with cognitive complaints had poorer cognitive function, whereas the non-PCSD group did not share these patterns. This further underscores the detrimental impact of sleep disturbance on neurocognitive function **(Supplemental Table 1)**. A previous review highlighted that more cognitive complaints were related to poorer self-reported sleep quality in almost all the included studies (Duivon et al., 2022). Self-reported cognitive complaints were correlated with worsened neurocognitive performance (Carone and Ben-Porath, 2014; Fortier-Brochu and Morin, 2014). Digital neurocognitive tasks provide a cost-saving and convenient tool for large-scale data collection and repeated measurements, and are suitable for screening for subtle changes in early neurocognitive function. Early identification of the subtle difference between the two groups is an important aspect of Long COVID-19, but this will require further confirmation via a cohort study.

Several reasons may explain the difference in neurocognitive performance between the two groups. First, sleep disturbance results in a decrease in sleep quality, including disruptions in sleep depth and continuity. Poor sleep quality can in turn have potential adverse effects on the brain's recovery and memory processing abilities (Tranah et al., 2011; Alperin et al., 2019). Second, sleep disturbance has been linked to worsened emotional distress, which may lead to a decline in neurocognitive function, including attention, memory, and decision-making abilities (Malik et al., 2022). Third, the inflammatory response caused by immune dysregulation in the body after recovery from COVID-19 infection may result in brain damage, leading to cognitive impairment (Muccioli et al., 2020). Accumulating evidence underscores that sleep disturbance activates cellular and molecular processes related to inflammation and increases the risk of neurocognitive impairment (Irwin and Vitiello, 2019). An interaction between sleep disturbance and the inflammatory effects of COVID-19 infection is proposed as a possible cause of the established group differences. However, further studies should focus on the lasting effect of Long COVID-19 on neurocognitive function. The above findings may guide the exploration of effective interventions for preventing impairment of neurocognitive function after Long COVID-19.

According to our results, there were no significant differences in neurocognitive function decline between survivors with asymptomatic or symptomatic infections, indicating that even without COVID-19-related symptoms, survivors still exhibit worsened neurocognitive performance, emphasizing the need to be attentive to the potential effects of PCSD. Moreover, survivors with COVID-19-related symptoms (such as loss of smell, upper respiratory tract infections, severe pneumonia, and other complications) exhibited worsened neurocognitive performance. Several studies have indicated that this could be attributed to factors such as inflammation and inadequate oxygen supply (Muccioli et al., 2020; Solomon et al., 2020). However, in this study, we revealed that COVID-19-related symptoms were not independent risk factors for worsened neurocognitive performance in survivors with PCSD.

In this study, we identified age as an independent risk factor for diminished neurocognitive performance. Although the regression analysis did not yield statistically significant differences for females, we could observe a noticeable trend towards inferior neurocognitive performance among PCSD females (OR=1.39, 95% CI: 0.99-1.97, P=0.060). Neurocognitive decline occurs with increasing age, and this decline has been demonstrated to be pervasive (Dzierzewski, 2022). Zhang et al. (2019) reported that the proportion of elderly COVID-19 survivors with deteriorated neurocognitive function was the highest in China, and female elderly individuals tended to experience more severe neurocognitive impairment, which is consistent with our findings. Previous studies have shown a greater incidence of insomnia in females following COVID-19 infection (Jee et al., 2020; Linh et al., 2023), and females generally exhibited poorer cognitive function than males in the insomnia population, particularly in terms of sustained attention (Corsi-Cabrera et al., 2003). Neuroimaging studies have demonstrated that females exhibited more pronounced changes in brain regions involved in sleep and memory processes than males (Santhi et al., 2016; Gong et al., 2021). These findings may help explain the trend in gender difference in neurocognitive function observed among survivors with sleep disturbance.

In this study, ethnicity (minority) and lower education were associated with worsened neurocognitive performance in a Chinese population. Previous studies in the United States have shown that sleep disturbance or

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neurocognitive impairments are more common among racial/ethnic minorities (i.e. Hispanics) than among Whites (Bryant et al., 2014; Chen et al., 2015; Jang et al., 2022). These differences could be attributed to cultural variances, dietary preferences, and diverse lifestyle practices among various ethnic groups, which may also be applicable to our results. For education level as a study parameter, we found that higher education was a protective factor against neurocognitive performance degradation. These findings align with previous studies indicating that higher education levels can enhance neurocognitive reserve and safeguard against neurocognitive impairment among PCSD individuals (Duindam et al., 2022; Liu et al., 2022; Valdes et al., 2022).

