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Prevalence, pathophysiology, prediction and health-related quality of life of long COVID: study protocol of the longitudinal multiple cohort CORona Follow Up (CORFU) study

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ABSTRACT

Introduction The variety, time patterns and long-term prognosis of persistent COVID-19 symptoms (long COVID-19) in patients who suffered from mild to severe acute COVID-19 are incompletely understood. Cohort studies will be combined to describe the prevalence of long COVID-19 symptoms, and to explore the pathophysiological mechanisms and impact on health-related quality of life. A prediction model for long COVID-19 will be developed and internally validated to guide care in future patients.

Methods and analysis Data from seven COVID-19 cohorts will be aggregated in the longitudinal multiple cohort CORona Follow Up (CORFU) study. CORFU includes Dutch patients who suffered from COVID-19 at home, were hospitalised without or with intensive care unit treatment, needed inpatient or outpatient rehabilitation and controls who did not suffer from COVID-19. Individual cohort study designs were aligned and follow-up has been synchronised. Cohort participants will be followed up for a maximum of 24 months after acute infection. Next to the clinical characteristics measured in individual cohorts, the CORFU questionnaire on long COVID-19 outcomes and determinants will be administered digitally at 3, 6, 12, 18 and 24 months after the infection. The primary outcome is the prevalence of long COVID-19 symptoms up to 2 years after acute infection. Secondary outcomes are health-related quality of life (eg, EQ-5D), physical functioning, and the prevalence of thromboembolic complications, respiratory complications, cardiovascular diseases and endothelial dysfunction. A prediction model and a patient platform prototype will be developed.

Ethics and dissemination Approval was obtained from the medical research ethics committee of Maastricht University Medical Center+ and Maastricht University (METC 2021-2990) and local committees of the participating cohorts. The project is supported by ZonMW and EuroQol Research Foundation. Results will be published in open access peer-reviewed scientific journals and presented at (inter)national conferences.

Trial registration number NCT05240742.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Survivors from seven existing COVID-19 cohorts will be asked to participate in CORona Follow Up (CORFU); clinical data will be aggregated and enriched with results from questionnaires on symptoms, health-related quality of life and societal impact at synchronised follow-up moments to estimate the prevalence and pathophysiological mechanisms of long COVID-19, the impact on health-related quality of life and their key determinants.

⇒ A control group of Dutch participants from the general population, who did not suffer from COVID-19, will be included for comparison with regard to the prevalence and health-related quality of life.

⇒ The heterogeneous cohort populations enable CORFU to investigate study aims in various subgroups (eg, home isolated vs hospitalised patients) and test pathophysiological hypotheses.

⇒ An over-representation of (former) COVID-19 patients admitted to the hospital (ward or intensive care unit) might exist, potentially resulting in over-representation of more severe cases of long COVID-19, all of which will be considered in the analysis and presentation.

INTRODUCTION

The WHO defines the post-COVID-19 condition, also known as long COVID, as a

condition that occurs 3 months from the onset of infection, with symptoms that last for at least 2 months and are not explained by an alternative diagnosis.[1] The prevalence of long COVID symptoms varies in literature, ranging from 40% to 68% six months after COVID diagnosis and up to 49% after 12 months.[2–4] Frequently reported symptoms include fatigue, shortness of breath, headache, cognitive impairment (eg, concentration problems), muscle weakness and joint stiffness.[5–8] Persistent long COVID symptoms are associated with poorer health-related quality of life.[9 10] Furthermore, there is an increased risk of incident cardiovascular complaints and cardiovascular diseases for people who suffered from COVID beyond the first month of infection.[11 12] Next to the physical and mental symptoms of long COVID, there is a psychological and emotional impact which might be induced by the social restrictions and financial impact (including income uncertainty) during the pandemic.[13 14]

Long COVID occurs both in patients with mild and with severe acute course. So far, the severity of the acute infection seems related to the risk of long COVID symptoms.[15–17] Additional factors affecting the risk of long COVID are the presence of one or more pre-existent comorbidities and being a middle-aged female.[16 18 19] Whether the type of SARS-CoV-2) strain relates to long COVID is unknown.

In patients suffering from critical COVID-19 in the intensive care unit (ICU), long COVID-19 symptoms may coexist with, or be indistinguishable from, the post-IC syndrome, defined as newly emerging physical, cognitive or mental limitations after suffering from severe disease during ICU stay.[20]

Due to the novelty of COVID-19, studies focus on short term physical functioning and mental well-being. However, less is known about persisting COVID-19 symptoms up to 2 years after acute infection, and the factors determining prognosis (if any). More knowledge will facilitate long COVID-19 (health)care and follow-up (eg, specific services such as (lung)rehabilitation and occupational support) for specific patient groups, guided by prognostic information. This knowledge may translate into national and international guidelines on the prevention, diagnosis and treatment of long COVID-19.

This paper describes the protocol of the CORona Follow Up (CORFU) study: a national longitudinal, multiple cohort study that aggregates data of existing cohorts and enriches these data with repeated digital follow-up questionnaires on long COVID symptoms and health-related quality of life up to 2 years after the first infection. Five aims, summarised in four work packages (WP), have been formulated:

- WP1:
  a. To describe the prevalence, severity, time patterns and duration of long COVID symptoms up to 2 years after acute infection and their relationship with health-related quality of life.
  b. To describe the received rehabilitation and paramedical support in relation to the persisting symptoms and health-related quality of life.
- WP2:
- To investigate the pathophysiological mechanisms that may cause long COVID symptoms and the role of vulnerability/resilience factors.
- WP3:
- To develop and validate a prediction model for the persistence of symptoms, stratified by severity of COVID.
- WP4 (in collaboration with EuroQol Research Foundation):
- Develop a patient platform prototype where patients can digitally consult their reported outcomes, compare them with previous outcomes, relate to reference information and find reported information that fits their situation.

