Overzicht belangrijkste bevindingen Post Covid onderzoeken (ZonMw)

Dit is een schematische weergave van de belangrijkste (tussen)resultaten uit Nederlands onderzoek naar het Post-COVID-syndroom, opgesteld door de Programmadirectie COVID-19 Zorg. De bevindingen zijn letterlijk overgenomen uit de publicaties. Er heeft **geen** vertaalslag plaatsgevonden naar beleid. Het gaat hier enkel om (tussentijdse) publicaties van onderzoeken die zijn gefaciliteerd door het Ministerie van Volksgezondheid, Welzijn en Sport via ZonMw. Bij de interpretatie van onderzoeksresultaten (en de vertaalslag naar beleidsontwikkeling) dient eerst een verificatie door onderzoeks- en projectleiders te worden verricht.

Onderwerp / titel van studie	Publicatiedatum- en plaats	Onderzoekers/ organisaties	Belangrijkste bevindingen
Multidisciplinaire integrale richtlijn COVID-19 nazorg	1 maart 2022 Via de Richtlijnendatabase van de NHG (en FMS): Langdurige klachten na COVID-19 (nhg.org)	Nederlandse Huisartsen Genootschap Federatie Medisch Specialisten Long Alliantie Nederland	Veel patiënten hebben langdurige klachten na het doormaken van COVID-19. Uitgaande van (de data van) ongevaccineerde patiënten is ongeveer de helft na 3 maanden klachtenvrij. De meest voorkomende klachten zijn vermoeidheid, verminderde inspanningstolerantie, spierzwakte, dyspneu, cognitieve klachten en reuk- of smaakstoornissen. Ook hebben veel patiënten last van angst en slaapproblemen na COVID-19. De behandeling neemt vaak meerdere consulten in beslag, met aandacht voor de biologische, psychologische en sociale aspecten. De basis van de behandeling bestaat uit voorlichting en adviezen, in samenspraak met de patiënt. Verwijs bij specifieke problematiek zo nodig voor een paramedische behandeling of tweedelijns consultatie. Overweeg verwijzing naar de tweede lijn voor een multidisciplinair overleg in de volgende gevallen: onvoldoende herstel van matig ernstige samenhangende klachten na 6 maanden behandeling in de eerste lijn grote complexiteit van de klachten diagnostische twijfel of de combinatie van klachten en het beloop passen bij langdurige klachten na COVID-19 Blijf bij langdurige (of verergerende) klachten na COVID-19 alert op andere of bijkomende oorzaken, zoals hartfalen, astma/COPD, angina pectoris, longembolie of een (nieuwe) respiratoire infectie.
Aanhoudende klachten na COVID-19: perspectief vanuit de	20 januari 2022 Via de projectwebsite ACTION:	Universitair Medisch Centrum Groningen	In dit project wordt een zorgpad voor de behandeling van patiënten met Long COVID ontwikkeld. Het Zorgpad geeft antwoord op de vraag: wie doet wat, wanneer en waarom. In de eerste fase van dit project zijn bestaande initiatieven in kaart gebracht en samengevat in een werkdocument. Op basis hiervan is een overkoepelend zorgpad opgesteld en in de eerste

