WELKOM

Updates Huisartsen Provincie Antwerpen

Donderdag 20 oktober 2022

Update flash ‘Long COVID’

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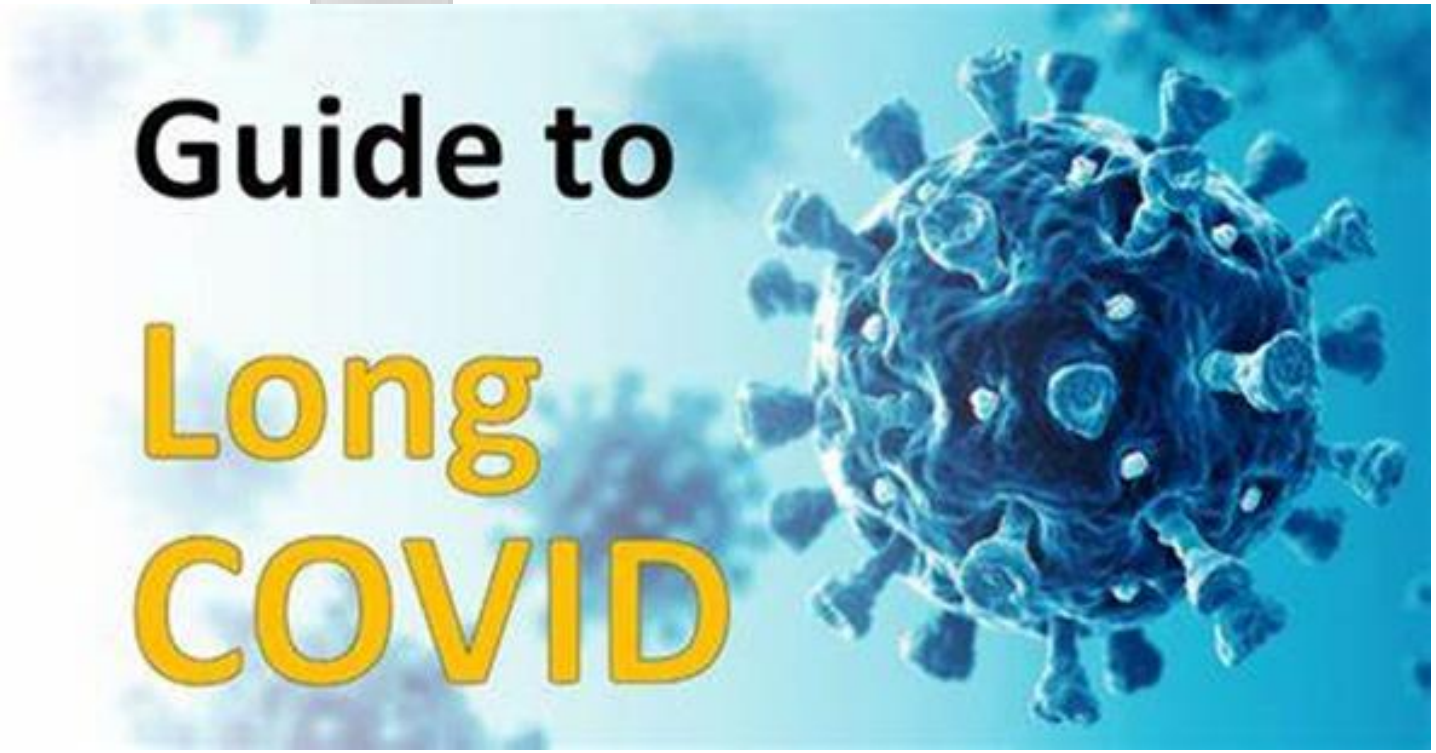
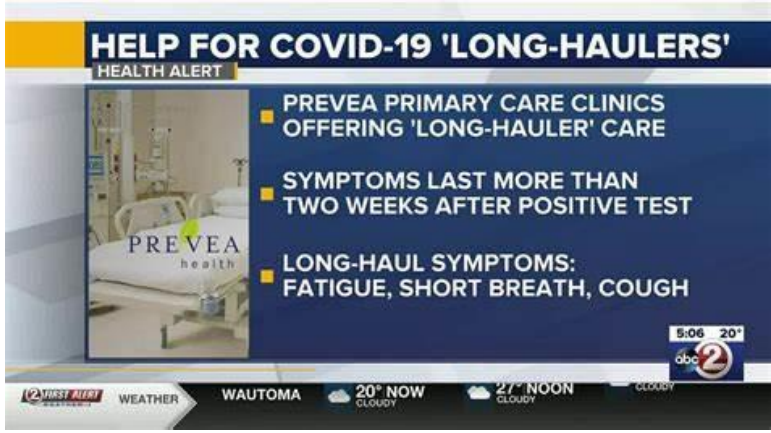


Gebruik Google Chrome
communiceer via CHAT

The LONG COVID CONUNDRUM

1) **Definitions and classification**
2) Risk factors
3) Pathophysiology



Guido Vanham, MD PhD

Global Health Institute UA

Definition for long-COVID or post-COVID

WHO [7]	*Post-COVID-19 conditions* • Adults with a history of probable or confirmed SARS-CoV-2 infection • ≥3 months from the onset of COVID-19, ≥2 months duration • It cannot be explained by an alternative diagnosis • Clustering of symptoms (fatigue, shortness of breath, and others) • Impact on everyday functioning • Symptoms may be new or persistent after recovery, fluctuate or relapse.

Raf 3 Juan Franco Int J Env Res & Pub Health August 2022

Timeline for acute and post-acute COVID-19

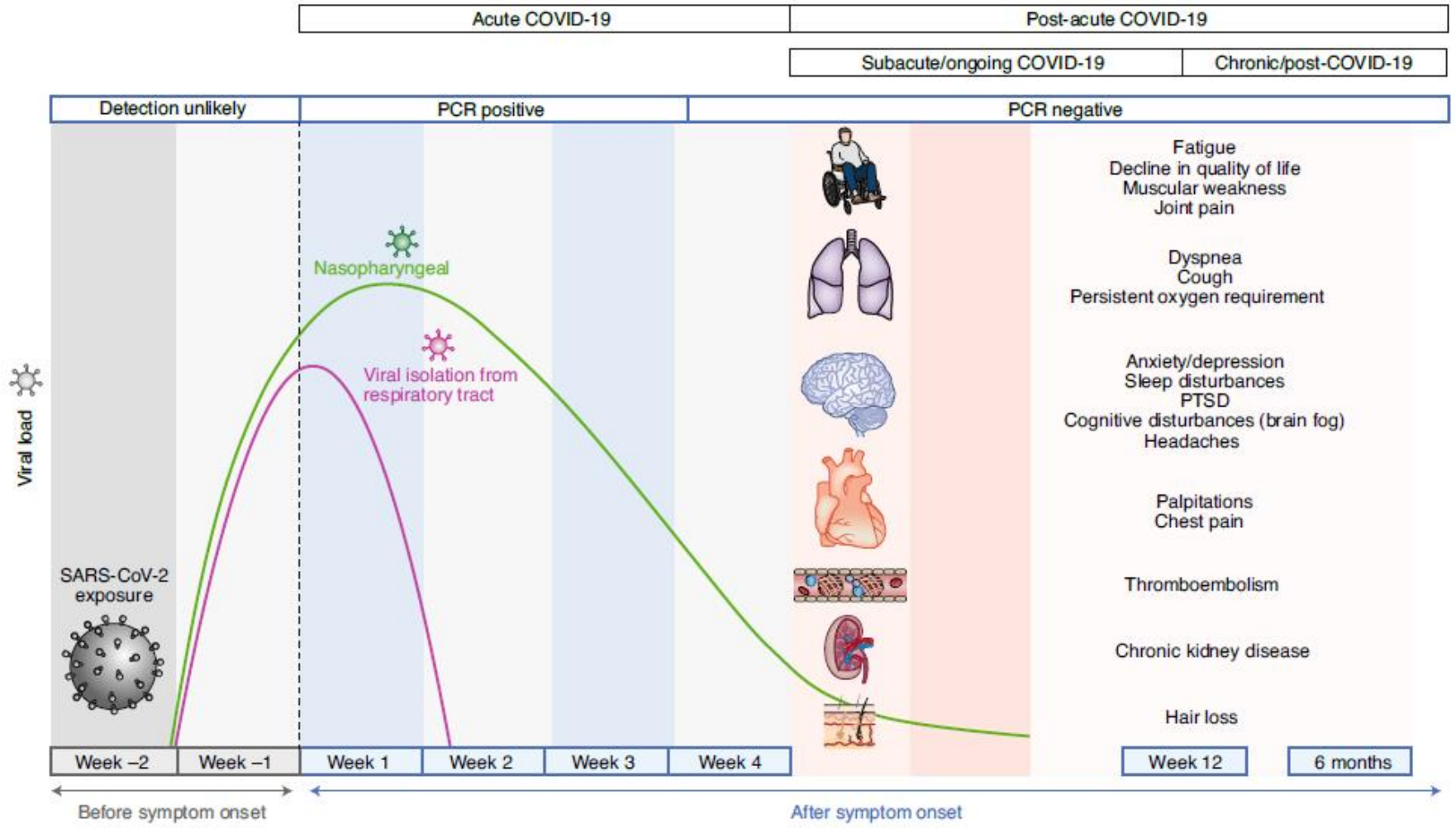
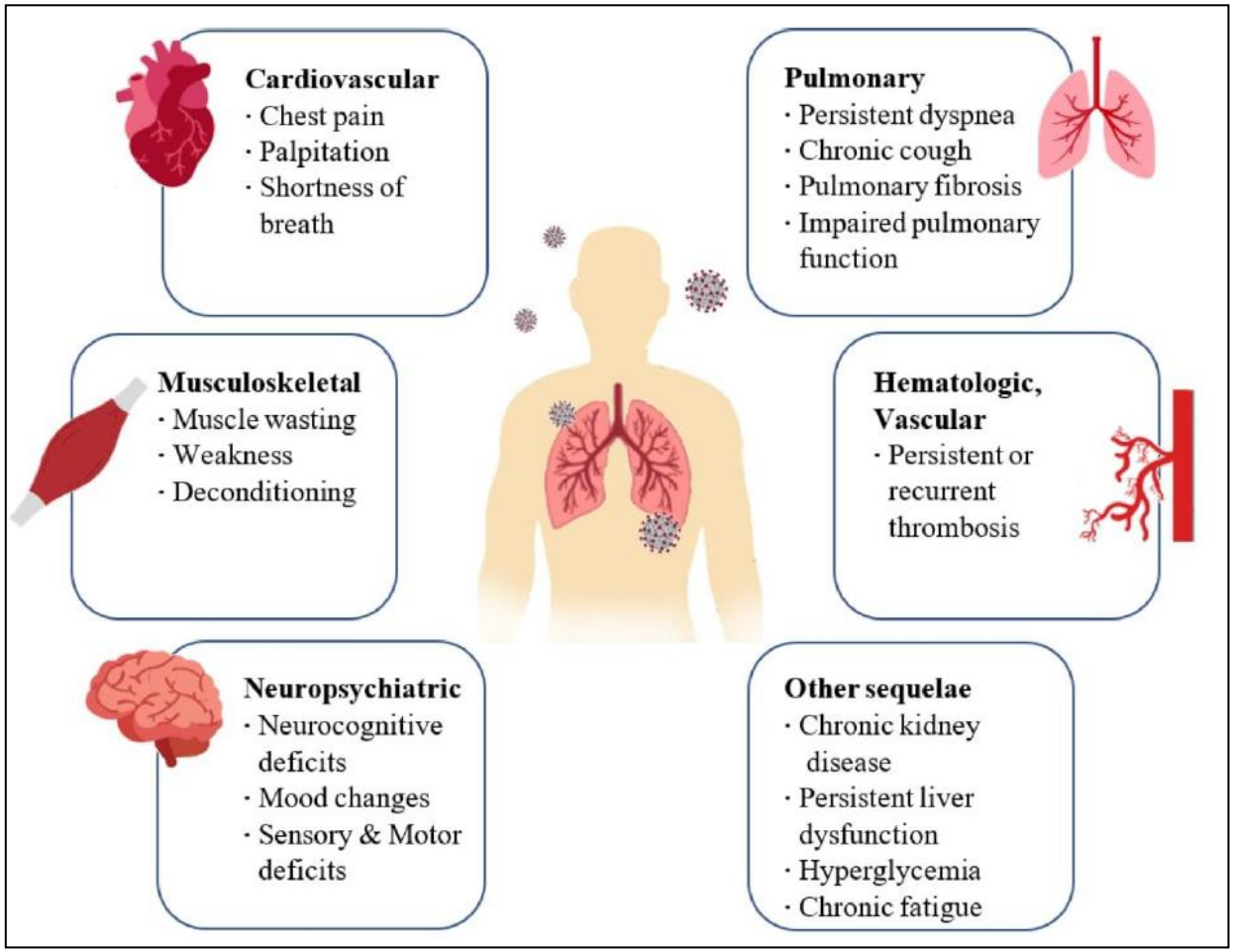


