Literatuurlijst Long Covid

Introductie

In de periode van 2021-2023 vond veel onderzoek plaats naar Long Covid. Op Pubmed zijn inmiddels vele artikelen te vinden. Een aantal hebben we gebundeld in bijgaande literatuurlijst.

Kijken we naar deze wetenschap, dan zoekt ca. 90% van de wetenschappers naar een lichamelijke oorzaak voor Long Covid. Het corona virus wordt gezien als de bron waarmee de klachten begonnen. En dit lijkt logisch, want dokters en publiek gaan er in het algemeen van uit dat lichamelijke klachten berusten op een lichamelijke oorzaak. Deze manier van denken heet het biomedisch model.

En toch, de mens is meer dan zijn lichaam. We zeggen dan dat lichaam en geest één zijn. Brein en psyche doen mee. Deze manier van denken heet het biopsychosociale model.

Kijken we naar de wetenschap, dan gaat slechts ca. 10% uit van dit biopsychosociale model.
Het psychosociale deel wil waarde geven aan de psychologie en met name aan emotie naast de lichamelijke feiten. Stichting Emovere sluit zich hierbij aan.

Een eerste voorbeeld van een artikel dat uitgaat van het biopsychosociale model is dat van **Donnino,** direct hieronder genoemd. Centraal hierin staat dat met goede gesprekken, visualisatie, schrijf-oefeningen en psycho-educatie klachten sterk afnemen of volledig herstel volgt. Bij de psycho-educatie wordt duidelijk gemaakt dat Long Covid klachten berusten op een storing in het brein (software). Deze storing wordt aangestuurd door een verdrongen emotie, actief geworden door het ziekzijn, het lichamelijk begin (hardware). Door de behandeling wordt de patiënt/cliënt zich bewust van de verdrongen emotie en verwerkt deze zoals bewuste emoties worden verwerkt, met als gevolg dat klachten sterk afnemen of volledig herstel volgt.

Emotiegericht

Donnino M, Howard P, Mehta S, et al. Psychophysiologic Symptom Relief Therapy (PSRT) for Post-acute Sequelae of COVID-19. Mayo Clin Proc Innov Qual Outcomes. 2023 May 19;7(4):337-48.
Conclusion: PSRT may effectively decrease symptom burden in patients suffering from PASC without evidence of organ injury.

Brehl AK, Schene AH, Kohn N, Fernández G. Maladaptive emotion regulation strategies in a vulnerable population predict increased anxiety during the Covid-19 pandemic: A pseudo-prospective study
Journal of Affective Disorders Reports. Vol. 4, April 2021, 100113
Maladaptive emotion regulation strategies such as giving up and self-evaluation predict increase in state anxiety during the Covid-19 pandemic.

Overzicht

Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Mar;21(3):133-146.

Although these key findings are critical to understanding long COVID, current diagnostic and treatment options are insufficient, and clinical trials must be prioritized that address leading hypotheses. Additionally, to strengthen long COVID research, future studies must account for biases and SARS-CoV-2 testing issues, build on viral-onset research, be inclusive of marginalized populations and meaningfully engage patients throughout the research process.

Lippi G, Sanchis-Gomar F, Henry BM. COVID-19 and its long-term sequelae: what do we know in 2023? Pol Arch Intern Med. 2023 Apr 19;133(4):16402.

Concerning the care for long-COVID patients, the greatest challenge is the fact that this syndrome cannot be considered a single clinical entity, and thus it needs an integrated multidisciplinary management, specifically tailored to the type and severity of symptoms.

Chee YJ, Fan BE, Young BE, Dalan R, Lye DC. Clinical trials on the pharmacological treatment of long COVID: A systematic review. J Med Virol. 2023 Jan;95(1):e28289.

This review included 6 published trials and 54 trial registration records. There is significant heterogeneity in the characterization of long COVID and ascertainment of primary outcomes. Most of the trials are focused on individual symptoms of long COVID or isolated organ dysfunction, classified according to cardiovascular, respiratory and functional capacity, neurological and psychological, fatigue, and olfactory dysfunction. Most of the interventions are related to the mechanisms causing the individual symptoms. Although the six published trials showed significant improvement in the symptoms or organ dysfunction studied, these initial studies lack internal and external validity limiting the generalizability

Laaggradige ontsteking

Astin R, Banerjee A, Baker MR, et al. Long COVID: mechanisms, risk factors and recovery. Exp Physiol. 2023 Jan;108(1):12-27.