populatie, patiënt, en zorg	Zorgpad – ACTION (actioncovid.nl)		werkconferentie bediscussieerd met patiënten en zorgverleners. Mechanismen en risicofactoren van aanhoudende klachten analyse wordt verwacht oktober 2022. Impact en zorgbehoefte naar aanleiding van aanhoudende klachten worden verwacht december 2022. **Bijlage 1: Concept zorgpad**
Aanhoudende klachten na COVID-19 infectie: epidemiologie, pathofysiologie, predictie, en communicatie, de CORona Follow Up (CORFU) studie	25 februari 2022 Via PubMed Cardiovascular outcome 6 months after severe coronavirus disease 2019 infection - PubMed (nih.gov)	Binnen deze studie werken onderzoekers uit het MUMC+ nauw samen met: - de stichting EuroQol, - Zuyderland Medisch Centrum - Adelante - onderzoekers van de academische centra in Utrecht, Nijmegen en Leiden.	**Objectives:** In coronavirus disease 2019 (COVID-19), cardiovascular risk factors and myocardial injury relate to increased mortality. We evaluated the extent of cardiac sequelae 6 months after hospital discharge in patients surviving ICU hospitalization for COVID-19. **Methods**: All survivors of Maastricht-ICU were invited for comprehensive cardiovascular evaluation 6 months after discharge from ICU. Cardiac screening included an electrocardiogram, cardiac biomarkers, echocardiography, cardiac magnetic resonance (CMR) and, wherever indicated, cardiac computed tomography or coronary angiogram. **Results:** Out of 52 survivors, 81% (n = 42) participated to the cardiovascular follow-up [median follow-up of 6 months, interquartile range (IQR) 6.1-6.7]. Eight patients (19%) had newly diagnosed coronary artery disease (CAD), of which two required a percutaneous intervention. Echocardiographic global longitudinal strain (GLS) was abnormal in 24% and CMR-derived GLS was abnormal in 12%, despite normal left ventricular ejection fraction in all. None of the patients showed elevated T1 relaxation times and five patients (14%) had an elevated T2 relaxation time. Late gadolinium enhancement (LGE) reflecting regional myocardial fibrosis was increased in eight patients (21%), of which three had myocarditis and three had pericarditis. **Conclusion:** Cardiovascular follow-up at 6 months after ICU-admission for severe COVID-19 revealed that one out of five invasively mechanically ventilated survivors had CAD, a quarter had subclinical left ventricular dysfunction defined as reduced echocardiographic GLS, and 42% of the patients had CMR abnormalities (reduced LVEF, reduced GLS, LGE presence, and elevated T2). On the basis of these findings, long-term cardiovascular follow-up is strongly recommended in all post-IC COVID-19 patients.
COVID-19 Follow-up care paths	13 december 2021	Erasmus MC	**Introduction** A large proportion of patients experiences a wide range of sequelae after acute COVID-19 infection, especially after severe illness. The

and Long-term Outcomes Within the Dutch health care system: a combined rehabilitation, pulmonary, and intensive care perspective (CO-FLOW study) **Eerste publicatie**: Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study	Via MedRxiv (preprint server for health sciences): Symptoms persisting after hospitalization for COVID-19		long-term health sequelae need to be assessed. Our objective was to longitudinally assess persistence of symptoms and clusters of symptoms up to 12 months after hospitalization for COVID-19, and to assess determinants of the main persistent symptoms. **Methods** In this multicenter prospective cohort study patients with COVID-19 are followed up for 2 years with measurements at 3, 6, 12, and 24 months after hospital discharge. Here, we present interim results regarding persistent symptoms up to 12 months. Symptoms were clustered into physical, respiratory, cognitive and fatigue symptoms. **Results** We included 492 patients; mean age was 60.2±10.7 years, 335 (68.1%) males, median length of hospital stay 11 (6.0-27.0) days. At 3 months after discharge 97.0% of the patients had at least 1 persisting symptom, this declined to 95.5% and 92.0% at 6 and 12 months, respectively (p=0.010). Muscle weakness, exertional dyspnea, fatigue, and memory and concentration problems were the most prevalent symptoms with rates over 50% during follow-up. Over time, muscle weakness, hair loss, and exertional dyspnea decreased significantly (p<0.001), while other symptoms, such as fatigue, concentration and memory problems, anosmia, and ageusia persisted. Symptoms from the physical and respiratory cluster declined significantly over time, in contrast to symptoms from the fatigue and cognitive clusters. Female gender was the most important predictor of persistent symptoms and co-occurrence of symptoms from all clusters. Shorter hospital stay and treatment with steroids were related with decreased muscle weakness; comorbidity and being employed were related with increased fatigue; and shorter hospital stay and comorbidity were related with memory problems. **Conclusion** The majority of patients experienced COVID-19 sequelae up to 12 months after hospitalization. Whereas physical and respiratory symptoms showed slow gradual decline, fatigue and cognitive symptoms did not evidently resolve over time. This finding stresses the importance of finding the underlying causes and effective treatments for post-COVID condition, beside adequate COVID-19 prevention.
COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care	April 2022 Via PubMed: Persistent health	Erasmus MC	**Rationale:** Data on longitudinal recovery after hospitalization for coronavirus disease (COVID-19) currently remain scarce, just as outcomes beyond 3 months of follow-up do. **Objectives:** To evaluate the sequelae up to 6 months after hospitalization for