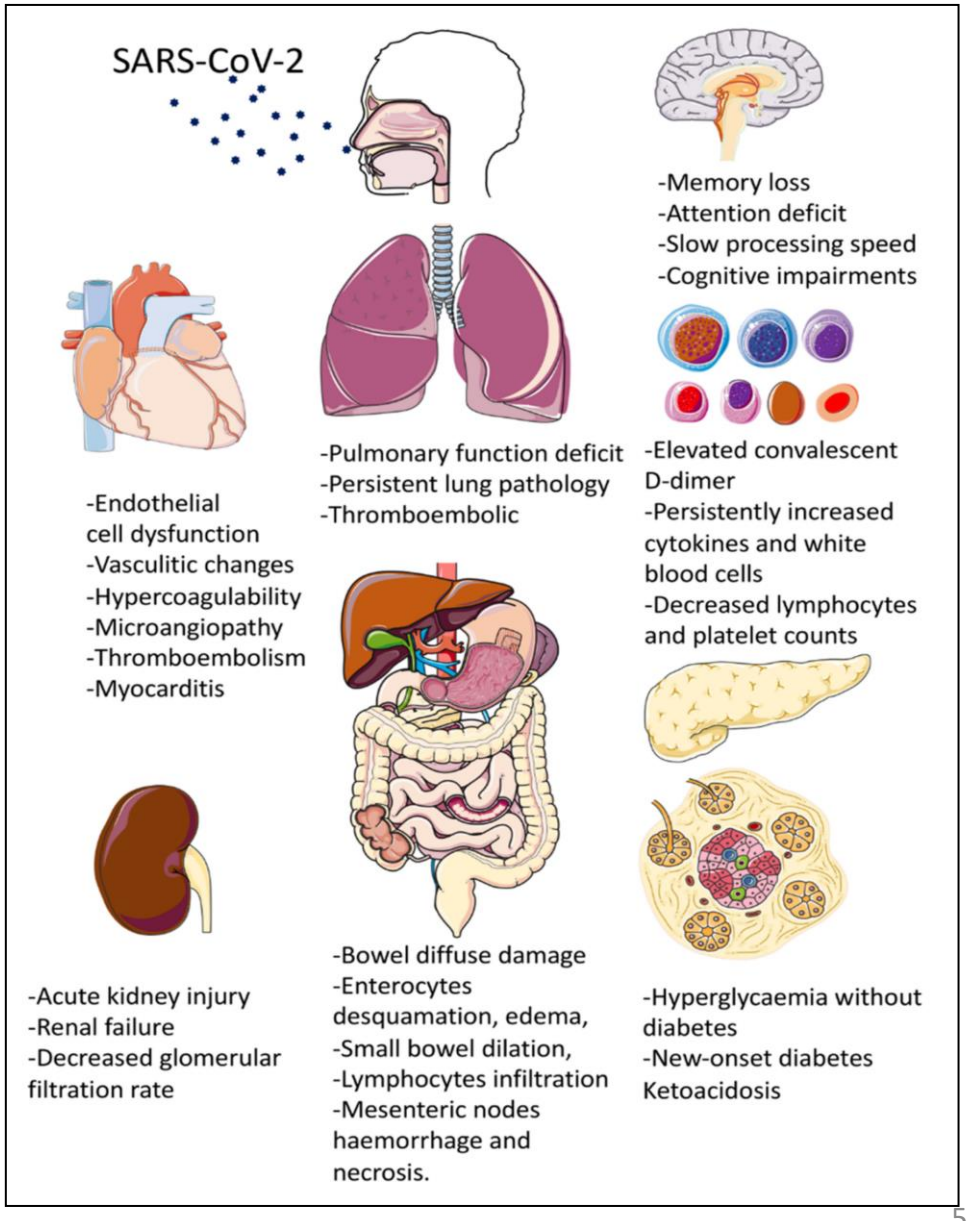
Fig. 1 | Timeline of post-acute COVID-19. Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized.

Ref 1 Ani Nalbandian Nat Med April 2021

Multi-system clinical presentation and pathophysiological mechanisms of Long COVID



Valentina Ruggiero Pharmaceutics 2022 vol 14 p 1135



Zhipeng Yan Biomedicines Aug 2021

Clinical evaluation of Long COVID

Table 1. Overall and time-specific incidence of long COVID symptoms

Symptom	Meta-analysis[a], % (95% CI)
Systemic	
Fever	1.1 (0.2 - 4.7)
Fatigue	31.0 (23.9 - 39.0)
Dizziness	4.5 (2.5 - 7.9)
Cardiopulmonary	
Cough	8.2 (4.9 - 13.4)
Sputum	5.5 (3.2 - 9.2)
Sore throat	4.7 (2.4 - 8.9)
Dyspnea	25.1 (17.9 - 34.0)
Chest pain/chest discomfort	6.4 (3.2 - 12.4)
Palpitation	9.7 (6.0 - 15.3)
Gastrointestinal	
Anorexia	17.5 (4.1 - 51.0)
Nausea/vomiting	6.7 (1.6 - 23.6)
Abdominal discomfort	18.0 (11.5 - 26.1)
Neurological	
Headache	4.9 (2.3 - 10.1)
Seizures/cramps	1.3 (0.5 - 2.9)
Taste disturbance	13.5 (9.0 - 19.9)
Smell disturbance	15.2 (10.8 - 21.0)
Tingling/paresthesia	9.1 (2.2 - 30.9)
Neurocognitive	
Concentration impairment	26.0 (21.0 - 31.7)
Memory impairment	17.9 (5.3 - 46.3)
Other cognitive impairment	17.8 (0.1 - 98.2)
Psychological	
Depression	8.1 (4.1 - 15.1)
Anxiety	18.7 (9.0 - 35.3)
Sleep disorder (insomnia)	18.2 (9.6 - 31.6)
Post-traumatic stress disorder	9.1 (3.7 - 21.0)
Musculoskeletal	
Muscle pain/myalgia	11.3 (6.2 - 19.8)
Joint pain/arthralgia	9.4 (5.7 - 15.0)
Other	
Hair loss	14.3 (5.3 - 33.2)
Skin rash	2.8 (1.0 - 8.2)

[a]Meta-analysis was conducted on a total of 10,951 patients with confi
countries, 12 weeks or more from the onset of symptoms.
COVID, coronavirus disease; CI, 95% confidence interval.