METHODS AND ANALYSIS

Study design

The CORFU study is a longitudinal multiple cohort study that aggregates data of seven existing Dutch COVID-19 cohorts, prospectively complemented with routinely collected outcome data on long COVID-19, with a maximum follow-up of 24 months after initial infection. Data will be collected between 1 October 2021 and 31 December 2022.

All cohorts were initiated and designed to conduct COVID-19 research. Six cohorts will collect data according to their individual clinical focus (figure 1). In addition, participants from the community-based POPulation health impact of the COVID-19 pandemic (POPCOrn) cohort will serve as a control group as this cohort partly consists of controls who did not suffer from COVID-19. However, at present, many of the POPCOrn participants could have suffered from (mild) COVID-19. Therefore, all POPCOrn participants will be asked repeatedly to report whether or not they suffered from (confirmed of suspected) COVID-19 and only the participants who did not suffer from COVID-19 will serve as a control. In the POPCOrn cohort, similar outcome data will be collected as in the other participating cohorts. As CORFU is open to new collaborations, it is likely that additional cohorts will join CORFU in the future. Participation of new cohorts will be reported when presenting the CORFU study findings.

The cohort-specific follow-up measurements will be complemented by a repeatedly administered CORFU questionnaire covering the full array of long COVID symptoms, health-related quality of life effects and their key determinants. Furthermore, (clinical) data that have already been collected in the participating cohorts during the acute COVID stage will be used to investigate the CORFU study aims.

Participants

The study population consists of Dutch (former) COVID-19 survivors and non-COVID-19 controls, who have been included in one of the cohorts. Former COVID-19 cases are either confirmed by a positive PCR

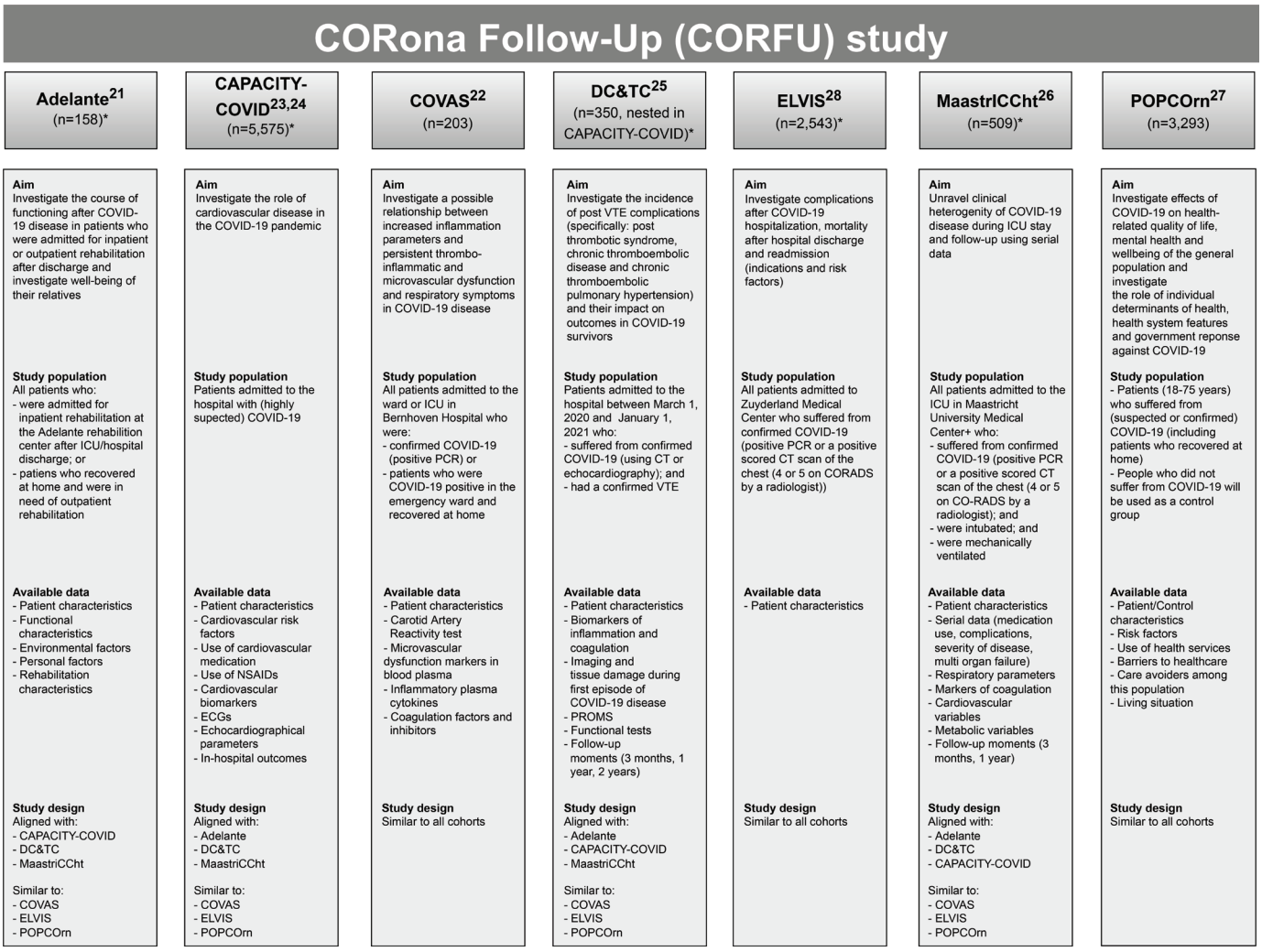

Figure 1 Overview of the participating COVID-19 cohorts in the CORFU study. The source population included in the individual cohorts is an estimate as of May 2022. The total number of CORFU study participants might not add up to the total source population (n=12 631) due to non-survivors, participants included in multiple cohorts and participants who might not want to participate in the CORFU study. *At the time of manuscript preparation, prospective inclusion is ongoing in five cohorts: Adelante, CAPACITY-COVID, DC&TC, ELVIS and MaastrICCht cohort. CAPACITY-COVID, Cardiac complications in patients with COVID-19 cohorts; CORADS, COVID-19 Reporting and Data System Score; COVAS, Bernhoven Early detection of Vascular damage after COVID-19 cohort; DC&TC cohort, Dutch COVID and Thrombosis Consortium cohort; ELVIS, ZuydErLand COVID-19 regiStry; ICU, lintensive care unit; MaastrICCht, Maastricht Intensive Care COVID cohort; NSAID, non-steroidal anti-inflammatory drug; POPCOrn, POPulation health impact of the COVID-19 pandemic; PROMS, Patient-Reported Outcome Measures; VTE, venous thromboembolic.