system: a combined rehabilitation, pulmonary, and intensive care perspective (CO-FLOW study) **Tweede publicatie:** Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for COVID-19: A Longitudinal Study of Respiratory, Physical, and Psychological Outcomes	problems beyond pulmonary recovery up to 6 months after hospitalization for SARS-CoV-2		COVID-19 by considering *1*) recovery as it relates to pulmonary function, radiological abnormalities, physical and mental health status, and health-related quality of life (HR-QoL) and *2*) the predictors of the most clinically relevant sequelae. **Methods:** Patients were evaluated at 6 weeks, 3 months, and 6 months after hospitalization by using pulmonary function testing, radiological evaluation, and online questionnaires on the physical and mental health status and HR-QoL. Outcomes were analyzed using repeated-measurement analyses. **Results:** Ninety-two patients were included (mean age, 58.2 ± 12.3 yr; 58 [63.0%] men). The estimated percentage of patients with impaired forced vital capacity improved from 25% at 6 weeks to 11% at 6 months; for impaired diffusion capacity, this percentage improved from 63% to 46%. Radiologically, ground-glass opacity decreased but fibrosis persisted. The majority of patients (89.1%) still reported one or more symptoms 6 months after discharge. Fatigue decreased significantly over time ($P = 0.006$). Nonetheless, fatigue remained in 51% of the patients at 6 months. HR-QoL (nearly) normalized in most domains at 6 months, except for physical role functioning, with persistent fatigue and the length of hospitalization being the most important predictors. **Conclusions:** During the first 6 months after hospitalization for COVID-19, most patients demonstrated continuing recovery across all health domains, but persistent sequelae were frequent. Fatigue was the most frequent residual and persistent symptom up to 6 months after hospitalization, importantly impacting HR-QoL.
COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system: a combined rehabilitation, pulmonary, and intensive care	21 augustus 2021 Via de National library of medicine: CO-FLOW: COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care	CO-FLOW project Erasmus MC	**Background:** First studies indicate that up to 6 months after hospital discharge, coronavirus disease 2019 (COVID-19) causes severe physical, cognitive, and psychological impairments, which may affect participation and health-related quality of life (HRQoL). After hospitalization for COVID-19, a number of patients are referred to medical rehabilitation centers or skilled nursing facilities for further treatment, while others go home with or without aftercare. The aftercare paths include 1] community-based rehabilitation; 2] in- and outpatient medical rehabilitation; 3] inpatient rehabilitation in skilled nursing facilities; and 4] sheltered care (inpatient). These aftercare paths and the trajectories of recovery after COVID-19 urgently need long-term in-depth evaluation to optimize and personalize treatment. CO-FLOW aims, by following