Most common symptoms of long-COVID:

- 25 %: Fatigue –dyspnea – concentration impairment
- 10 % : Memory –anxiety – sleep disorder
  Anorexia – abdominal discomfort
  Taste and smell disturbance
  Hair loss
  Muscle weakness and joint pain

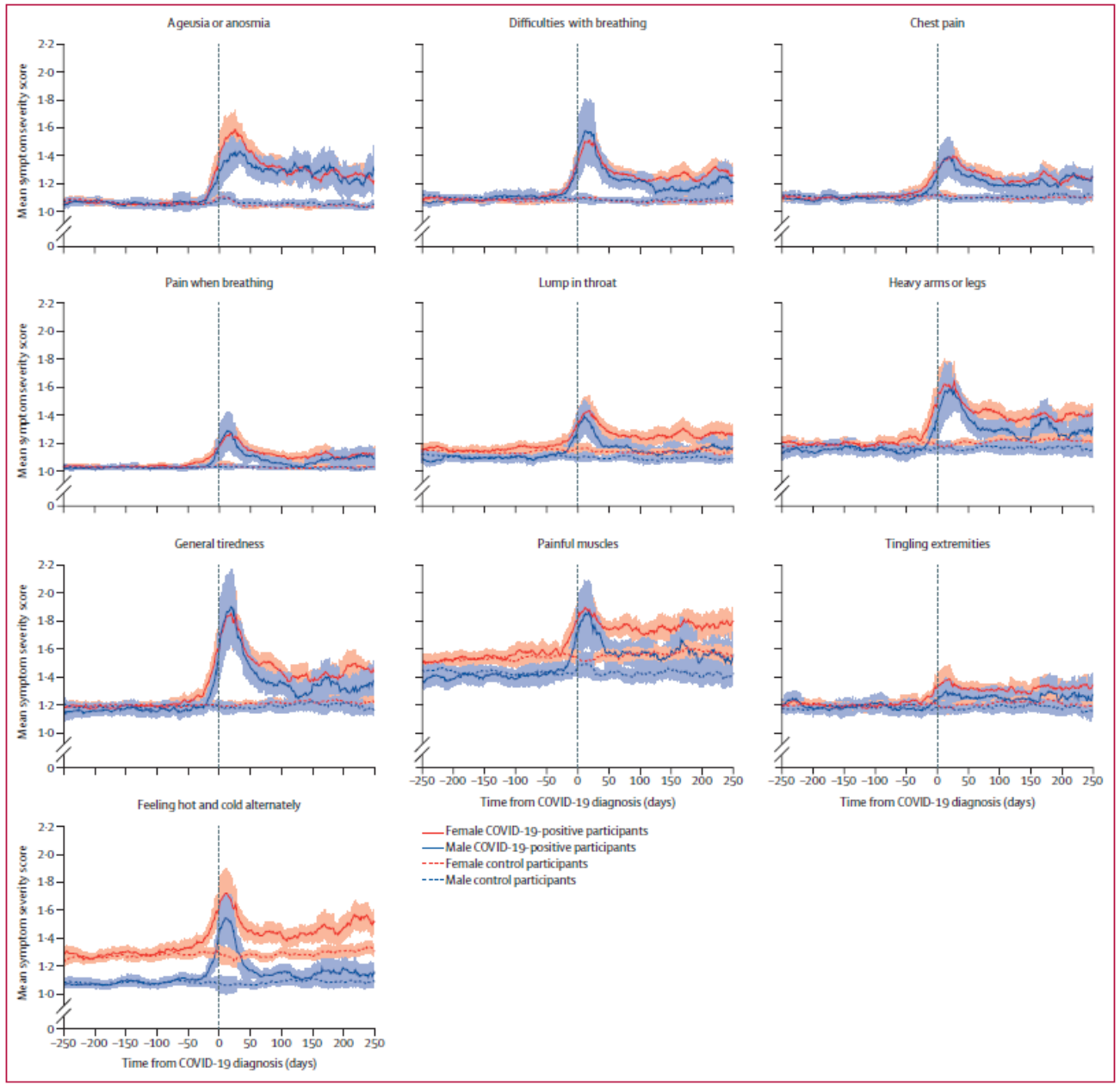
To be excluded as diseases that may develop after COVID, but are NOT long COVID

Table 2. Diseases that may develop after COVID-19

Classification	Systemic diseases
Circulatory system	Myocarditis, pericarditis, microvascular angina, cardiac arrhythmias (atrial flutter, atrial fibrillation), dysautonomia (postural orthostatic tachycardia syndrome)
Respiratory system	Interstitial lung disease, pulmonary emboli
Gastrointestinal system	Hepatitis, abnormal liver enzymes, pancreatitis
Endocrine system	New-onset diabetes (diabetic ketoacidosis, *etc.*), thyroiditis (subacute thyroiditis, Graves' disease, Hashimoto thyroiditis, *etc.*), adrenal insufficiency
Neurological system	Cerebral venous thrombosis, myelopathy, neuropathy, neurocognitive disorders, dysphonia, encephalitis, Guillain-Barré syndrome
Musculoskeletal system	Arthritis, myositis
Other	Renal impairment (tubulopathies, glomerulonephritis) Autoimmune diseases (systemic lupus erythematosus, vasculitis, sarcoidosis) Mast cell activation syndrome New-onset allergies/anaphylaxis Perniosis

Yoonjung Kim Infect Chemother. 2022 Sep;54(3):566-597

12.7 % of COVID patients present persistent somatic symptoms in Northern Netherlands 31 March 2020 – 2 Aug 2021



	Presence of symptom of at least moderate severity		Substantial increase in symptom severity to at least moderate severity	
	Controls (n=4353)	COVID-19-positive participants (n=1942)	Controls (n=4130)	COVID-19-positive participants (n=1782)
Ageusia or anosmia	37 (0·8%)	158 (8·1%)*	17 (0·4%)	135 (7·6%)*
Difficulties with breathing	38 (0·9%)	68 (3·5%)*	21 (0·5%)	43 (2·4%)*
Chest pain	44 (1·0%)	63 (3·2%)*	24 (0·6%)	43 (2·4%)*
Pain when breathing	13 (0·3%)	20 (1·0%)*	<10 (<0·2%)	16 (0·9%)*
Lump in throat	59 (1·4%)	61 (3·1%)*	24 (0·6%)	42 (2·4%)*
Heavy arms or legs	130 (3·0%)	126 (6·5%)*	65 (1·6%)	75 (4·2%)*
General tiredness	159 (3·7%)	136 (7·0%)*	87 (2·1%)	88 (4·9%)*
Painful muscles	378 (8·7%)	262 (13·5%)*	134 (3·2%)	130 (7·3%)*
Tingling extremities	145 (3·3%)	98 (5·0%)*	65 (1·6%)	52 (2·9%)*
Fever	19 (0·4%)	16 (0·8%)	18 (0·4%)	12 (0·7%)
Wet cough	83 (1·9%)	58 (3·0%)	40 (1·0%)	28 (1·6%)
Dry cough	81 (1·9%)	50 (2·6%)	43 (1·0%)	28 (1·6%)
Headache	239 (5·5%)	166 (8·5%)*	111 (2·7%)	76 (4·3%)
Itchy eyes	143 (3·3%)	96 (4·9%)*	78 (1·9%)	51 (2·9%)
Feeling hot and cold alternately	155 (3·6%)	112 (5·8%)*	70 (1·7%)	63 (2·5%)*
Sore throat	84 (1·9%)	48 (2·5%)	51 (1·2%)	29 (1·6%)
Runny nose	217 (5·0%)	110 (5·7%)	94 (2·3%)	50 (2·8%)
Nausea	128 (2·9%)	72 (3·7%)	74 (1·8%)	37 (2·1%)
Sneezing	210 (4·8%)	101 (5·2%)	74 (1·9%)†	35 (2·1%)‡
Back pain	413 (9·5%)	210 (10·8%)	182 (4·4%)	88 (4·9%)
Stomach pain	108 (2·5%)	53 (2·7%)	58 (1·4%)	25 (1·4%)
Dizziness	93 (2·1%)	46 (2·4%)	56 (1·4%)	25 (1·4%)
Diarrhoea	80 (1·8%)	38 (2·0%)	52 (1·3%)	19 (1·1%)
Total	1275 (29·3%)	790 (40·7%)*	749 (18·1%)	526 (29·6%)*

Data are n (%). Symptoms are ordered according to their relative increase in frequency in COVID-19-positive participants compared with controls. A substantial increase in severity was defined as an increase in symptom severity of at least 1 point on the 5-point scale. *p<0·001. †n=3988; sneezing was assessed in 23 surveys instead of 24. ‡n=1704; sneezing was assessed in 23 surveys instead of 24.

Table 2: **Frequencies of participants who had presence of, or a substantial increase to, symptoms of at least moderate severity at 90–150 days after COVID-19 diagnosis or matched timepoint**

Aranka Ballering *Lancet* 2022; 400: 452–61

Persistent COVID-19 symptoms in a community study of 606,434 people in England Sept 2020-May 2021

Table 1 Proportions of respondents in (i) rounds 3–5 and (ii) round 6 who still reported one or more (or three or more) symptoms 12 weeks after initial symptom onset.

	n	*n* with prior symptomatic COVID-19 and 12 weeks' observation time	% with one or more symptoms at 12 weeks	% with three or more symptoms at 12 weeks
Rounds 3–5	508,707	76,155	37.7 [37.4–38.1]	17.47 [17.2–17.7]
Round 6	97,727	13,170	21.6 [20.9–22.3]	11.94 [11.4–12.5]
Round 6 (extended symptom list)			22.8 [22.1–23.5]	13.82 [13.2–14.4]