We then interrogate the mechanisms that underlie long COVID symptoms, with a focus on impaired oxygen delivery due to micro-clotting and disruption of cellular energy metabolism, before considering treatment strategies that indirectly or directly tackle these mechanisms. These include remote inspiratory muscle training and integrated care pathways that combine

rehabilitation and drug interventions with research into long COVID healthcare access across different populations

Lai CC, Hsu CK, Yen MY, et al. Long COVID: An inevitable sequela of SARS-CoV-2 infection. J Microbiol Immunol Infect. 2023 Feb;56(1):1-9.

Long COVID may be caused by SARS-CoV-2 direct injury or its associated immune/inflammatory response.

Wallukat G, Hohberger B, Wenzel K, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. J Transl Autoimmun. 2021;4:100100.

The spectrum of symptoms was mostly of neurological origin (29/31 patients), including post-COVID-19 fatigue, alopecia, attention deficit, tremor and others. Combined neurological and cardiovascular disorders were reported in 17 of the 31 patients. Two recovered COVID-19 patients were free of follow-up symptoms. All 31 former COVID-19 patients had between 2 and 7 different GPCR-$_f$AABs that acted as receptor agonists.

Klein J, Wood J, Jaycox J, et al. Distinguishing features of Long COVID identified through immune profiling. medRxiv. 2022 Aug 10:2022.08.09.22278592.

Integration of immune phenotyping data into unbiased machine learning models identified significant distinguishing features critical in accurate classification of Long COVID, with decreased levels of cortisol being the most significant individual predictor.

Neurologie

Cho SM, White N, Premraj L, et al. Neurological manifestations of COVID-19 in adults and children. Brain. 2023 Apr 19;146(4):1648-1661.

The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Monje M, Iwasaki A. The neurobiology of long COVID. Neuron. 2022 Nov 2;110(21):3484-3496.

We review what is understood about the pathobiology of post-acute COVID-19 impact on the CNS and discuss possible neurobiological underpinnings of the cognitive symptoms affecting COVID-19 survivors.

Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021 Dec 31;144(12):3576-3588

Potential pathogenic mechanisms in the acute phase include coagulopathies with associated cerebral hypoxic-ischaemic injury, blood-brain barrier abnormalities with endotheliopathy and possibly viral neuroinvasion accompanied by neuro-immune responses. Established diagnostic tools are limited by a lack of clearly defined COVID-19 specific neurological syndromes.

Rau A, Schroeter N, Blazhenets G, et al. Widespread white matter oedema in subacute COVID-19 patients with neurological symptoms. Brain. 2022 Sep 14;145(9):3203-3213.

While neuropathological examinations in patients who died from COVID-19 revealed inflammatory changes in cerebral white matter, cerebral MRI frequently fails to detect abnormalities even in the presence of neurological symptoms. Diffusion microstructure imaging detects even small volume shifts of water. In summary, diffusion microstructure imaging in subacute COVID-19 patients revealed widespread volume shifts compatible with vasogenic oedema, affecting various supratentorial white matter tracts. These changes were associated with cognitive impairment and COVID-19 related changes in 18F-FDG PET imaging.

Visser D, Golla SSV, Verfaillie SCJ, et al. Long COVID is associated with extensive in-vivo neuroinflammation on [18F]DPA-714 PET medRxiv preprint doi: https://doi.org/10.1101/2022.06.02.22275916

Here we present in-vivo evidence of widespread neuroinflammation in long COVID, using a quantitative assessment, [18F]DPA 714 PET, in two long COVID patients. We reanalyzed historical data from three matched healthy control subjects, for comparison purposes. Both patients with long COVID had widespread increases in [18F]DPA-714 binding throughout the brain. This implicates profound neuroinflammation in the pathophysiology of long COVID.

Harrison PJ, Taquet M. Neuropsychiatric disorders following SARS-CoV-2 infection. Brain. 2023 Jun 1;146(6):2241-2247.

Eight key questions are addressed, comprising: (i) the nature and magnitude of the risks; (ii) their association with severity of infection; (iii) their duration; (iv) whether the risks differ between adults and children, or between men and women; (v) whether prior vaccination protects against them; (vi) the risk profile associated with different SARS-CoV-2 strains; (vii) what the underlying mechanisms might be; and (viii) whether the sequelae can be predicted. We consider the major unknowns, the limitations of electronic health records for research in this area, and the use of additional approaches to help characterize and understand the neuropsychiatric burden of COVID-19.