test for SARS-CoV-2 and/or a positive CT scan of the chest based on the COVID-19 Reporting and Data System (CO-RADS) Score (score 4–5 by a radiologist), or likely based on self-reported questionnaires (ie, unspecified positive COVID-19 test or the presence of COVID-19-related symptoms). The study population is categorised into five subgroups:

- Patients who suffered from confirmed COVID-19 admitted to the hospital ward.
- Patients who suffered from confirmed COVID-19 admitted to the ICU.
- Patients who suffered from either confirmed or likely (ie, self-reported) COVID-19 at home.
- Patients who suffered from confirmed COVID-19 and needed inpatient or outpatient rehabilitation after infection at home or in the hospital (ward and/or ICU).
- Controls who (likely, ie, self-reported) did not suffer from COVID-19.

Adult participants (≥18 years) with confirmed or suspected COVID-19 and non-COVID-19 controls who sufficiently master the Dutch language will be eligible for inclusion in the CORFU study. No additional exclusion criteria will be used. In addition to provided consent or no declared objection for initial cohort participation, all participants will be asked to give written and/or digital informed consent prior to the first CORFU follow-up questionnaire (if not already covered by the specific cohort inclusion scheme).

Data sources: COVID-19 cohorts

Data will be derived from the following seven COVID-19 cohorts:

- Adelante cohort.[21]
- Bernhoven early detection of vascular damage after COVID-19 (COVAS) cohort.[22]
- Cardiac complications in patients with COVID-19 (CAPACITY-COVID) cohort.[23 24]
- Dutch COVID-19 and Thrombosis Consortium cohort.[25]
- MaastrICCht cohort.[26]
- POPulation health impact of the COVID-19 pandemic (POPCOrn) cohort.[27]
- ZuydErLand COVID-19 regiStry (ELVIS) cohort.[28]

Figure 1 shows the aims, study population and outcomes of each cohort. Electronic case report forms will be used to facilitate data aggregation in order to answer the CORFU study aims. Moreover, the study designs of the majority of the individual cohorts have been aligned in the conceptualisation phase. This includes synchronisation of the follow-up moments during which CORFU data will be collected prospectively, as well as a synchronisation of the additional (clinical) data that will be collected in the individual cohorts, including their level of measurement.

In May 2022, the total source population of the participating cohorts included 12 631 participants. However, the total number of CORFU participants will be lower, as it depends on the survival and the CORFU response rates in the individual cohorts, as well as the number of participants which are included in multiple cohorts. In addition, five out of seven cohorts are prospectively including new patients. The CORFU study population will be described in more detail when reporting the study findings.

Data collection: CORFU questionnaire

Besides the clinical data collection in the cohorts, the CORFU questionnaire will be periodically administered to study participants up to 2 years after suffering from COVID-19. The CORFU questionnaire is based on an internationally developed basic questionnaire on persistent symptoms after COVID-19.[27] It is digitally adaptive and includes questions on the following outcomes and determinants:

Outcomes

- Long COVID symptoms, with a five-level severity scale.
- Health-related quality of life (EuroQol 5 Dimenions 5 Levels (EQ-5D-5L), EuroQol Visual Analogue Scale (EQ-VAS)).
- Anxiety and depression (Hospital Anxiety and Depression Scale (HADS), Generalized Anxiety Disorder 2-item (GAD-2), Patient Health Questionnaire-2 (PHQ-2)).
- Social participation and connectedness.
- Experienced stigmatisation and resilience.
- Consequences for employment status and personal income.

Determinants

- COVID-19-related factors (eg, date of diagnosis and/or clinical admission, severity, wave as surrogate for SARS-CoV-2 strain).
- Sociodemographic and diversity factors (eg, age, sex, gender, socioeconomic).
- Presence of chronic disease or pre-existing vulnerability.
- Impact on healthcare access and experienced quality, healthcare avoidance and self-care.
- Vaccination status at the moment of acute infection.

The CORFU questionnaire will be digitally administered at 3, 6, 12, 18 and 24 months after COVID-19 via a web-based survey or, if requested, on paper. On an individual level, the follow-up moments on which the CORFU questionnaire will be administered depends on the date of first infection (diagnosis and/or admission). In retrospect, not all follow-up moments will apply to all participants. As the CORFU study duration is 15 months, participants will receive a maximum of three CORFU questionnaires. Completing the questionnaire takes, on average, 20–25 min, and participants will receive regular reminders to optimise the response rate.

As study participants were included at different time point in the COVID-19 pandemic, depending on their date of first infection, different contextual factors might apply such as lockdowns, the availability of testing material and testing policy, and the vaccination strategy at that time. These factors are presented in detail in online supplemental table S1.

Outcome variables

The primary outcome is the prevalence of long COVID symptoms up to 2 years after infection. Symptoms include, but are not limited to, fatigue, muscle weakness, respiratory complaints, cardiovascular complaints, cognitive impairment, anxiety and depression. Secondary outcomes are health-related quality of life, physical functioning, and the prevalence of thromboembolic complications, respiratory complications, cardiovascular diseases and endothelial dysfunction.