5 Limitations and future directions

This study has several limitations. First, the use of a cross-sectional design prevented us from establishing causality between variables. Second, the lack of baseline data on neurocognitive function prior to infection limited our ability to assess the impact of COVID-19-related neurocognitive impairments during the recovery period. Third, no formal measure of insomnia was used in the tests, thus further research should implement standard interviews or questionnaires to assess insomnia incidence. Finally, due to the different device configurations and software packages, digital neurocognitive assessments might have caused systematic measurement biases during the testing process, which could impact the accuracy and generalizability of the test results.

6 Conclusion

In summary, PCSD was related to worsened neurocognitive performance, proving our hypothesis. Age, ethnicity and lower education level were found to be independent risk factors for worsened neurocognitive performance in PCSD individuals. For survivors with long-term PCSD, adopting interventions such as cognitive behavioural therapy for insomnia may be a promising option to improve sleep quality and neurocognitive performance.

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Data availability statement

The dataset used or analyzed during the current study is available from the corresponding author on reasonable request.

Acknowledgments

This work is supported by the National Key R&D Program of China [grant number 2021YFC2501500], National Natural Science Foundation of China [grant number 82271525, and grant number 82071488], Nanfang Hospital Clinical Research Project of Southern Medical University [grant number 2021CR009].

Author contributions

SD was responsible to the statistical analyses. LF and SD wrote the first draft of the manuscript. SZ, LF, XL, SZ, YX, YL, DL, SZ and HY reviewed the participants and organized the primary data. BZ designed the study and provided supervision in the implementation of the study. BZ was responsible for the overall content as the guarantor. All authors approved the final manuscript.

Compliance with ethics guidelines

All authors declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the ethics committee of Nanfang Hospital, Southern Medical University. Informed consent was obtained from all patients for being included in the study.

References

Alperin, N., Wiltshire, J., Lee, S.H.et al., 2019. Effect of sleep quality on amnestic mild cognitive impairment vulnerable brain regions in cognitively normal elderly individuals. Sleep, 42(3).

https://doi.org/10.1093/sleep/zsy254.

Amdal, C.D., Pe, M., Falk, R.S.et al., 2021. Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review. Qual Life Res, 30(12): 3367-3381. https://doi.org/10.1007/s11136-021-02908-z.

Becker, J.H., Vannorsdall, T.D., Weisenbach, S.L., 2023. Evaluation of Post–COVID-19 Cognitive Dysfunction: Recommendations for Researchers.

JAMA Psychiatry, 80(11): 1085. https://doi.org/10.1001/jamapsychiatry.2023.2820.

Bowie, C.R., Harvey, P.D., 2006. Administration and interpretation of the Trail Making Test. Nat Protoc, 1(5): 2277-2281. https://doi.org/10.1038/nprot.2006.390.

Bryant, A.N., Ford, K., Kim, G., 2014. Racial/Ethnic Variations in the Relation Between Body Mass Index and Cognitive Function Among Older Adults. Am J Geriatr Psychiatry, 22(7): 653-660. https://doi.org/10.1016/j.jagp.2013.08.006.

Carone, D.A., Ben-Porath, Y.S., 2014. Dementia does not Preclude Very Reliable Responding on the MMPI-2 RF: A Case Report. Clin Neuropsychol, 28(6): 1019-1029. https://doi.org/10.1080/13854046.2014.930182.

Ceban, F., Ling, S., Lui, L.M.W.et al., 2022. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun, 101: 93-135. https://doi.org/10.1016/j.bbi.2021.12.020.

Chen, S., Wang, S., Bai, Y.et al., 2022. Comparative Study on Topological Properties of the Whole-Brain Functional Connectome in Idiopathic Rapid Eye Movement Sleep Behavior Disorder and Parkinson's Disease Without RBD. Front Aging Neurosci, 14: 820479. https://doi.org/10.3389/fnagi.2022.820479.