Needham EJ, Ren AL, Digby RJ, et al. Brain injury in COVID-19 is associated with dysregulated innate and adaptive immune responses. Brain. 2022 Nov 21;145(11):4097-4107.

During hospitalization, sera from patients with COVID-19 demonstrated elevations of NfL and GFAP in a severity dependent manner, with evidence of ongoing active brain injury at follow-up 4 months later. These biomarkers were associated with elevations of pro-inflammatory cytokines and the presence of autoantibodies to a large number of different antigens. Autoantibodies were commonly seen against lung surfactant proteins but also brain proteins such as myelin associated glycoprotein. Commensurate findings were seen in the influenza cohort. A distinct process characterized by elevation of serum total tau was seen in patients at follow-up, which appeared to be independent of initial disease severity and was not associated with dysregulated immune responses unlike NfL and GFAP. These results demonstrate that brain injury is a common consequence of both COVID-19 and influenza, and is therefore likely to be a feature of severe viral infection more broadly. The brain injury occurs in the context of dysregulation of both innate and adaptive immune responses, with no single pathogenic mechanism clearly responsible.

Asadi-Pooya AA, Akbari A, Emami A, et al. Long COVID syndrome-associated brain fog. J Med Virol. 2022 Mar;94(3):979-984.

In this large population-based study, we report that chronic post-COVID "brain fog" has significant associations with sex (female), respiratory symptoms at the onset, and the severity of the illness (ICU admission).

Hugon J, Msika EF, Queneau M, et al. Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. J Neurol. 2022 Jan;269(1):44-46.

Many patients who have suffered from acute COVID infections have long-lasting symptoms affecting several organs including the brain. This long COVID status can include "brain fog" and cognitive deficits that can disturb activities of daily living and can delay complete recovery. Here, we report two cases of neurological long COVID with abnormal FDG PET findings marked by hypometabolic regions of the cingulate cortex.

Biomarkers

Lai YJ, Liu SH, Manachevakul S, et al. Biomarkers in long COVID-19: A systematic review. Front Med (Lausanne). 2023 Jan 20;10:1085988.

Our study found significant associations between specific biomarkers and long COVID symptoms.

113 biomarkers were significantly associated with long COVID: (1) Cytokine/Chemokine (38, 33.6%); (2) Biochemical markers (24, 21.2%); (3) Vascular markers (20, 17.7%); (4) Neurological markers (6, 5.3%); (5) Acute phase protein (5, 4.4%); and (6) Others (20, 17.7%). Compared with healthy control or recovered patients without long COVID symptoms, 79 biomarkers were increased, 29 were decreased, and 5 required further determination in the long COVID patients. Of these, up-regulated Interleukin 6, C-reactive protein, and tumor necrosis factor alpha might serve as the potential diagnostic biomarkers for long COVID. Moreover, long COVID patients with neurological symptoms exhibited higher levels of neurofilament light chain and glial fibrillary acidic protein whereas those with pulmonary symptoms exhibited a higher level of transforming growth factor beta.

Kruger A, Vlok M, Turner S, Venter C, Laubscher GJ, Kell DB, Pretorius E. Proteomics of fibrin amyloid microclots in long COVID/post-acute sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system. Cardiovasc Diabetol. 2022 Sep 21;21(1):190.

Our results confirm the presence of pro-inflammatory molecules that may also contribute to a failed fibrinolysis phenomenon, which could possibly explain why individuals with long COVID suffer from chronic fatigue, dyspnoea, or cognitive impairment. In addition, significant platelet hyperactivation was noted.

Sneller MC, Liang CJ, Marques AR, et al. A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings. Ann Intern Med. 2022 Jul;175(7):969-979.

Conclusion**:** A high burden of persistent symptoms was observed in persons after COVID-19. Extensive diagnostic evaluation revealed no specific cause of reported symptoms in most cases. Antibody levels were highly variable after COVID-19.

Maamar M, Artime A, Pariente E, et al. Post-COVID-19 syndrome, low-grade inflammation and inflammatory markers: a cross-sectional study. Curr Med Res Opin. 2022 Jun;38(6):901-909.