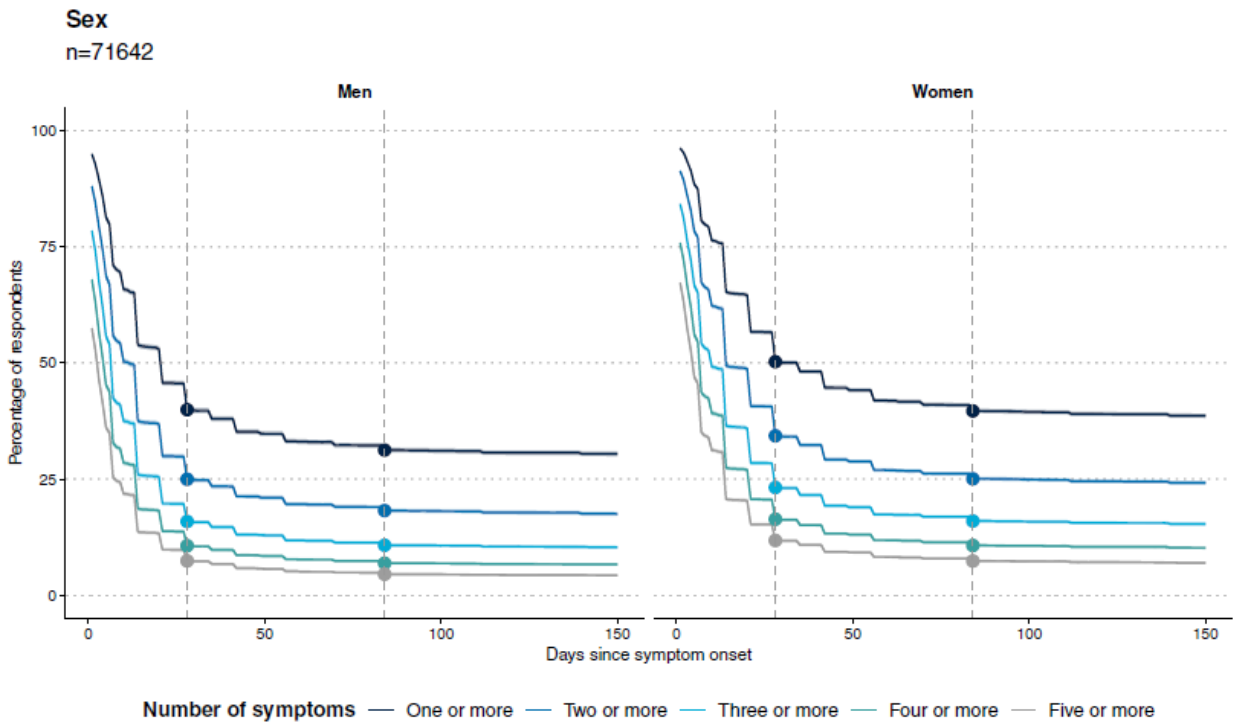


Fig. 2 Persistence of symptoms over time. Plots showing persistence of symptoms as a proportion of those who reported symptoms at any time, among $n = 71{,}642$ respondents for whom we had 150 days' observation time. Women have higher rates of persistent symptoms; a slower decline in symptom prevalence is observed after 12 weeks in both sexes. The vertical dashed lines show 4 and 12 weeks post symptom onset, respectively.

Matthew Whitaker Nat Comm April 2022

Persistent COVID-19 symptoms in a community study of 606,434 people in England Sept 2020-May 2021

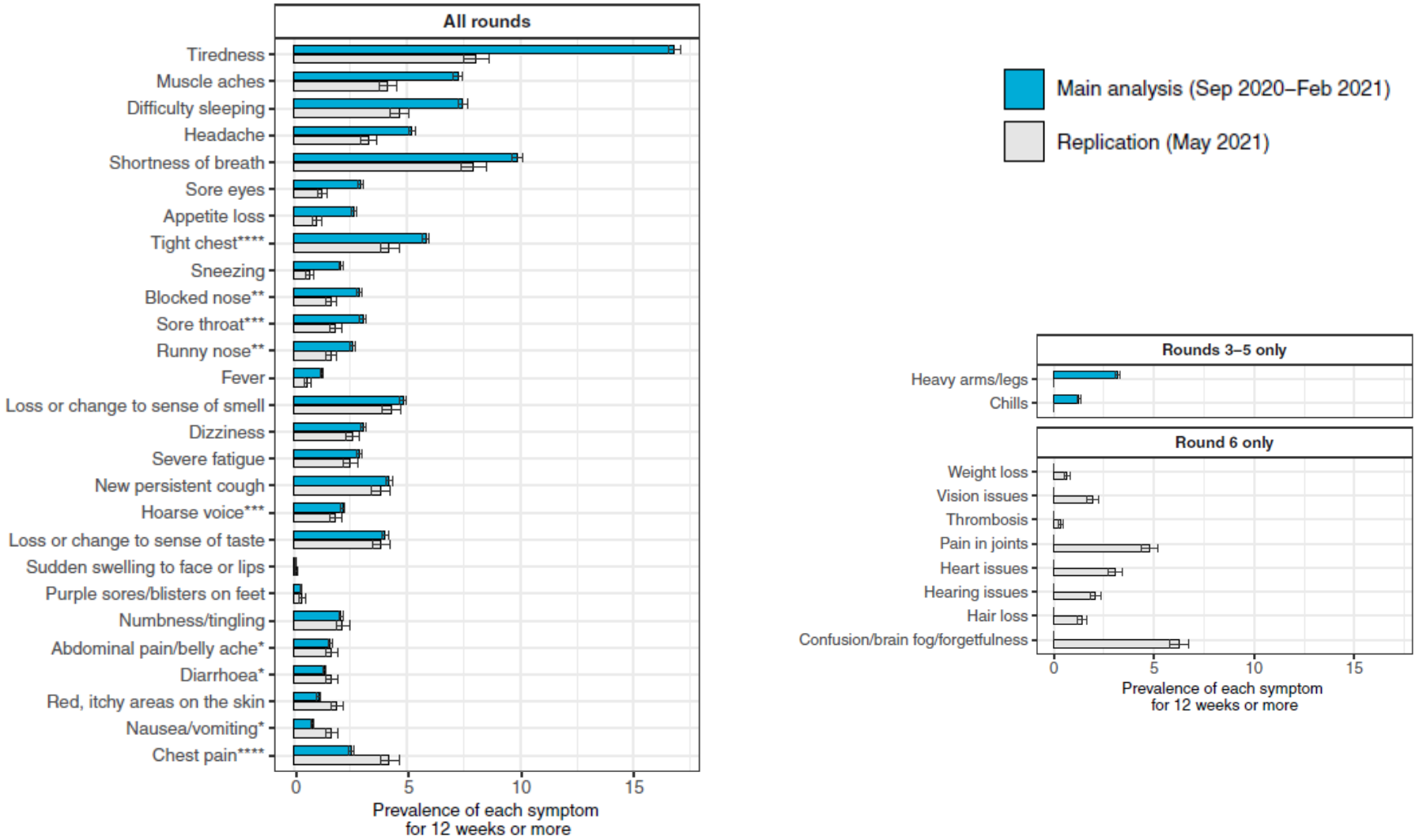


Fig 3: Symptoms prevalence in Sept 2020-Feb 2021 (round 3-5) and in May 2021 (round 6)

Matthew Whitaker Nat Comm April 2022

The LONG COVID CONUNDRUM

1) Definition, scope and classification

2) Risk factors

3) Pathophysiology

Persistent COVID-19 symptoms in a community study of 606,434 people in England Sept 2020-May 2021

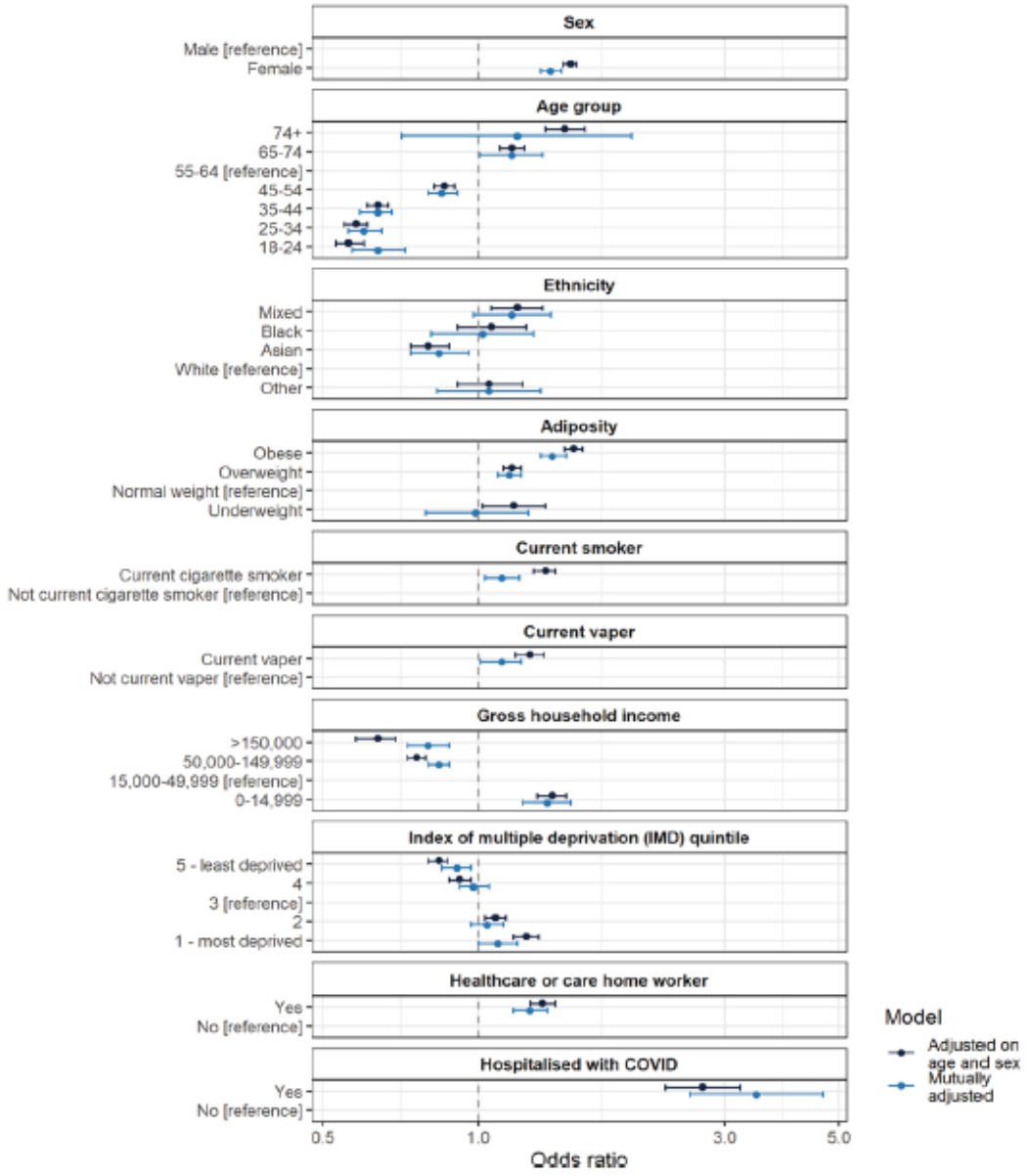


Fig 4: Risk factors for persistent symptoms

- **Female sex**
- **Increasing age**
- **Mixed ethnicity (↑); Asian (↓)**
- **Overweight**
- **Smoker or vapor**
- **Lower income**
- **Deprived**
- **Care worker**
- **Having been hospitalized**

Matthew Whitaker Nat Comm April 2022

Established Risk factors for long COVID:

Mid-older age,

Children: less long COVID than adults?