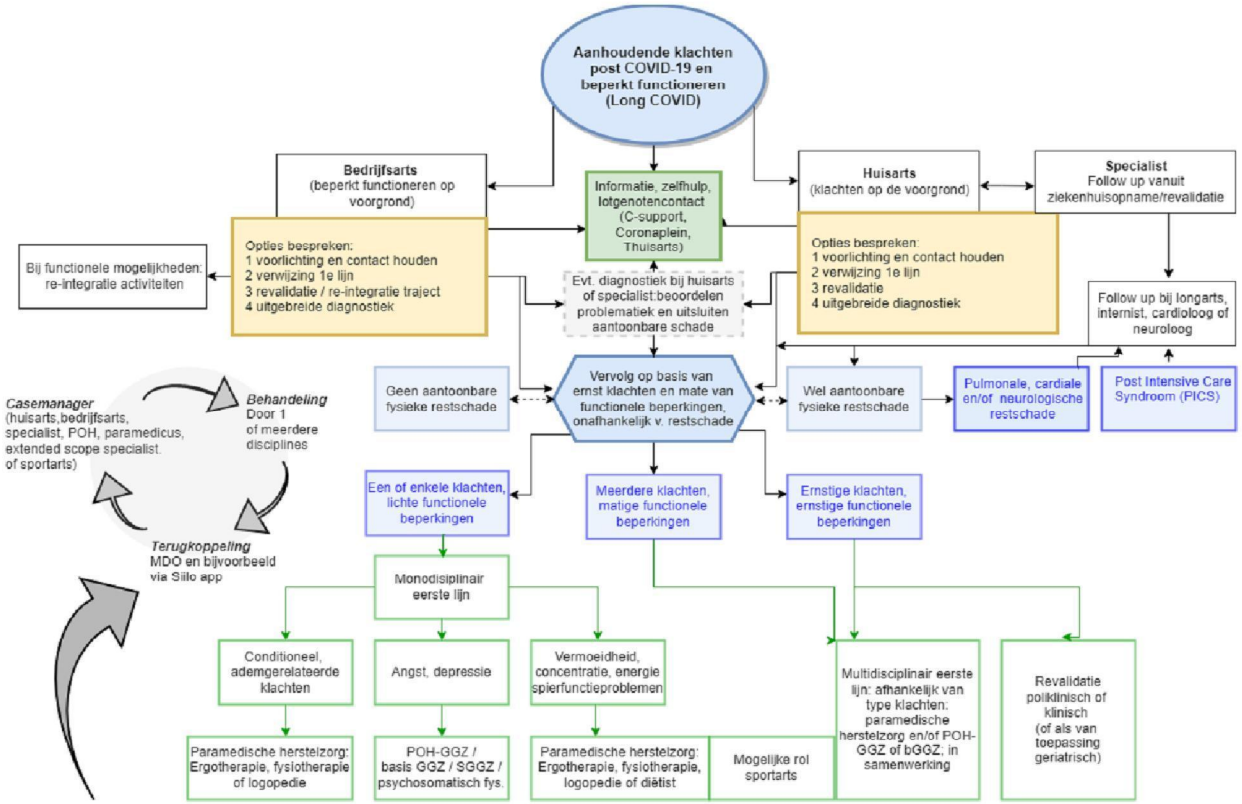
perspective (CO-FLOW study) **Derde publicatie:** CO-FLOW study protocol	system: study protocol of a multicenter prospective cohort study following patients 2 years after hospital discharge - PMC (nih.gov)		the outcomes and aftercare paths of all COVID-19 patients after hospital discharge, to systematically study over a 2-year period: 1] trajectories of physical, cognitive, and psychological recovery; 2] patient flows, healthcare utilization, patient satisfaction with aftercare, and barriers/facilitators regarding aftercare as experienced by healthcare professionals; 3] effects of physical, cognitive, and psychological outcomes on participation and HRQoL; and 4] predictors for long-term recovery, health care utilization, and patient satisfaction with aftercare. **Methods:** CO-FLOW is a multicenter prospective cohort study in the mid-west of the Netherlands with a 2-year follow-up period. Measurements comprise non-invasive clinical tests and patient reported outcome measures from a combined rehabilitation, pulmonary, and intensive care perspective. Measurements are performed at 3, 6, 12, and 24 months after hospital discharge and, if applicable, at rehabilitation discharge. CO-FLOW aims to include at least 500 patients who survived hospitalization for COVID-19, aged ≥18 years. **Discussion:** CO-FLOW will provide in-depth knowledge on the long-term sequelae of COVID-19 and the quality of current aftercare paths for patients who survived hospitalization. This knowledge is a prerequisite to facilitate the right care in the right place for COVID-19 and comparable future infectious diseases.
COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system: a combined rehabilitation, pulmonary, and intensive care perspective (CO-FLOW study) **Vierde publicatie**: Puzzling persisting symptoms after Covid-19.	19 april 2022 Via PubMed: Puzzling persisting symptoms after COVID-19 | European Respiratory Society (ersjournals.com)	Dr. M.E. (Merel) Hellemons Erasmus MC	There is an increasingly evident discrepancy between experienced symptoms and underlying pulmonary injury, thus motivating further research to identify the underlying mechanisms of persistent pulmonary symptoms after COVID19