The data obtained in the present cross-sectional study seems to demonstrate a consistent association between postcovid syndrome and upper ranges of the neutrophil count, neutorphil ratio, fibrinogen, and CRP in the LGI range. LGI was defined as CRP >0.3 and <1.0 mg/dL.. D-dimer levels were analysed, and were normal.

Al-Hakeim HK, Al-Rubaye HT, Al-Hadrawi DS, et al. Long-COVID post-viral chronic fatigue and affective symptoms are associated with oxidative damage, lowered antioxidant defenses and inflammation: a proof of concept and mechanism study. Psychiatry. 2023 Feb;28(2):564-578

In conclusion, the impact of acute COVID-19 on the symptoms of Long COVID is partly mediated by OSTOX/ANTIOX, especially lowered Gpx and zinc, increased MPO and NO production and lipid peroxidation-associated aldehyde formation. The results suggest that post-viral somatic and mental symptoms have a neuroimmune and neuro-oxidative origin.

Schultheiß C, Willscher E, Paschold L, et al. The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. Cell Rep Med. 2022 Jun 21;3(6):100663.

PASC is not associated with autoantibodies, but with elevated IL-1β, IL-6, and TNF plasma levels, which we confirm in a validation cohort with 333 additional participants and a longer time from infection of 10 months. Blood profiling and single-cell data from early infection suggest the induction of these cytokines in COVID-19 lung pro-inflammatory macrophages creating a self-sustaining feedback loop.

Cognitieve gedragstherapie

Vink M, Vink-Niese A. Could Cognitive Behavioural Therapy Be an Effective Treatment for Long COVID and Post COVID-19 Fatigue Syndrome? Lessons from the Qure Study for Q-Fever Fatigue Syndrome. Healthcare (Basel). 2020 Dec 11;8(4):552.

Consequently, CBT has no subjective clinically meaningful effect in nine out of every ten patients that are treated with it. Additionally, the subjective improvement in fatigue was not matched by an improvement in disability, even though the disability was fatigue related according to the researchers. On top of this, CBT did not lead to an objective improvement in physical performance. Therefore, it cannot be said that CBT is an effective treatment for Q-fever fatigue syndrome either. It seems therefore unlikely that CBT will reduce disability or lead to objective improvement in long COVID or in post-COVID-19 fatigue syndrome.

Vink M, Vink-Niese F. Is It Useful to Question the Recovery Behaviour of Patients with ME/CFS or Long COVID? Healthcare (Basel). 2022 Feb 18;10(2):392.

This confirms the conclusion from the British National Institute for Health and Care Excellence (NICE), which has recently published its updated ME/CFS guideline and concluded that CBT and GET are not effective and do not lead to recovery. Studies on CBT and GET for long COVID have not yet been published. However, this review offers no support for their use in improving the recovery of patients with an ME/CFS-like illness after infection with COVID-19, nor does it lend any support to the practice of questioning the recovery behaviour of these patients.

Kuut TA, Müller F, Csorba I, et al. Efficacy of Cognitive-Behavioral Therapy Targeting Severe Fatigue Following Coronavirus Disease 2019: Results of a Randomized Controlled Trial. Clin Infect Dis. 2023 Sep 11;77(5):687-695.

Among patients, who were mainly nonhospitalized and self-referred, CBT was effective in reducing fatigue. The positive effect was sustained at 6-month follow-up.

Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM; Lifelines Corona Research Initiative. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet. 2022 Aug 6;400(10350):452-461.

In 12·7% of patients, these symptoms could be attributed to COVID-19, as 381 (21·4%) of 1782 COVID-19-positive participants versus 361 (8·7%) of 4130 COVID-19-negative controls had at least one of these core symptoms substantially increased to at least moderate severity at 90–150 days after COVID-19 diagnosis or matched timepoint.

Ballering AV, Oertelt-Prigione S, Olde Hartman TC, Rosmalen JGM; Lifelines Corona Research Initiative. Sex and Gender-Related Differences in COVID-19 Diagnoses and SARS-CoV-2 Testing Practices During the First Wave of the Pandemic: The Dutch Lifelines COVID-19 Cohort Study.
J Womens Health (Larchmt). 2021 Dec;30(12):1686-1692

We found no sex differences in COVID-19 diagnoses and testing in the general population. Among health care workers, a male preponderance in COVID-19 diagnoses and testing was observed. This could be explained by more pronounced COVID-19 symptoms in males or by gender inequities.