SUMMARY

In December 2019, one of the most devastating pandemics in history began. Within its first year, the Coronavirus Disease (COVID-19), triggered by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), affected a staggering 12.56% of the global population. The virus spread rapidly and inflicted severe illness, with many patients requiring hospital admission or even critical care, placing immense pressure on healthcare systems worldwide. Reports of neurological manifestations, most prevalent among severely ill patients, raised concerns about COVID-19's impact on the brain, prompting questions about implications for cognition. Patients' complaints about memory problems, attention difficulties, and mental slowness underscored these fears, leaving uncertainty about the duration of these symptoms. It was recognized that similar symptoms frequently manifest following other medical conditions requiring critical care and that these often persist for months or even years. In addition to physical and cognitive complaints, critical care patients often experience emotional distress, including anxiety, depression, and post-traumatic stress symptoms. This emotional distress is likely attributed to the traumatic experiences of critical illness and the associated treatments, such as mechanical ventilation, sedation, and pain management. Additional to these experiences, COVID-19 patients faced social isolation, uncertainty surrounding the health effects of COVID-19, and overwhelmed hospitals. These additional stressors could intensify the emotional distress and also extend to patients in general hospital wards, thereby increasing the potential number of individuals affected by lasting health consequences.

This aim of this thesis was to enhance the understanding of long-term neurological symptoms (self-reported neurological symptoms and brain abnormalities) and neuropsychological sequelae (subjective and objective cognitive consequences, emotional distress, fatigue, sleep disturbances), and their influence on participation and quality of life of COVID-19. The background of the research is presented in **Chapter 1**.

Chapter 2 describes the study protocol including the background, rationale, and research questions of the NeNeSCo (Neurological and Neuropsychological Sequelae of COVID-19) study and provides a detailed overview of the methods. The aim was to recruit 200 COVID-19 patients with no prior cognitive dysfunction from general (N=100) and critical care (N=100) wards of six Dutch hospitals admitted during the first European infection wave. At least six months after hospital discharge, these patients were planned to undergo a 3T MRI brain scan, extensive multi-domain cognitive testing, and complete questionnaires. Questionnaire completion was scheduled a second time another six months later to evaluate the development of symptoms over time. Data related to COVID-19 hospitalization were to be extracted from the patients' medical records.

Chapter 3 describes results of the NeNeSCo study, examining a cohort of 104 general ward and 101 critically ill patients. MRI scans and cognitive assessment were performed nine months after hospital discharge by trained professionals during a hospital visit and patients completed questionnaires. Structural brain abnormalities were evaluated by a neuroradiologist based on the MRI scans. Cognitive dysfunction was defined as a substantial decrease in performance on the cognitive tests in comparison to a normative sample. This sample comprised a large group of individuals of similar educational background, age, and gender. Our results indicated that general ward and critical care patients differed only with regards to MRI brain abnormalities, with critical care patients showing a higher prevalence and number of cerebral microbleeds, particularly in the corpus callosum. Despite this discrepancy, cognitive dysfunction affected a similar proportion of patients in both groups, about 12%. However, a striking number of patients from both groups, over 60%, reported numerous cognitive problems such as memory problems, mental slowness, and attention difficulties, with more than half experiencing severe fatigue. A higher prevalence of self-reported symptoms compared with cognitive dysfunction suggests psychosocial influences.

In **Chapter 4**, we conducted a comprehensive analysis of the nature of cognitive dysfunction in the NeNeSCo sample. Subsequently, we validated the Montreal Cognitive Assessment (MoCA) as a screening tool in detecting cognitive dysfunction. Nine months after hospital discharge, the participating patients underwent a cognitive assessment across six cognitive domains, namely mental speed, attention, executive function, (working) memory, visuospatial-, and language abilities. Each patient's performance was compared to that of a normative sample comprising a large group of healthy individuals matched for education, age, and gender. A cognitive domain was considered impaired when a patient's performance significantly deviated from that of the normative sample. Cognitive dysfunction was defined as at least one impaired cognitive domain. The results indicated that 12% of patients had cognitive dysfunction with the highest prevalences on memory and processing speed. Using the commonly applied cut-off score of <26 out of 30, the MoCA demonstrated good sensitivity (83%) and specificity (66%) in detecting cognitive dysfunction. The optimal cut-off, defined as highest sensitivity and specificity, was identified to be <24, which maintained sensitivity while further enhancing specificity to 81%. Our findings show that the MoCA is a valuable screening tool that can detect cognitive dysfunctions in initially hospitalized COVID-19 patients with good accuracy.

In **Chapter 5**, we aimed to explore the role of psychological and social factors alongside biomedical factors in understanding persistent post-COVID-19 cognitive complaints and fatigue. Our analysis examined connections between various factors with fatigue severity and cognitive complaints in the NeNeSCo sample. Demographic and premorbid

factors, illness severity, neuro-cognitive factors, and psychological and social factors were investigated. Results showed that psychological and social factors played a significant role in both fatigue severity and cognitive complaints, explaining 5% and 11% of variance, respectively. Interestingly, objective neuro-cognitive factors such as brain abnormalities and cognitive dysfunctions were not strongly associated with symptoms. Instead, younger age, lower physical functioning, and depressive symptoms were associated with fatigue severity and more perceived social support with cognitive complaints. These results suggest that a multidomain treatment approach, including psychosocial care, may be crucial in addressing persistent post-COVID-19 symptoms and reducing associated distress.

The study presented in **Chapter 6** delved into the prevalence and development of post-COVID-19 neuropsychological symptoms over time. In this longitudinal questionnaire analysis, we examined fatigue, cognitive complaints, insomnia, anxiety, depression, and post-traumatic stress symptoms in the NeNeSCo sample nine months and fifteen months after their hospital discharge. Approximately half of the patients consistently experienced cognitive complaints and severe fatigue at both time points. Insomnia persisted in a quarter of the patients throughout the study period. Clinically relevant anxiety, depression, and post-traumatic stress symptoms were less prevalent, consistently below 20%. Most symptoms exhibited stability over time, with patients reporting a symptom nine months after hospital discharge highly likely to continue experiencing it half a year later. Conversely, patients who did not report a symptom initially were also likely to remain symptom-free half a year later. A significant majority, sixty percent, endured at least one persistent symptom. Furthermore, despite the overall stability of symptoms, a subgroup of patients (32%) exhibited delayed symptom onset, meaning these symptoms were absent nine months after hospital discharge but emerged half a year later.

Chapter 7 consolidates the preceding chapters through a comprehensive discussion of the main findings, alongside methodological considerations. Additionally, we describe clinical implications and propose directions for future research. In essence, severe COVID-19 emerges as a multi-dimensional disease which requiring a holistic biopsychosocial treatment approach. Cognitive screening, using the MoCA, can identify patients with potential cognitive dysfunction, requiring further neuropsychological evaluation. When patients present with persistent symptoms, including cognitive complaints and/or fatigue, it becomes imperative to assess biological, psychological, and social factors on individual patient level. While biomedical care remains important, particularly during the acute phase following infection, psychosocial interventions are likely of added value, especially in the long term. Though such interventions may not directly target biologically-rooted symptoms, they can alleviate the associated emotional distress.