Prospective cohort study of non-hospitalised COVID-19 patients: determining length of isolation and patient clinical development at home (COVID-HOME study)	20 december 2021 Via PubMed: Mild Coronavirus Disease 2019 (COVID-19) Is Marked by Systemic Oxidative Stress: A Pilot Study - PubMed (nih.gov)	Universitair Medisch Centrum Groningen	Oxidative stress has been implicated to play a critical role in the pathophysiology of coronavirus disease 2019 (COVID-19) and may therefore be considered as a relevant therapeutic target. Serum free thiols (R-SH, sulfhydryl groups) comprise a robust marker of systemic oxidative stress, since they are readily oxidized by reactive oxygen species (ROS). In this study, serum free thiol concentrations were measured in hospitalized and non-hospitalized patients with COVID-19 and healthy controls and their associations with relevant clinical parameters were examined. Serum free thiol concentrations were measured colorimetrically (Ellman's method) in 29 non-hospitalized COVID-19 subjects and 30 age-, sex-, and body-mass index (BMI)-matched healthy controls and analyzed for associations with clinical and biochemical disease parameters. Additional free thiol measurements were performed on seven serum samples from COVID-19 subjects who required hospitalization to examine their correlation with disease severity. Non-hospitalized subjects with COVID-19 had significantly lower concentrations of serum free thiols compared to healthy controls ($p = 0.014$), indicating oxidative stress. Serum free thiols were positively associated with albumin (St. $\beta = 0.710$, $p < 0.001$) and inversely associated with CRP (St. $\beta = -0.434$, $p = 0.027$), and showed significant discriminative ability to differentiate subjects with COVID-19 from healthy controls (AUC = 0.69, $p = 0.011$), which was slightly higher than the discriminative performance of CRP concentrations regarding COVID-19 diagnosis (AUC = 0.66, $p = 0.042$). **This study concludes that systemic oxidative stress is increased in patients with COVID-19 compared with healthy controls. This opens an avenue of treatment options since free thiols are amenable to therapeutic modulation.**
ReCOVer: A randomized controlled trial testing the efficacy of cognitive behavioural therapy for preventing chronic postinfectious fatigue among patients	2 december 2021 Via Pubmed: A randomised controlled trial testing the efficacy of Fit after COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue	Amsterdam UMC	**Background** Coronavirus disease 2019 (COVID-19) results in debilitating long-term symptoms, often referred to as Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), in a substantial subgroup of patients. One of the most prevalent symptoms following COVID-19 is severe fatigue. Prompt delivery of cognitive behavioural therapy (CBT), an evidence-based treatment that has shown benefit in reducing severe fatigue in other conditions, may reduce post-COVID-19 fatigue. Based on an existing CBT protocol, a blended intervention of 17 weeks, *Fit after COVID*, was developed to treat severe fatigue after the acute phase of infection with SARS-CoV-2.