Chen, X., Wang, R., Zee, P.et al., 2015. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). Sleep, 38(6): 877-888. https://doi.org/10.5665/sleep.4732.

Corsi-Cabrera, M., Sánchez, A.I., Del-Río-Portilla, Y.et al., 2003. Effect of 38 h of total sleep deprivation on the waking EEG in women: sex differences.Int J Psychophysiol, 50(3): 213-224. https://doi.org/10.1016/s0167-8760(03)00168-5.

Crivelli, L., Palmer, K., Calandri, I.et al., 2022. Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis. Alzheimers Dement, 18(5): 1047-1066. https://doi.org/10.1002/alz.12644.

Davis, H.E., Assaf, G.S., McCorkell, L.et al., 2021. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine, 38: 101019. https://doi.org/10.1016/j.eclinm.2021.101019.

Díez-Cirarda, M., Yus, M., Gómez-Ruiz, N.et al., 2023. Multimodal neuroimaging in post-COVID syndrome and correlation with cognition. Brain, 146(5): 2142-2152. https://doi.org/10.1093/brain/awac384.

Duindam, H.B., Kessels, R.P.C., van den Borst, B.et al., 2022. Long-term cognitive performance and its relation to anti-inflammatory therapy in a cohort of survivors of severe COVID-19. Brain Behav Immun Health, 25: 100513. https://doi.org/10.1016/j.bbih.2022.100513.

Duivon, M., Giffard, B., Desgranges, B.et al., 2022. Are Sleep Complaints Related to Cognitive Functioning in Non-Central Nervous System Cancer? A Systematic Review. Neuropsychol Rev, 32(3): 483-505. https://doi.org/10.1007/s11065-021-09521-4.

Dzierzewski, J.M., 2022. Insomnia and subjective cognitive decline in older adults: avenues for continued investigation and potential intervention. Sleep, 45(11): 1. https://doi.org/10.1093/sleep/zsac216.

Fortier-Brochu, É., Morin, C.M., 2014. Cognitive Impairment in Individuals with Insomnia: Clinical Significance and Correlates. Sleep, 37(11): 1787-1798. https://doi.org/10.5665/sleep.4172.

Gong, L., Shi, M., Wang, J.et al., 2021. The Abnormal Functional Connectivity in the Locus Coeruleus-Norepinephrine System Associated With Anxiety Symptom in Chronic Insomnia Disorder, Front Neurosci, 15: 678465. https://doi.org/10.3389/fnins.2021.678465.

Iqbal, F.M., Lam, K., Sounderajah, V.et al., 2021. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine, 36: 100899. https://doi.org/10.1016/j.eclinm.2021.100899.

unedited

Irwin, M.R., Vitiello, M.V., 2019. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. Lancet Neurol, 18(3): 296-306. https://doi.org/10.1016/s1474-4422(18)30450-2.

Jahrami, H.A., Alhaj, O.A., Humood, A.M.et al., 2022. Sleep disturbances during the COVID-19 pandemic: A systematic review, meta-analysis, and meta-regression. Sleep Med Rev, 62: 101591. https://doi.org/10.1016/j.smrv.2022.101591.

Jang, Y., Haley, W.E., Choi, E.Y.et al., 2022. Racial/Ethnic Differences in Correspondence Between Subjective Cognitive Ratings and Cognitive Impairment. Am J Geriatr Psychiatry, 30(5): 627-635. https://doi.org/10.1016/j.jagp.2021.10.015.

Jee, H.J., Shin, W., Jung, H.J.et al., 2020. Impact of Sleep Disorder as a Risk Factor for Dementia in Men and Women. Biomol Ther (Seoul), 28(1): 58-73. https://doi.org/10.4062/biomolther.2019.192.

Kalafatis, C., Modarres, M.H., Apostolou, P.et al., 2021. Validity and Cultural Generalisability of a 5-Minute AI-Based, Computerised Cognitive Assessment in Mild Cognitive Impairment and Alzheimer's Dementia. Front Psychiatry, 12: 706695. https://doi.org/10.3389/fpsyt.2021.706695 .

Khaligh-Razavi, S., Habibi, S., Sadeghi, M.et al., 2019. Integrated Cognitive Assessment: Speed and Accuracy of Visual Processing as a Reliable Proxy to Cognitive Performance. Sci Rep, 9(1): 1102. https://doi.org/10.1038/s41598-018-37709-x.