Initially, the WHO definition will be used to define long COVID.[1] Potentially identified long COVID phenotypes as part of WP1 and other international developments within the field will also be further considered throughout the study.

Data management and data safety

The data will be stored and accessible according to Findability, Accessibility, Interoperability and Reusability (FAIR) data standards.[29] For this, we will apply a machine-readable metadata scheme. Two trusted third parties will administer the digital questionnaires in the individual cohorts: Durrer Center for Cardiovascular Research, Amsterdam, the Netherlands, and Triqs, Zwolle, the Netherlands. Durrer Center facilitates autonomous and secure data management and is founded by the Netherlands

Heart Institute. Triqs is an innovative research agency facilitating data collection through digital questionnaires.

The data flow is as follows. First, Durrer Center will receive participants' contact details from the participating cohorts, check these for any flaws (eg, missing contact details and duplications) and encrypt the contact details except email prior to sharing these with Triqs. Next, Triqs will invite the participants for consent and, subsequently, for participation in the CORFU questionnaire. On consent, participants will digitally receive the questionnaires. After that, Triqs will store the resulting data records (still encrypted) and send these to Durrer Center. Durrer Center will decrypt and subsequently verify each data record and create a pseudoanonymised dataset which will be made available to the CORFU research group and the participating cohorts. As part of the data process, obligatory General Data Protection Regulation contracts will be created between the participating hospitals (care units), Durrer Center, Triqs and the CORFU study unit. In addition, data access agreements will be arranged between the CORFU study unit and the participating cohorts; poststudy secondary analysis of the survey data has been agreed on in collaboration with the EuroQol Research Foundation. Both Durrer Center and Triqs work processes and facilities meet the Dutch privacy legislation standards (International Organization for Standardization and NEderlandse Norm (NEN) norms).

WPs and data analysis

This paragraph describes a generic outline of aims and methods of the WPs. Future manuscripts on CORFU WP findings will describe the aims and used methods in more detail. Table 1 displays the WPs and the corresponding aims and involved cohorts. Within all WPs, baseline data of participants will be described in detail, stratified by subgroup if necessary. Missing data will be imputed if the percentage of incomplete records exceeds 5% using multiple imputation with fully conditional specification. The number of imputations will be set to the percentage of incomplete records, and values will be drawn using predictive mean matching.[30] The primary analyses of the WPs 1–3 aims will be performed with data from CORFU participants who (likely) suffered from COVID-19. Sensitivity analyses will be performed for the subgroup of participants who suffered from confirmed COVID-19 (ie, positive PCR test for SARS-CoV-2 and/or a CO-RADS Score of 4–5).

WP1 will investigate the first and second study aims. First, data of the seven cohorts will be aggregated and used to estimate the prevalence and severity of long COVID symptoms, expressed as a percentage with a 95% CI and as a distribution of severity scores at every follow-up moment. Next, the association between symptom severity and health-related quality of life will be quantified using linear regression analysis and repeated measurements analysis, adjusted for potential confounders. Finally, rehabilitation and paramedical support will be described using descriptive statistics. Analyses will be stratified by participant subgroups (ie, suffered from COVID at home, admitted to hospital ward, admitted to ICU). Furthermore, long COVID 'phenotypes' (ie, subtypes: patients with similar expressions of symptoms) will be estimated. Important phenotypes may depend on combinations of previously reported domains of symptoms (eg, respiratory, cardiovascular), but phenotypes may also depend on previously unidentified combinations. Clusters of patients will be estimated using unsupervised machine learning techniques with K-means and hierarchical clustering, which are data supportive and thereby not confirmatory (of prior hypotheses) in nature.[31]

WP2 will investigate the third study aim. Each cohort will formulate specific long COVID research questions related to various pathophysiological mechanisms and

Table 1 Overview of the work packages, including study aims and cohorts

WP	Aim	Cohorts involved*
WP1	1. Describe the prevalence, severity, time patterns and duration of long COVID symptoms up to 2 years after acute infection and their relationship with health-related quality of life. 2. Describe the received rehabilitation and paramedical support in relation to the persisting symptoms and health-related quality of life.	Data from all cohorts will be used.
WP2	3. Describe the pathophysiological mechanisms that may cause long COVID symptoms and the role of vulnerability/resilience factors.	Every cohort will deliver results for specific pathophysiological hypotheses.
WP3	4. Develop and validate a prediction model for the persistence of symptoms, stratified by severity of COVID-19.	Data from all cohorts will be used.
WP4	5. Develop a patient platform prototype where patients can digitally consult their reported outcomes, compare them with previous outcomes, relate to reference information and find reported information that fits their situation.	The platform will be developed and tested in a limited no of cohorts (to be determined).

*CORFU cohorts include Adelante, CAPACITY-COVID, COVAS, DC&TC, ELVIS, MaastrICCht and POPCOrn.
CAPACITY-COVID, Cardiac complications in patients with COVID-19 cohorts; DC&TC cohort, Dutch COVID and Thrombosis Consortium cohort; COVAS, Bernhoven Early detection of Vascular damage after COVID-19 cohort; ELVIS, ZuydErLand COVID-19 regiStry; MaastrICCht, Maastricht Intensive Care COVID cohort; POPCOrn, POPulation health impact of the COVID-19 pandemic; WP, work package.