FEMALE sex

Non-white ethnicity (or socio-economic and education?)

ICU > hospitalized > ambulatory

Variant: omicron proportionally less long COVID

Successive infections: progressive increase in prevalence of long COVID

Vaccination: partial protection

Pre-existing **comorbidities** including obesity, diabetes , neurological, respiratory/ cardiovascular disease and hypertension

Immune suppression

The LONG COVID CONUNDRUM

1) Definition, scope and classification

2) Risk factors

3) **Pathophysiology:** hypotheses and associations

Pathophysiology hypotheses and associations:

- **General**
- Pulmonary
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- Kidney
- Diabetes
- Gastro-intestinal disorder

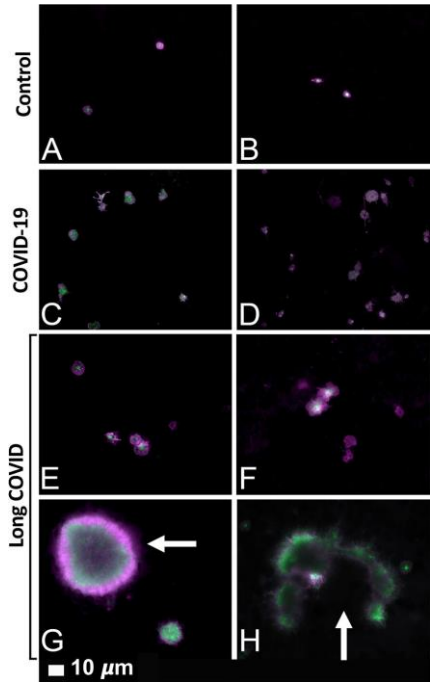
Three major pathogenic hypotheses for long-COVID

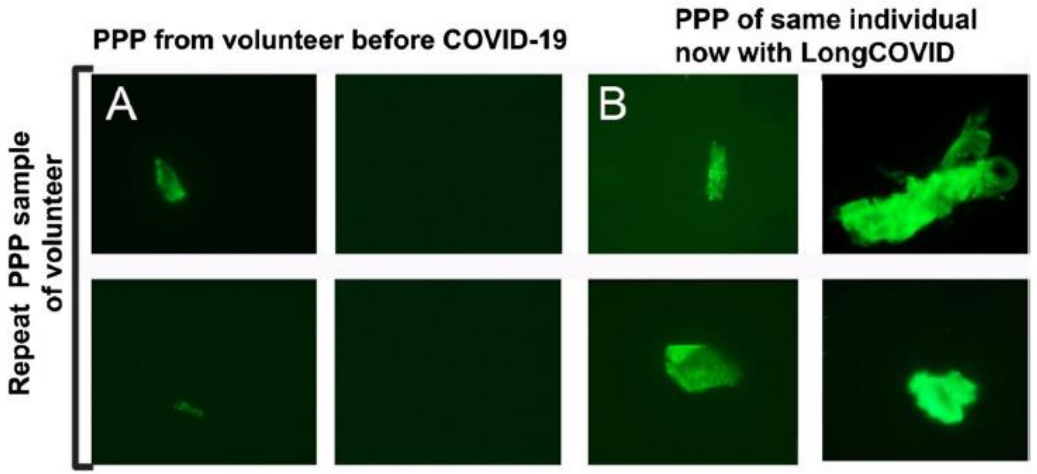
1) Microclots? generated by coagulopathy during acute phase, could obstruct small vessels in
- Lungs → respiratory complaints;
- Heart → cardiac dysfunction
- Brain → "fog" and fatigue;
- Dysregulating autonomous nerves: disrupt heart rate, breathing, and digestive function.

2) Persistent virus ?

3) Immune system in constant high alert and low cortisol

Jennifer Couzin-Frankel Science 16 June 2022





Large microclot aggregates in platelet poor plasma (PPP) from long-COVID

Pretorius. Cardiovasc Diabetol (2021) 20:172

Prolonged presence of SARS-CoV-2 viral RNA in faecal samples

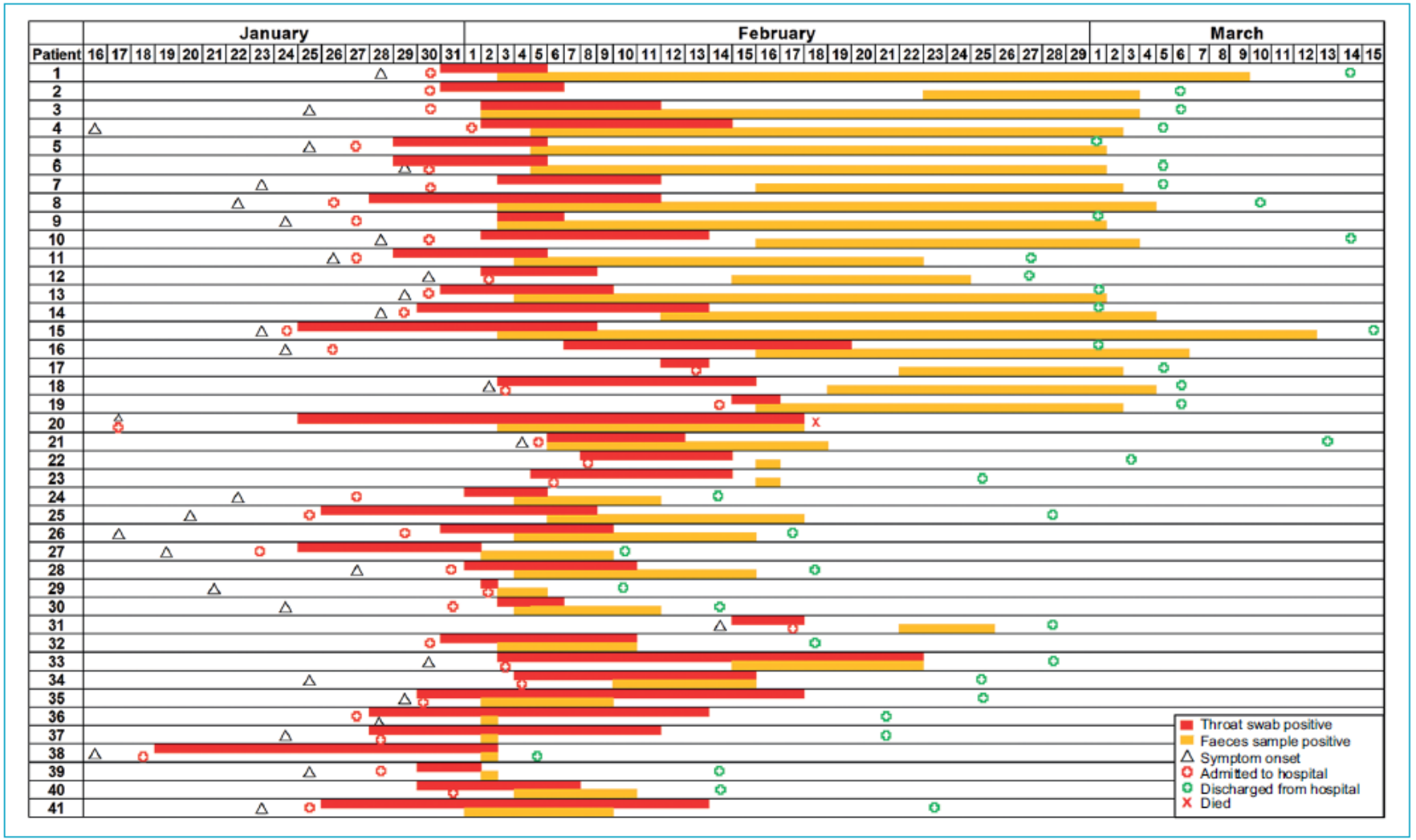
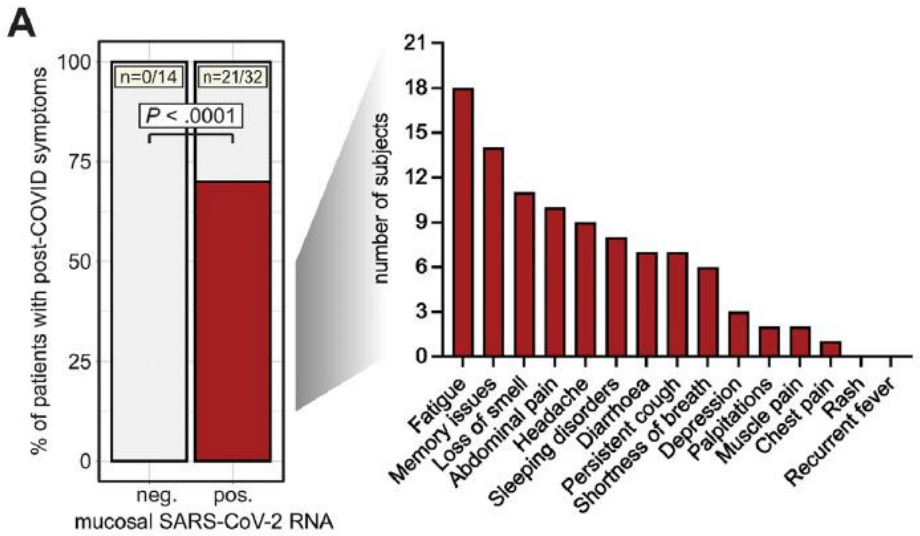


Figure: Timeline of results from throat swabs and faecal samples through the course of disease for 41 patients with SARS-CoV-2 RNA positive faecal samples, January to March, 2020

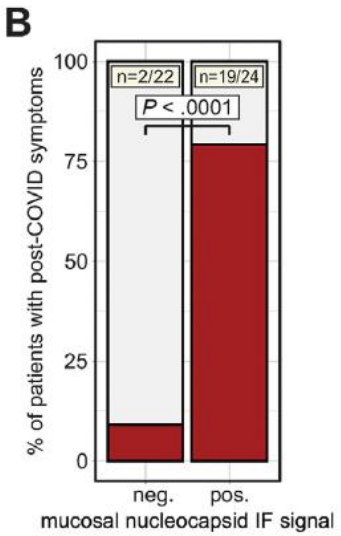
Yongjian Wu Lancet Gastroenterol May 2020

Long COVID is characterized by gut SARS-CoV-2 persistence in Inflammatory Bowel Diseases

RT- PCR



Immunofluoresence

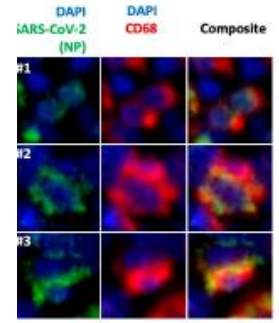


Presence of various long-COVID symptoms is associated with viral persistence (PCR and immunofluorescence) in 46 patients with inflammatory bowel disease (IBD) 219 days (range, 94–257) after a confirmed COVID-19 infection

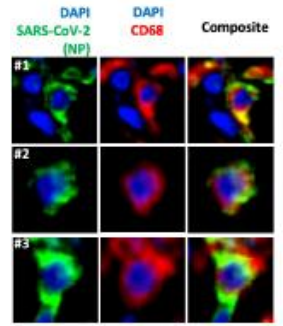
Case report: Persistence of residual antigen and RNA of SARS-CoV-2 in tissues of two patients with long COVID

TABLE 1 Cohort characteristics.