Linh, T.T.D., Ho, D.K.N., Nguyen, N.N.et al., 2023. Global prevalence of post-COVID-19 sleep disturbances in adults at different follow-up time points: A systematic review and meta-analysis. Sleep Med Rev, 71: 101833. https://doi.org/10.1016/j.smrv.2023.101833.

Liu, Y., Chen, Y., Wang, Q.et al., 2022. One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China. JAMA Neurol, 79(5): 509. https://doi.org/10.1001/jamaneurol.2022.0461.

Malik, P., Patel, K., Pinto, C.et al., 2022. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis. J Med Virol, 94(1): 253-262. https://doi.org/10.1002/jmv.27309.

Muccioli, L., Pensato, U., Cani, I.et al., 2020. COVID-19–Associated Encephalopathy and Cytokine-Mediated Neuroinflammation. Ann Neurol, 88(4): 860-861. https://doi.org/10.1002/ana.25855.

Oliver, S.F., Lazoff, S.A., Popovich, J.et al., 2023. Chronic Neurocognitive, Neuropsychological, and Pulmonary Symptoms in Outpatient and Inpatient Cohorts After COVID-19 Infection. Neurosci Insights, 18: 1986152394. https://doi.org/10.1177/26331055231186998.

Pearson, O., Uglik-Marucha, N., Miskowiak, K.W.et al., 2023. The relationship between sleep disturbance and cognitive impairment in mood disorders: A systematic review. J Affect Disord, 327: 207-216. https://doi.org/10.1016/j.jad.2023.01.114.

Salfi, F., Amicucci, G., Corigliano, D.et al., 2023. Poor sleep quality, insomnia, and short sleep duration before infection predict long-term symptoms after COVID-19. Brain Behav Immun, 112: 140-151. https://doi.org/10.1016/j.bbi.2023.06.010.

Santhi, N., Lazar, A.S., McCabe, P.J.et al., 2016. Sex differences in the circadian regulation of sleep and waking cognition in humans. Proc Natl Acad Sci U S A, 113(19): E2730-E2739. https://doi.org/10.1073/pnas.1521637113.

Shore, J., Kalafatis, C., Stainthorpe, A.et al., 2023. Health economic analysis of the integrated cognitive assessment tool to aid dementia diagnosis in the United Kingdom. Front Public Health, 11: 1240901. https://doi.org/10.3389/fpubh.2023.1240901.

.Solomon, I.H., Normandin, E., Bhattacharyya, S.et al., 2020. Neuropathological Features of Covid-19. N Engl J Med, 383(10): 989-992. https://doi.org/10.1056/NEJMc2019373.

Tedjasukmana, R., Budikayanti, A., Islamiyah, W.R.et al., 2023. Sleep disturbance in post COVID-19 conditions: Prevalence and quality of life. Front Neurol, 13: 1095606. https://doi.org/10.3389/fneur.2022.1095606.

Tranah, G.J., Blackwell, T., Stone, K.L.et al., 2011. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol, 70(5): 722-732. https://doi.org/10.1002/ana.22468.

Unsal, P., Sengul Aycicek, G., Deniz, O.et al., 2021. Insomnia and falls in older adults: are they linked to executive dysfunction?. Psychogeriatrics, 21(3): 359-367. https://doi.org/10.1111/psyg.12677.

unedited

Valdes, E., Fuchs, B., Morrison, C.et al., 2022. Demographic and social determinants of cognitive dysfunction following hospitalization for COVID-19.J Neurol Sci, 438: 120146. https://doi.org/10.1016/j.jns.2022.120146.

Werheid, K., Hoppe, C., Thone, A.et al., 2002. The Adaptive Digit Ordering Test: clinical application, reliability, and validity of a verbal working memory test. Arch Clin Neuropsychol, 17(6): 547-565. https://doi.org/10.1016/S0887-6177(01)00134-2.

World Health Organization WHO Coronavirus (COVID-19) Dashboard 2023; https://covid19.who.int accessed 1.29.23.

World Health Organization A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus Data. 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

Zaheed, A.B., Chervin, R.D., Spira, A.P.et al., 2023. Mental and physical health pathways linking insomnia symptoms to cognitive performance 14 years later. Sleep, 46(3). https://doi.org/10.1093/sleep/zsac262 .