Table 2 Overview of work package 2 (WP2) hypotheses on pathophysiological mechanisms that might cause long COVID symptoms

Pathophysiological mechanism	Main research questions include, but are not limited to:	Cohort (minimally) involved
Thromboembolic complications	1. What is the impact of venous thromboembolic complications on long-term functional outcomes in COVID-19 survivors?	DC&TC
Cardiovascular diseases	2. What is the impact of myocardial damage during hospital ward or ICU stay due to COVID-19 on angina pectoris and dyspnoea over time?	CAPACITY-COVID
Endothelial dysfunction	3. What is the relationship between elevated inflammation parameters and persistent thrombo-inflammation, coagulation, microvascular and macrovascular dysfunction, and respiratory symptoms after COVID-19 disease?	COVAS
Multi organ failure	4. What is the impact of multiorgan failure during ICU stay on long-term functional outcomes and (health-related) quality of life in COVID-19 survivors?	MaastrICCht
Pre-existing coronary atherosclerosis	5. What is the relationship between pre-existing clinical and subclinical coronary atherosclerosis, angina pectoris and respiratory symptoms after COVID-19 infection?	ELVIS
NA	6. What is the level of functioning during the course of disease in patients following a rehabilitation programme after COVID-19-related ICU admission?	Adelante

CAPACITY-COVID, Cardiac complications in patients with COVID-19 cohorts; DC&TC cohort, Dutch COVID and Thrombosis Consortium cohort; COVAS, Bernhoven Early detection of Vascular damage after COVID-19 cohort; ELVIS, ZuydErLand COVID-19 regiStry; ICU, intensive care unit; MaastrICCht, Maastricht Intensive Care COVID cohort; NA, not applicable; POPCOrn, POPulation health impact of the COVID-19 pandemic.

data availability. Table 2 shows examples of research questions that will be studied. To explore these pathophysiological mechanisms, data of different cohorts will be aggregated when possible. Next, we will develop directed acyclic graphs (DAGs), presenting (presumed) causal relationships based on current knowledge and new hypotheses while considering long COVID phenotypes identified in WP1. Subsequently, multivariable regression modelling will be used to test the various causal models (expressed in DAGs). Confounding, effect modification and mediation will be considered by testing as model parameters. Associations will be presented as regression coefficients or ORs, including 95% CIs. Analyses will be performed separately for the individual cohort data and for the joint cohort data in which the same outcome measures were used.

WP3 will investigate the fourth study aim. In order to develop a prediction model, we will aim to identify the set of predictors, measured at time of COVID-19 diagnosis and during the course of the disease, that will maximise the ability to discriminate patients who experience long COVID-19 symptoms from patients who do not experience these symptoms. Potential predictors will be selected from the living review by Wynants *et al* and recent literature.[32] Using backward stepwise elimination on the Akaike information criterion in logistic regression analysis, the initial model structure and parameters (including follow-up period) will be estimated. In addition, the model will be internally validated using bootstrapping techniques.

WP4 will address the fifth study aim: developing and testing a patient platform prototype. As the patient platform will be connected to the digital questionnaire platform, individual CORFU questionnaire responses can be presented individually to the corresponding patient. It offers the possibility for patients to consult their own situation, compare this with the past and with the situation of similar patients, profit from suggestions of other patients in similar situations, and gain insight into their future health. The specific content (eg, which symptom domains and other domains of interest) to be presented in the patient platform will be based on focus groups with healthcare professionals, (former) patients and patient representatives. Patient platforms aim to increase empowerment and reassurance (outcomes tested) and might provide guidance in healthcare-seeking and self-care. By providing feedback on the given answers, the platform increase patients' knowledge and self-consciousness about the potential existence of long COVID-19 symptoms and change over time, thereby putting them in own data-driven control on their health situation.

Sample size calculation

The sample size for this study is established pragmatically. A heterogeneous sample of COVID-19 patients is included by choosing different cohorts with considerable heterogeneity in the severity of the disease, national coverage and without any exclusion criteria. This resulted in a collection of seven small to very large cohorts. Our

sample size calculations of WP1, WP2 and WP3 are based on the smallest subgroup of patients that will be analysed in this study.

First, for estimating the prevalence of long COVID symptoms (WP1), for the least favourable percentage of 50% (the variance of a percentage is highest at 50%), the maximum width of the 95% CI will be approximately plus and minus 5%. For all other percentages, the CI will be even smaller. Second, for investigating the pathophysiological mechanisms that may cause long COVID symptoms (WP2), there will be sufficient power to detect associations with symptom severity, expressed in standardised effect size (Cohen's d) of 0.3, with a power of 80% and a type-I error of 5%. Third, for the development of a prediction model for long COVID complaints (WP3), we anticipate a large number of cases, taking into account that 57% of patients suffered from at least one long COVID complaint up to 6 months after infection.[15] Depending on the response rate and resulting sample size, we will determine the maximum number of candidate predictors we can use for multivariable modelling with the method of Riley *et al*, allowing a maximum shrinkage of predictor coefficients of 0.9.[33]

Statistical tests or estimations are not part of WP4. Therefore, sample size or statistical power calculations are not applicable for WP4.

Patient and public involvement

Patient organisations (family and patient centred intensive care, IC Connect and the 'Hartenraad') and patients of the Maastricht University Medical Centre+ (MUMC+) intensive care panel were involved in the design of the CORFU study. Patients were involved in the development and testing of the international basic questionnaire on persistent symptoms after COVID-19, which serves as the basis for the CORFU questionnaire. In addition, patients provided feedback on the phrasing of questions, the fill-out time of the questionnaire and the willingness to fill out the questionnaire periodically. Participants will be able to provide feedback on the (missing) content of the CORFU questionnaire through an open-ended question. Comments will be discussed and implemented prospectively when deemed relevant, making the CORFU questionnaire a continuously developing measurement instrument.

Patients will have an advisory role in developing the patient platform prototype (WP4), which allows patients to digitally consult their answers in real time and compare them with reference populations. In addition, advice will be asked on the (type of) provided feedback questions, the formatting and visualisation of answers, and the relevant reference groups to be considered. Eventually, CORFU findings will be presented in a lay summary, and a flyer on long COVID will be developed in close collaboration with patients. The dissemination strategy of CORFU findings and the long COVID flyer will be based on patient and public preferences, in which also the involved patient organisations will have an important role.