diagnosed with COVID-19 disease **Eerste publicatie:** Study protocol	following COVID-19 (ReCOVer): study protocol - PubMed (nih.gov)		**Method** The ReCOVer study is a multicentre 2-arm randomised controlled trial (RCT) to test the efficacy of *Fit after COVID* on severe post-infectious fatigue. Participants are eligible if they report severe fatigue 3 up to and including 12 months following COVID-19. One hundred and fourteen participants will be randomised to either *Fit after COVID* or care as usual (ratio 1:1). The primary outcome, the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue), is assessed in both groups before randomisation (T0), directly post CBT or following care as usual (T1), and at follow-up 6 months after the second assessment (T2). In addition, a long-term follow-up (T3), 12 months after the second assessment, is performed in the CBT group only. The primary objective is to investigate whether CBT will lead to a significantly lower mean fatigue severity score measured with the CIS-fatigue across the first two follow-up assessments (T1 and T2) as compared to care as usual. Secondary objectives are to determine the proportion of participants no longer being severely fatigued (operationalised in different ways) at T1 and T2 and to investigate changes in physical and social functioning, in the number and severity of somatic symptoms and in problems concentrating across T1 and T2. **Discussion** This is the first trial testing a cognitive behavioural intervention targeting severe fatigue after COVID-19. If *Fit after COVID* is effective in reducing fatigue severity following COVID-19, this intervention could contribute to alleviating the long-term health consequences of COVID-19 by relieving one of its most prevalent and distressing long-term symptoms.
ReCOVer: A randomized controlled trial testing the efficacy of cognitive behavioural therapy for preventing chronic postinfectious fatigue among	22 januari 2022 Via de National Library of Medicine: A research agenda for post-COVID-19 fatigue.	Amsterdam UMC	This paper outlines research priorities for post-COVID-19 fatigue. In May 2021, an international workshop with experts in the field of PIFS (Post-Infective Fatigue Syndrome) was organized by COFFI, the International Collaborative on Fatigue Following Infection [10,11]. Participating experts presented current knowledge about PIFS within their respective disciplines. Furthermore, they formulated research questions that, from their field of expertise, need to be addressed to foster our understanding of post-COVID-19 fatigue specifically, and PIFS in general. The following three research categories were identified as priorities. 3.1. Etiology of post-COVID-19 fatigue 3.2. Impact of post-COVID-19 fatigue on daily functioning and health economic

patients diagnosed with COVID-19 disease **Tweede publicatie:** A research agenda for post-COVID-19 fatigue			outcomes 3.3. Interventions for PIFS Although post infective fatigue appears unlikely to be unique to COVID-19, the scale of the affected population is unprecedented. The resources and possibilities now available to study post-COVID-19 fatigue can potentially improve our understanding and management of PIFS in general. This is a research opportunity we can't pass up.

Bijlage 1: Concept zorgpad (ACTION-studie)


Aanhoudende klachten post COVID-19 en beperkt functioneren (Long COVID)
Bedrijfsarts (beperkt functioneren op voorgrond)
Informatie, zelfhulp, lotgenotencontact (C-support, Coronaplein, Thuisarts)
Huisarts (klachten op de voorgrond)
Specialist Follow up vanuit ziekenhuisopname/revalidatie
Bij functionele mogelijkheden: re-integratie activiteiten
Opties bespreken: 1 voorlichting en contact houden 2 verwijzing 1e lijn 3 revalidatie / re-integratie traject 4 uitgebreide diagnostiek
Evt. diagnostiek bij huisarts of specialist:beoordelen problematiek en uitsluiten aantoonbare schade
Opties bespreken: 1 voorlichting en contact houden 2 verwijzing 1e lijn 3 revalidatie 4 uitgebreide diagnostiek
Follow up bij longarts, internist, cardioloog of neuroloog
Casemanager (huisarts,bedrijfsarts, specialist, POH, paramedicus, extended scope specialist of sportarts)
Behandeling Door 1 of meerdere disciplines
Terugkoppeling MDO en bijvoorbeeld via Siilo app
Geen aantoonbare fysieke restschade
Vervolg op basis van ernst klachten en mate van functionele beperkingen, onafhankelijk v. restschade
Wel aantoonbare fysieke restschade
Pulmonale, cardiale en/of neurologische restschade
Post Intensive Care Syndroom (PICS)
Een of enkele klachten, lichte functionele beperkingen
Meerdere klachten, matige functionele beperkingen
Ernstige klachten, ernstige functionele beperkingen
Monodisciplinair eerste lijn
Conditioneel, ademgerelateerde klachten
Angst, depressie
Vermoeidheid, concentratie, energie spierfunctieproblemen
Multidisciplinair eerste lijn: afhankelijk van type klachten: paramedische herstelzorg en/of POH-GGZ of bGGZ; in samenwerking
Revalidatie poliklinisch of klinisch (of als van toepassing geriatrisch)
Paramedische herstelzorg: Ergotherapie, fysiotherapie of logopedie
POH-GGZ / basis GGZ / SGGZ / psychosomatisch fys.
Paramedische herstelzorg: Ergotherapie, fysiotherapie, logopedie of diëtist
Mogelijke rol sportarts