Zhang, Q., Wu, Y., Han, T.et al., 2019. Changes in Cognitive Function and Risk Factors for Cognitive Impairment of the Elderly in China: 2005–2014. Int J Environ Res Public Health, 16(16): 2847. https://doi.org/10.3390/ijerph16162847.

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Supplementary information:

Supplemental Table 1. Comparison of neurocognitive function in Non-PCSD individuals in different subgroups

	PCSD	**ICA-RT (ms)**		**ICA-Accuracy (%)**		**NOT total score**		**NOT trial accuracy (%)**	
	n =4456	**Median(IQR)**	***P* value**	**Median(IQR)**	***P* value**	**Median(IQR)**	***P* value**	**Median(IQR)**	***P* value**
COVID-19 related symptoms									
Asymptomatic infection			**0.009**		**0.006**		0.094		0.485
No	4209 (94.50)	938.41 (861.09, 1027.07)		93.00 (89.00, 95.00)		53.76 (45.88, 62.04)		89.00 (83.00, 94.00)	
Yes	247 (5.50)	953.04 (886.49, 1049.50)		92.00 (87.00, 95.00)		52.08 (43.37, 62.04)		90.00 (82.00, 95.00)	
Upper respiratory infection			**0.003**		**0.011**		**0.114**		0.094
No	425 (9.50)	952.53 (881.88, 1059.25)		92.00 (87.00, 95.00)		53.00 (44.37, 62.04)		90.00 (83.00, 95.00)	
Yes	4031 (90.50)	938.25 (860.50, 1025.97)		93.00 (89.00, 95.00)		53.76 (45.92, 62.04)		89.00 (83.00, 94.00)	
Loss of smell or taste			0.619		0.875		**0.007**		0.141
No	2928 (65.70)	938.62 (864.44, 1029.05)		93.00 (89.00, 95.00)		54.56 (45.92, 62.30)		89.00 (83.00, 94.00)	
Yes	1528 (34.30)	940.04 (860.87, 1027.92)		93.00 (89.00, 95.00)		53.00 (45.57, 61.10)		89.00 (82.00, 94.00)	
Underlying diseases			**<0.001**		**<0.001**		**<0.001**		0.410
No	4014 (90.10)	934.75 (859.80, 1021.58)		93.00 (89.00, 95.00)		54.56 (46.11, 62.30)		89.00 (83.00, 94.00)	

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Yes	442 (9.90)	992.04 (896.15, 1097.42)		91.00 (86.00, 94.75)		50.63 (41.58, 58.00)	90.00 (83.00, 94.00)	
Severe pneumonia			**0.002**		0.231		0.051	0.502
No	4423 (99.30)	938.67 (862.18, 1028.05)		93.00 (89.00, 95.00)		53.68 (45.57, 62.04)	89.00 (83.00,94.00)	
Yes	33 (0.70)	1015.70 (920.44, 1093.43)		91.00 (88.00, 94.00)		48.98 (42.63, 57.85)	88.00 (80.00,95.00)	
Post-COVID-19 cognitive complaints								
Inflexible thinking after recovery			0.319		0.307		0.068	**0.001**
No	1998 (44.80)	943.00 (861.13, 1033.57)		93.00 (89.00, 95.00)		54.56 (46.02, 62.30)	89.00 (83.00, 94.00)	
Yes	2458 (55.20)	936.77 (863.97, 1027.10)		93.00 (89.00, 95.00)		53.06 (45.57, 61.41)	89.00 (82.00, 94.00)	
Slowed processing speed after recovery			0.097		0.206		0.186	**0.001**
No	2224 (49.90)	942.92 (863.20, 1034.82)		93.00 (89.00, 95.00)		53.95 (45.92, 62.05)	89.00 (83.00, 94.00)	
Yes	2232 (50.10)	936.49 (862.19, 1025.86)		92.00 (89.00, 95.00)		53.68 (45.57, 62.04)	89.00 (82.00, 94.00)	

P value in bold indicate statistical significance. Abbreviations: PCSD: post-COVID-19 sleep disturbance; ICA: Integrated Cognitive Assessment; NOT: umber Ordering Test; RT: reaction time.

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