DISCUSSION

The CORFU study has the opportunity to investigate the prevalence, pathophysiological mechanisms, and prediction of long COVID, and its relationship with health-related quality of life. CORFU will aggregate data from seven existing COVID cohorts and will enrich the data with prospective follow-up of long COVID outcomes and determinants up to a maximum of 2 years after acute infection. A prediction model and patient platform prototype will be developed to guide future patient care.

Estimation of the prevalence of long COVID symptoms up to 2 years after infection will be based on the multidimensional CORFU questionnaire, including physical and psychological complaints after COVID. The extensive set of physical complaints gives the opportunity to study symptoms in great detail. The additional focus on psychological impact addresses the call to take COVID psychopathology into account when designing new studies. It reflects the current knowledge that mental well-being is worse in patients who suffered from COVID compared with healthy respondents, and that there is a high rate of mental health complaints up to 1 year after acute infection.[27 34]

CORFU findings may be used to inform national and international guidelines on diagnostics, treatment and follow-up of long COVID and contribute to developing a (new) more accurate long COVID definition, likely differentiating long COVID phenotypes. Available guidelines and definitions on long COVID are currently, as expected, based on short-term follow-up studies, whereas CORFU will report long COVID symptoms up to 2 years after infection.[1 35] Besides, the current WHO long COVID definition remains broad and unspecific, thereby lacking accurate differentiation of its heterogeneous appearance into clinical phenotypes. Defining such phenotypes with potentially adding clinical parameters (biomarkers, imaging, etc) might enhance clinical workability, and thereby diagnostics, and the development of tailored therapies based on underlying pathophysiology.

An important strength of the CORFU study is that data will be aggregated from seven cohorts of (former) COVID-19 patients. Due to mortality and non-response, the effective number might be slightly lower. Nevertheless, the large CORFU sample size allows for robust analysis. Furthermore, the difference in designs of the cohorts allows us to answer study aims for various subgroups (eg, COVID-19 at home vs hospitalised (ward and/or ICU)) and to test multiple, detailed, pathophysiological hypotheses, depending on the characteristics of the patients included in the participating cohorts, also related to COVID-19 variants by using wave at the time of infection as a surrogate marker. Furthermore, the ability to aggregate data of multiple cohorts is an efficient way of (close) national collaboration which contributes to more robust and reliable findings compared with multiple, parallel, single cohort studies with smaller sample sizes.

Another strength is that CORFU will use data from a large control group of respondents who did not suffer

from COVID-19. This allows the comparison of the prevalence of long COVID-19 symptoms with the prevalence of these symptoms in the general Dutch, non-COVID-19 population, potentially highlighting the secondary impacts of the pandemic. This is a crucial comparison currently lacking in the majority (79%) of long COVID-19 research but required to identify and quantify attributable symptoms objectively.[36] For instance, the (social) restrictions may significantly impact the quality of life and (mental) well-being of the general population.[13 27 37 38] These factors need to be considered when analysing and interpreting the CORFU findings. Lastly, as part of WP4, patients will receive personalised feedback on their own questionnaire outcomes and those of other patients in similar situations.

Potential limitations of the CORFU study also merit consideration. First, combining data from seven cohorts is challenging. As each cohort has specific study aims regarding the pathophysiological processes causing long COVID symptoms, not all cohorts collect the same (clinical) information from their participants. To ensure that data from all cohorts can be integrated and that between-cohort comparisons are possible, a minimal set of variables was (post-hoc) harmonised among the participating cohorts regarding background characteristics (eg, sociodemographics, employment status, social, economic status, cultural background), comorbidities and potential confounders. Furthermore, to optimise the data integration process, data received from the cohorts will be transferred into a machine-readable metadata scheme prior to merging the various datasets. Second, there will be an over-representation of (former) COVID patients admitted to the hospital ward and/or ICU compared with those who suffered from COVID at home. This affects estimations of long COVID prevalence, which can be evaluated by post hoc stratification using community-based cases. The epidemiological basis used for the statistical models to develop prediction models is independent of inpatient/outpatient distribution and depends solely on the associations and interactions found within specific patient groups, as COVID severity will be added as a covariate. Moreover, analyses will be stratified by disease severity for subgroup-specific conclusions. Third, especially in the first COVID wave (1 March 2020–30 June 2020) for non-hospitalised patients, not all suspected COVID cases were tested due to capacity and test-material constraints in the Netherlands. For CORFU, this means that there is a lack of confirmed infections for participants of the community-based POPCORN cohort who self-reported to have (likely) suffered from COVID based on an unspecified positive test or the presence of COVID-19-related symptoms. In order to reduce the impact of this limitation, the primary analyses will be repeated in the sensitivity analyses on the subgroup of COVID cases with a confirmed infection. The same holds for controls from the POPCORN cohort who (likely) did not suffer from COVID: there is a possibility that these controls did suffer from COVID, but that they, for example, did not test due to the absence of symptoms or test-material constraints, or that their tests were false negative (online supplemental table S1). This might result in some misclassification of cases that had no or only very mild symptoms, never got tested, and will likely report never having suffered from COVID. This will be described when reporting CORFU study results, and, when deemed relevant, additional (stratified) analyses will be conducted.

Ethics and dissemination

This study will be conducted according to the latest update of the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT05240742). Ethics approval was obtained from the medical research ethics committee (MREC) of Maastricht University Medical Center+ and Maastricht University (committee reference number METC2021-2990) and the local MRECs of the participating cohorts (online supplemental table S2). Participants will be asked for written or digital informed consent, by the cohort in which they are participating, prior to administering the first CORFU questionnaire and will be informed that participation is voluntary. Data will be made available (Open Science/FAIR) subject to ethical approval and standard access and anonymisation procedures.