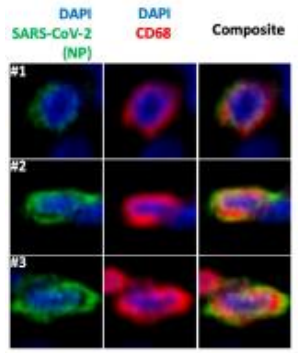
	ID	1	2
Patient profile	Age/Sex	44/Female	45/Female
	Pertinent medical history/comorbidities	Peritonitis, appendiceal lymphoid hyperplasia	Ductal carcinoma in situ
COVID-19 History	Date of symptom onset	07/03/2020	14/03/2020
	Hospitalization (Y/N)	N	Y
	ICU admission (Y/N)	N	N
	Symptomatic (Y/N)	Y	Y
	Post COVID-19 symptoms and complication(s)	**Otorhinolaryngology:** Lingual tonsil hyperplasia, mucositis, tongue inflammation breakouts, laryngospasm, recurrent pharyngitis with secondary bacterial infection, tinnitus **Ocular:** Loss of near vision, conjunctivitis, dry eye **Respiratory:** Bronchospasm, bronchial hyperresponsiveness **Cardiac:** Reactive sinus tachycardia with minimal effort **Digestive:** Inflammatory bowel disease **Neurological:** Chronic fatigue syndrome/post-COVID-19 encephalomyelitis, headache, dizziness, mental fog, loss of spatial orientation **Osteomuscular:** Myalgia, cervicalgia, dorsalis with breakouts **Dermatology:** Skin flare-ups co-occurring with the acute phase of COVID-19 for 18 months **Gynaecological:** Menstrual disorders	**Respiratory:** Mild paralysis of the right hemidiaphragm, dyspnoea **Cardiac:** Tachycardia, high blood pressure **Digestive:** Stomachache, loss of appetite, pain in the liver and spleen area **Neurological:** Headache, mental confusion, dysarthria, mood swings, sleep disorders, lack of concentration **Osteomuscular:** Muscle pain, arthralgia, asthenia, extremity debilitation **Dermatology:** Spontaneous bruises
Surgical History and Sample Collection	Type of Surgery	Exploratory laparotomy and appendectomy	Partial breast resection
	Surgery date (Days upon symptom onset)	06/05/2021 (426 days)	04/09/2020 (175 days)
	Tissue(s) obtained	Appendix, skin	Breast, sentinel lymph nodes
Investigation and Results	RNAscope for SARS-CoV-2 (+/-)	+ (appendix)	+ (breast)
	Multiplex IHC for SARS-CoV-2 (+/-)	+ (appendix) + (skin)	+ (breast)



Appendix of patient 1



Skin of patient 1

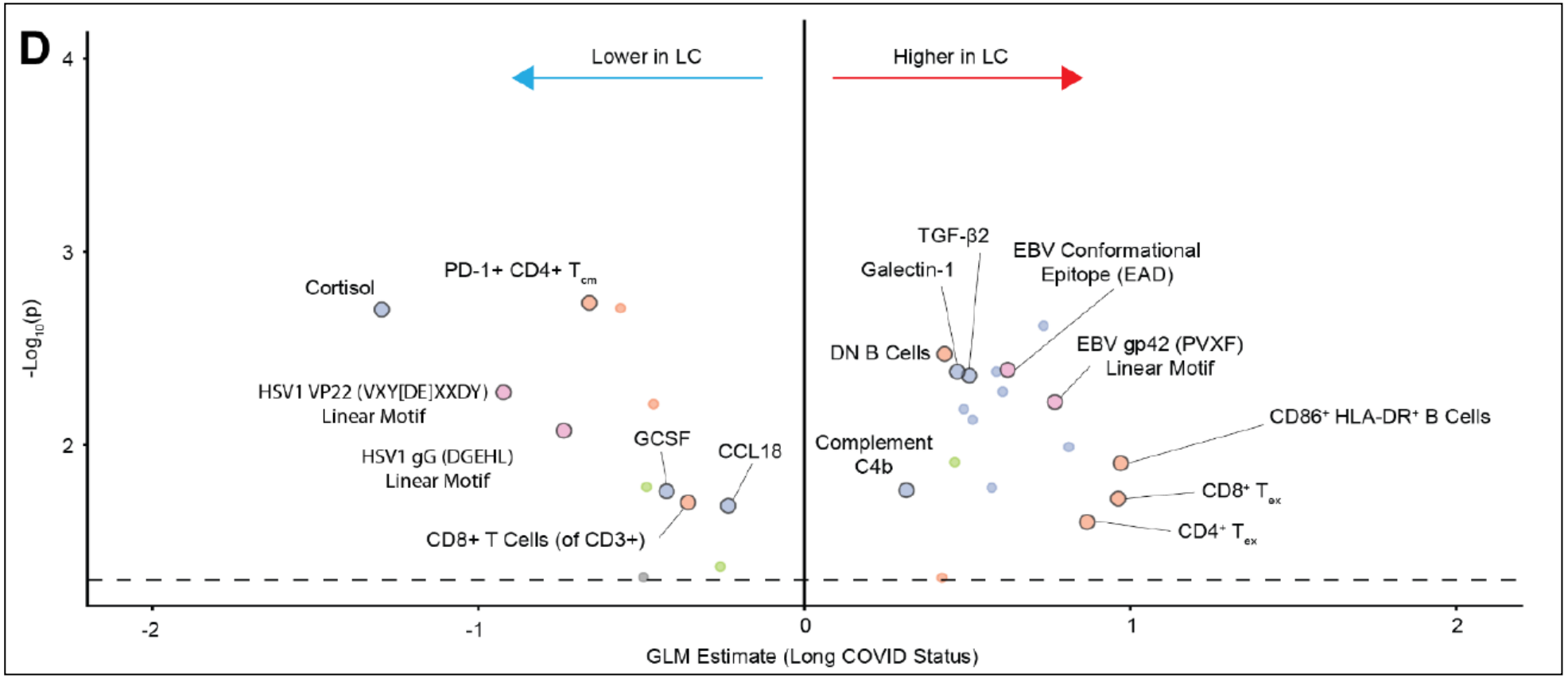


Breast tissue of patient 2

Denise Goh Front Immunol Sept 2022

Distinguishing features of Long COVID (LC) identified through immune profiling

LASSO = regression analysis with high predictive value



Long-COVID: higher levels of	some soluble factors: TGF-β2, Galectin-1, Complement C4b = **inflammation** some lymphocyte subsets e.g. **exhausted** CD4+ and CD8+ T cells; **activated** B cells (CD86, HLA-DR+) antibodies to EBV epitopes: **reactivation?**
low levels of cortisol	

Jon Klein medRxiv 10 August 2022

Pathophysiology hypotheses and associations:

- General
- **Pulmonary**
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- Kidney
- Diabetes
- Gastro-intestinal disorder

What Are the Major Long-term Pulmonary Sequelae in Survivors of Critical COVID-19?

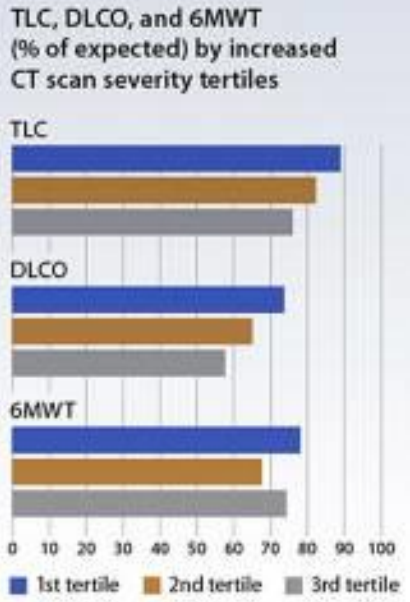
STUDY DESIGN

- Descriptive observational ICU survivor cohort of 62 adult patients with diagnosis of SARS-CoV-2 and ARDS in two Spanish hospitals between March and June 2020
- All needed at least HFNC during ICU stay and 62.9% were intubated
- At follow-up, assessed quality of life, performed CT scan of chest, and measured pulmonary function tests (TLC and DLCO), and 6-minute walk test (6MWT)

RESULTS

Three months after hospital discharge:

- An abnormal CT scan was seen in **70.2%** of patients, with fibrosis seen in **21.1%**
- Patients had a 6MWT distance of **128m less** than the healthy population (25-75% IQR -185.03; -62.66)
- **81.9%** of patients had DLCO impairment
- **15.2%** had altered depression scores and **22.1%** altered anxiety scores