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SUPPLEMENTARY TABLES

Prevalence, pathophysiology, prediction and health-related quality of life of long COVID: design of the longitudinal multiple cohort CORona Follow Up (CORFU) study

Table S1. COVID-19 lockdown, testing policy and vaccination strategy timelines in the Netherlands from 2020 to 2022

National lockdown and reopening timeline	
2020	
February 28	First COVID-19 patient in the Netherlands.
March 1	Advise to stay at home when returning from a foreign high risk area and with mild COVID-19 symptoms.
March 12	Advise to work from home for all civil servants in non-critical functions.
March 13	Assembly ban for more than 100 people.
March 15	**Partial lockdown**: Advice to keep 1.5m distance; Closure of cafes, bars and restaurants, clubs, discotheques, cinemas, theaters, indoor and outdoor sport facilities, fitness centers and wellness centers.
March 16	Closure of "contact professions" (with the exception of (para)medical professions), primary and secondary schools and day care.
March 20	Visitors are no longer allowed in nursing homes.
May 11	Partial reopening of contact professions, primary schools and day care. It is allowed to sport outside with 1.5m distance.
June 1	Partial reopening of primary secondary schools; Reopening of cafes, bars and restaurants, cinemas and theaters with a maximum of 30 people.
June 1	It is mandatory to wear a mask in public transport.
June 8	100% reopening of primary schools and day care.
June 15	Nursing home residents are allowed to have 1 fixed visitor per day.
July 1	The assembly ban for larger assemblies is abolished.
August 18	Assembly ceiling is lowered to 6 visitors (>12 years) at home per day.
August 31	100% reopening of secondary schools.
September 29	Assembly ceiling is lowered to 3 visitors (>12 years) at home per day; Cafes, bars and restaurants must close at 22.00; Contact professions are obliged to register clients; Closure of sports cafeterias; Sports competitions are without any audience.
October 14	**Partial lockdown:** Advise to wear masks in publicly accessible locations inside; Assembly ceiling is lowered to 3 visitors (>12 years) at home per day; Assembly ban for more than 30 people inside; Closure of cafes, bars and restaurants; Event and sports competitions ban; Students in secondary schools, MBO, HBO and universities are obliged to wear mask outside of class; Assembly ban for sports with more than 4 people.
November 4	The advice is to stay at home; Assembly ceiling is lowered to 2 visitors or 1 household at home per day (both inside and outside); Closure of publicly accessible locations; Assembly ban for sports with more than 2 people.
December 1	It is mandatory to wear a mask (>12 years) in publicly accessible locations inside.
December 14	**Lockdown:** Closure of all non-essential shops, indoor and outdoor sports facilities, fitness centers, primary and secondary schools and day care.
2021	
January 20	Assembly ceiling is lowered to 1 visitor (>12 years) at home per day.

January 23	Curfew between 21:00-04.30.
February 8	Reopening of primary schools and day care; Non-essential shops are allowed to open for "click and collect".
March 1	Partial reopening of secondary schools and MBO.
March 3	Partial reopening of contact professions, non-essential shops (appointment-based); Assembly ban for outside sports is abolished for people ≤ 26 years within their own sports club.
March 8	Vaccinated nursing home residents are allowed to have 2 visitors per day.
March 16	Assembly ceiling for outside sports is increased to 4 people.
March 31	Curfew between 22:00-4:30.
April 26	Partial reopening of HBO and universities.
April 28	Curfew is abolished; Assembly ceiling is increased to 2 visitor (>12 years) at home per day; Reopening of terraces between 12:00-18:00 with a maximum of 2 persons or 1 household per table; Reopening of non-essential stores with a maximum of 1 customer per $25m^2$.
May 19	Assembly ceiling for outside sports is increased to 30 adults; Reopening of swimming pools, sports facilities and fitness centers with an assembly ban of more than 30 people; Reopening of outside publicly accessible locations (appointment-based) and libraries.
June 5	Assembly ceiling is increased to 4 visitors (>12 years) at home per day; Assembly ban for outside groups of more than 4 people; Assembly ceiling for outside sports is increased to 50 adults; Reopening of dressing rooms and sports cafeterias; Reopening of cafes, bars and restaurants including terraces between 06:00-22:00, museums, cinemas and theatres,
June 26	Assembly ban for visitors at home is abolished; No more regulations for a maximum number of people outside in a group; It is mandatory to wear masks when there is no 1.5m distance; Prolonged opening hours for cafes, bars, restaurants, shops and theaters; Reopening of clubs and discotheques; Advise to work from home 50% of the time; Events are allowed with a covid certificate; Amateur sports competitions can be held with an audience.
July 10	Closure of clubs and discotheques; Events have a maximum duration of 24 hours and participants must be seated (67% capacity); Cafes, bars and restaurants must close at 00:00 and visitors must be seated.
July 19	Working from home unless this is not possible.
August 8	Returning from countries with a yellow travel advice is only possible with a covid certificate.
August 30	Partial reopening of MBO, HBO and universities without 1.5m distance.
September 25	Covid certificate is mandatory (> 12 years) in cafes, bars and restaurants, at festivals and events, at sports competitions, cinemas and theaters.
September 25	It is no longer mandatory to keep 1.5m distance; Working from home if possible; Maximum number of visitors for inside festivals, shows, parties and sports competitions which must close at 00:00.
November 3	Work from home for at least 50% of the time.
November 6	Wear a mask in buildings without the need for a covid certificate; Use of the mandatory covid certificate is expended.
November 12	Keep 1.5m distance in places without mandatory covid certificate; Non-essential stores must close at 18:00h; Cafes, bars and restaurants must close at 20:00; Events must stop at 17:00h and visitors must have a fixed seat with a maximum of 1.250 visitors; No audience at sports competitions; Assembly ceiling lowered to 75 people per room in MBO, HBO and

	universities; Work from home; Assembly ceiling is lowered to 4 visitors (>12 years) at home per day.
November 26	Everything must close at 17:00h, except for essential stores which must close at 20:00h; Teachers and students at primary and secondary school must wear a mask and test regularly.
December 14	Primary schools and day care close a week before Christmas holidays.
December 19	**Lockdown:** Stay at home if possible; Assembly ceiling of 2 persons or 1 household outside; Assembly ceiling lowered to 2 visitors (>12 years) at home per day; Closure of publicly accessible locations and schools.
2022	
January 10	Reopening of primary and secondary schools and day care.
January 15	Reopening of MBO, HBO and universities, cultural lessons inside and outside (without audience), sporting facilities inside and outside; Non-essential shops must close at 17:00, Essential shops must close at 20:00, contact professions must close at 17:00; It is advised to wear a mask; Assembly ceiling increased to 4 visitors (>12 years) at home per day.
January 26	Cafes, bars, restaurants, theaters, cinemas, museums, concert halls, zoos and theme parks are open between 5:00-22:00 under the conditions of a covid certificate, wearing a mask, and fixed seats; Reopening of events inside and outside with fixed seats and an assembly ban of more than 1.250 visitors (festivals are not allowed); Audience is permitted at sports competitions.
February 15	No assembly ceiling for visitors at home; Working from home 50% of the time.
February 18	Everything is allowed to be open until 01:00; With a covid certificate it is no longer obligated to be seated during events and to wear masks.
February 25	Everything is allowed to have normal opening hours; End of the 1.5m distance regulation; End of the obligatory seated events; It is only obligated to wear a mask at public transport and the Dutch airports; It is no longer obligated to make use of the covid certificate.
March 15	All regulations are converted into advices.
March 23	It is no longer obligated to wear a mask in public transport.
May 20	It is no longer obligated to wear a mask at the Dutch airports.
Testing policy timeline	
2020	
April 6	Testing only for citizens who experience COVID-19 symptoms for at least 24 hours AND accommodate specific criteria (e.g. key workers in healthcare and other key professions such as law enforcement, and people with a high risk of severe COVID-19 disease) at the Municipal Health Service.
May 6	Testing also for teachers and day care personnel who experience COVID-19 symptoms for at least 24 hours at the Municipal Health Service.
May 11	Testing also for the majority of the contact professions who experience COVID-19 symptoms for at least 24 hours at the Municipal Health Service.
May 18	Testing also for informal care givers who experience COVID-19 symptoms for at least 24 hours at the Municipal Health Service.
June 1	Testing of any citizen experiencing COVID-19 symptoms at the Municipal Health Service.
December 1	Testing of citizens without COVID-19 symptoms when they have been in contact with a SarS-CoV-2 positive person at the Municipal Health Service.

2021	
March 31	Everyone can buy COVID-19 self-tests in the Dutch pharmacies, but testing at the Municipal Health Service is still required.
December 2	Citizens with COVID-19 symptoms can perform self-test or go to the Municipal Health Service for a test. A positive self-test should be confirmed at the Municipal Health Service.
2022	
March 15	No more need to test without experiencing of COVID-19 symptoms.
April 11	Everyone can use a self-test when experiencing COVID-19 symptoms, it is no longer mandatory to confirm this at the Municipal Health Service.
Vaccination strategy timeline	
2021	
January 6	Start of first vaccination round for key healthcare workers.
January 18	Start of first vaccination round for nursing home residents.
January 29	Start of first vaccination round for every citizen ≥18 years (start with the eldest age groups).
July 2	Start of first vaccination round for teenagers (12-17 years).
November 18-23	Start of first booster round for citizens 60-80+, nursing home residents and healthcare workers with patient contact.
December 20	Start of first vaccination round for children (5-11 years) with a high-risk medical indication.
2022	
January 18	Start of first vaccination round for children (5-11 years) without a medical indication.
January 6	Start of first booster round for every citizen ≥18 years.
February 24	Start of second booster round for 70+ citizens, nursing home residents and citizens with severely compromised resistance.
March 7	Start of first booster round for teenagers (12-17 years).
September 19	Start of second booster vaccination round for every citizen ≥12 years (start with key healthcare workers and people with a high risk of severe COVID-19 disease).

The information depicted by this table is available from:

1. *The National Institute for Public Health and the Environment (In Dutch: Rijksinstituut voor Volksgezondheid en Milieu (RIVM) from https://www.rivm.nl/gedragsonderzoek/tijdlijn-maatregelen-covid*
2. *The Dutch Government (In Dutch: Rijksoverheid) from*
    a. *https://www.rijksoverheid.nl/onderwerpen/coronavirus-tijdlijn*
    b. https://www.rijksoverheid.nl/onderwerpen/coronavirus-vaccinatie/nieuws

Table S2. Overview of ethics approval information per cohort

Cohort acronym	Corresponding MREC	MREC Registration ID	Additional cohort registration
Adelante	MREC Zuyderland	METCZ20200086	n.a.
CAPACITY-COVID	MREC Utrecht	CAPACITY 1: 20-161/C CAPACITY 2: 21-097/M DEFENCE: 21-532/C	ClinicalTrials.gov: NCT04325412
COVAS	MREC Oost Nederland	NL74101.091.20	n.a.
DC&TC	n.a.	n.a.	n.a.
ELVIS	MREC Z - Zuyderland	METCZ20200121	n.a.
MaastrICCht	MREC Maastricht University Medical Center+ / Maastricht University	Follow Up cohort: 2020-2368-A-2; 2020-2368-A-1; 2020-2368 Initial cohort: 2020-1565/300523	The Netherlands Trial Register: NL8613
POPCOrn	MREC Erasmus Medical Center, Rotterdam	MEC-2020-0266	n.a.

Abbreviations: CAPACITY-COVID: Cardiac complications in patients with COVID-19 cohorts; COVAS: Bernhoven Early detection of Vascular damage after COVID-19 cohort; DC&TC cohort: Dutch COVID & Thrombosis Consortium cohort; ELVIS: ZuydErLand COVID-19 regiStry; MaastrICCht: Maastricht Intensive Care COVID cohort; MREC: Medical Research Ethics Committee; n.a.: not applicable; POPCOrn: POPulation health impact of the COVID-19 pandemic