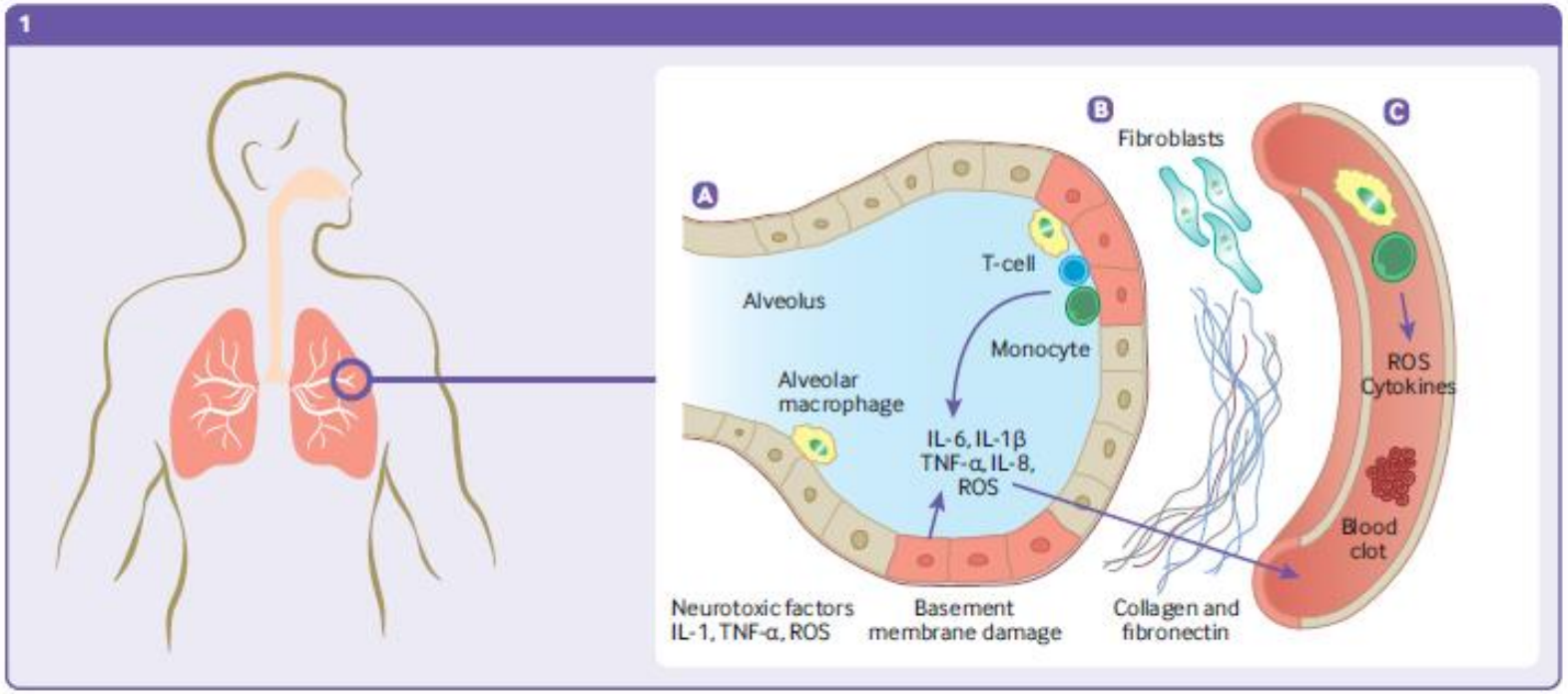
In survivors hospitalized in the ICU with COVID-19 and ARDS, lung involvement at 3 months post-discharge remained significant.

González Gutiérrez J, et al. *CHEST* July 2021
@journal_CHEST | https://doi.org/10.1016/j.chest.2021.02.062

CHEST

Abbreviations: ICU = intensive care unit; HFNC = high flow nasal canule (with oxygen); CT = computerized tomography; TLC = Total Lung Capacity; DLCO = diffusion capacity; 6MWT = six minutes walking test

Long term sequalae of covid-19 in the alveoli of the lungs



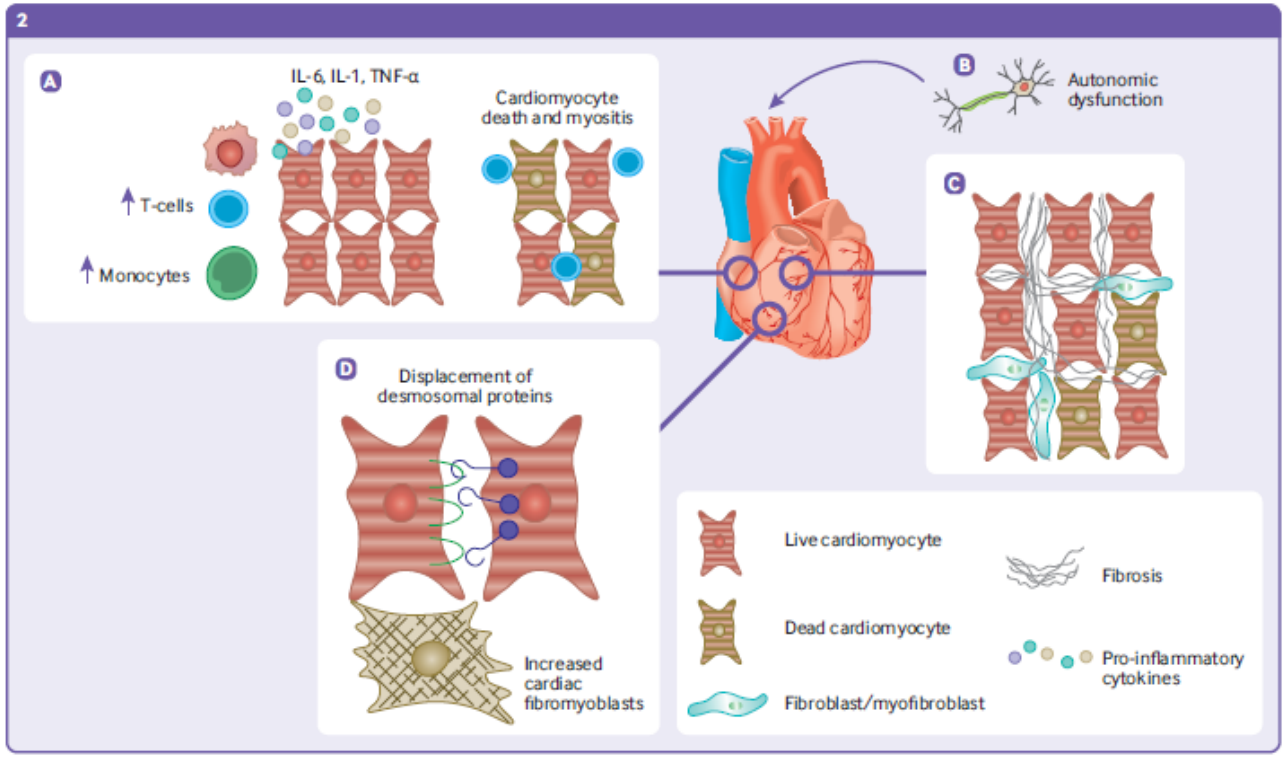
(A) **Pro-inflammatory cytokines and reactive oxygen species** (ROS) released into the tissue and bloodstream.
(B) **Endothelial damage** triggers fibroblasts, in fibrotic changes.
(C) Endothelial injury, complement activation, platelet activation, and platelet-leukocyte interactions, release of pro-inflammatory cytokines, disruption of normal coagulant pathways, and hypoxia may result in the development of a **prolonged hyperinflammatory and hypercoagulable state**, increasing the risk of thrombosis.

Harry Crook BMJ 2021;374:n1648

Pathophysiology hypotheses and associations:

- General
- Pulmonary
- **Cardiovascular**
- Anosmia (ageusia)
- Neurological
- Kidney
- Diabetes
- Gastro-intestinal disorder

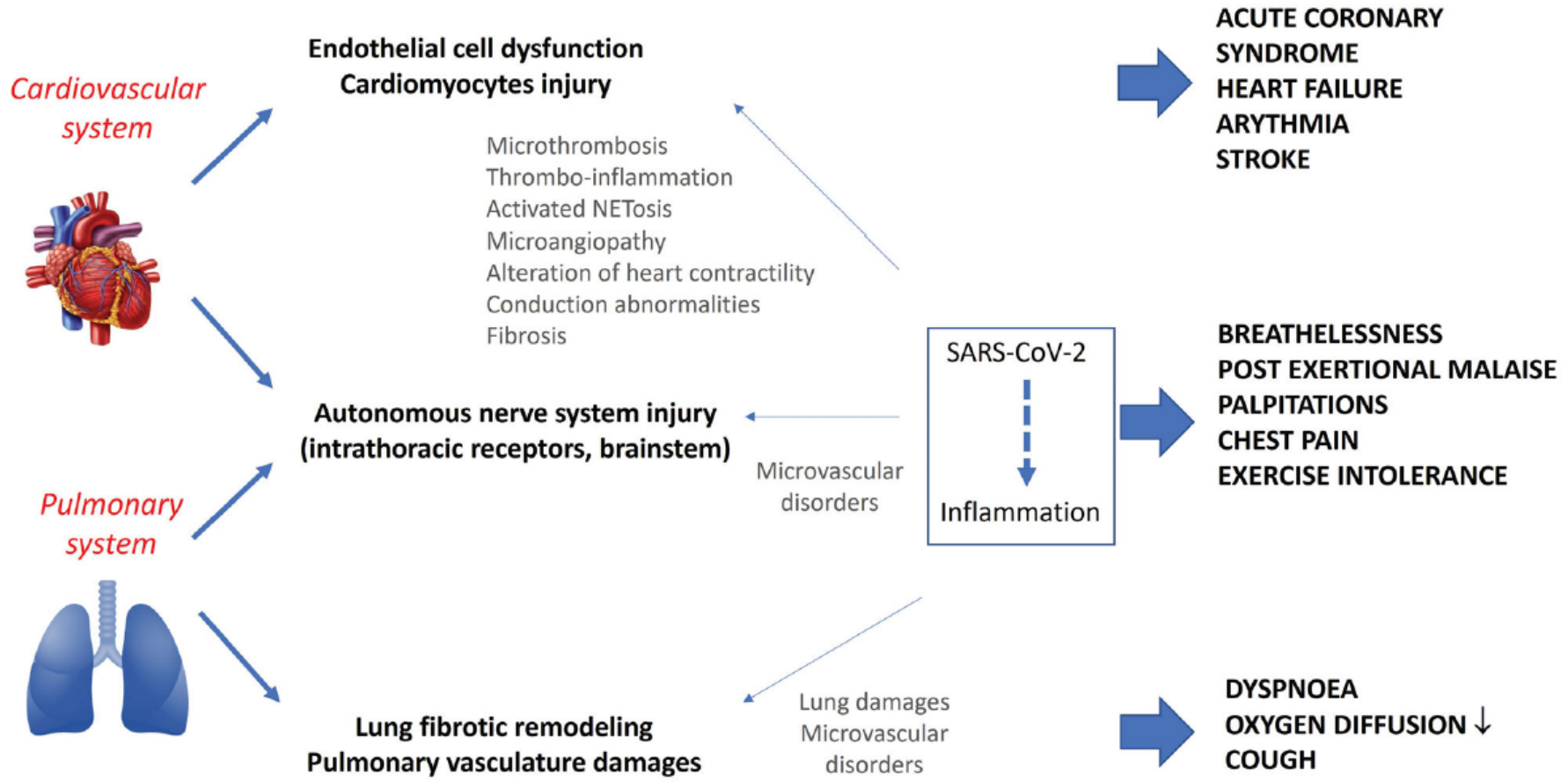
Long term sequalae of covid-19 in the heart



(A) **Chronic inflammation** of cardiomyocytes can result in myositis and cause cardiomyocytes death.
(B) **Dysfunction of the afferent autonomic nervous system** can cause complications such as postural orthostatic tachycardia syndrome.
(C) **Prolonged inflammation and cellular damage** prompts fibroblasts to secrete extracellular matrix molecules and collagen, resulting in fibrosis.
(D) Fibrotic changes are accompanied by increase in cardiac fibromyoblasts, damage to desmosomal proteins results in reduced cell-to-cell adhesion.

Harry Crook BMJ 2021;374:n1648

Integrated view on cardio-respiratory long-term consequences of COVID



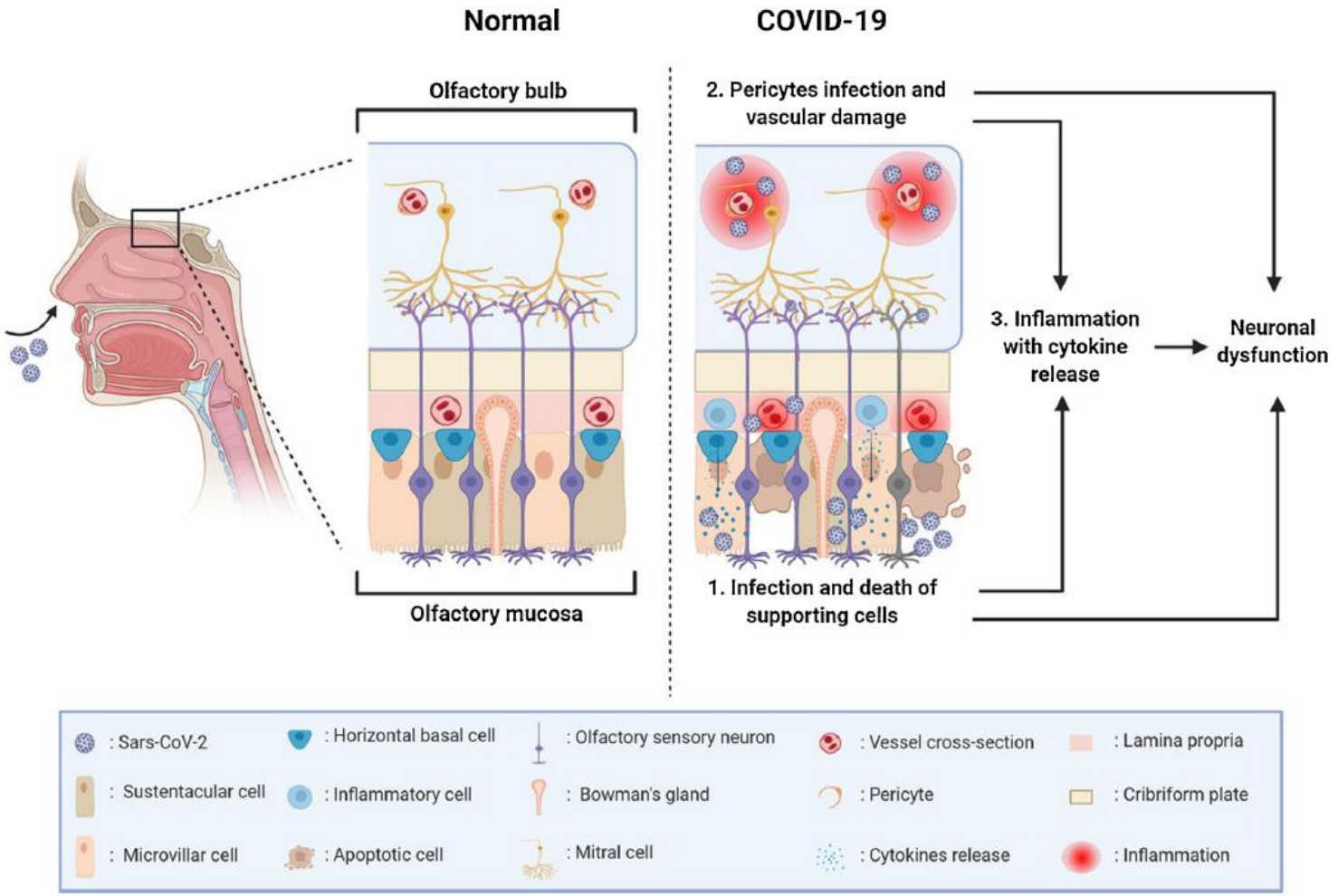
Besides local injury in heart and lung, also autonomous nerve injury, as a consequence of microvascular disorder (e.g., by microthombi or endothelitis) could have a role "functional" symptoms

Castanares-Zapatero Annals of Med vol 54 p. 1473, 2022

Pathophysiology hypotheses and associations:

- General
- Pulmonary
- Cardiovascular
- **Anosmia (ageusia)**
- Neurological
- Kidney
- Diabetes
- Gastro-intestinal disorder

Anosmia (ageusia) purely <u>local</u> or regional pathogenesis?



1) Infection and damage of supporting cells of the olfactory epithelium,→ inflammation
2) Infection or immune-mediated damage of endothelial cells and vascular pericytes → hypoperfusion and inflammation.
3) Inflammatory cells, cytokines and neurotoxic compounds may indirectly influence the neuronal signaling

Andrea Mastrangelo Neuroscience Letters Jan 2021

Pathophysiology hypotheses and associations:

- General
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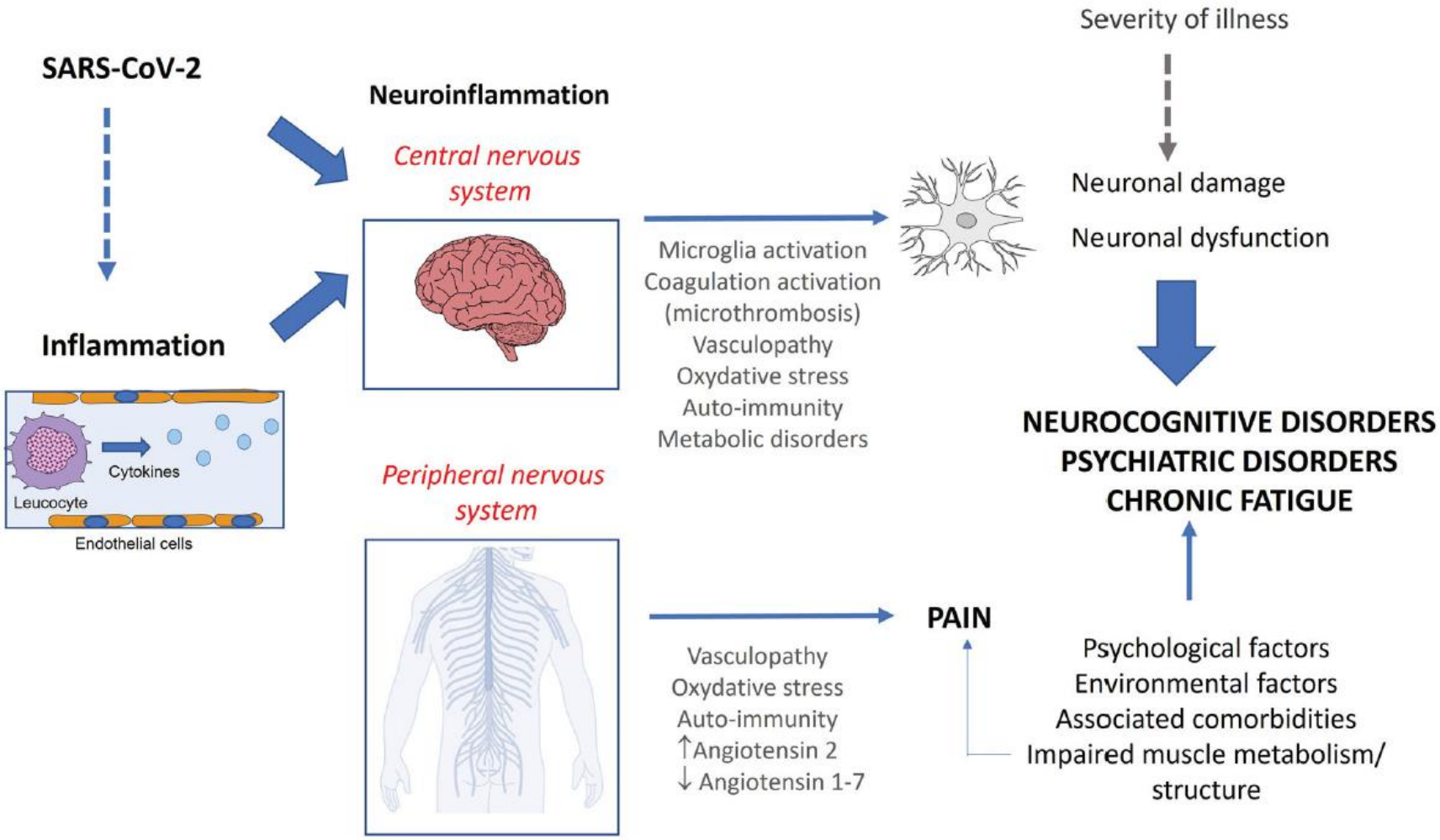
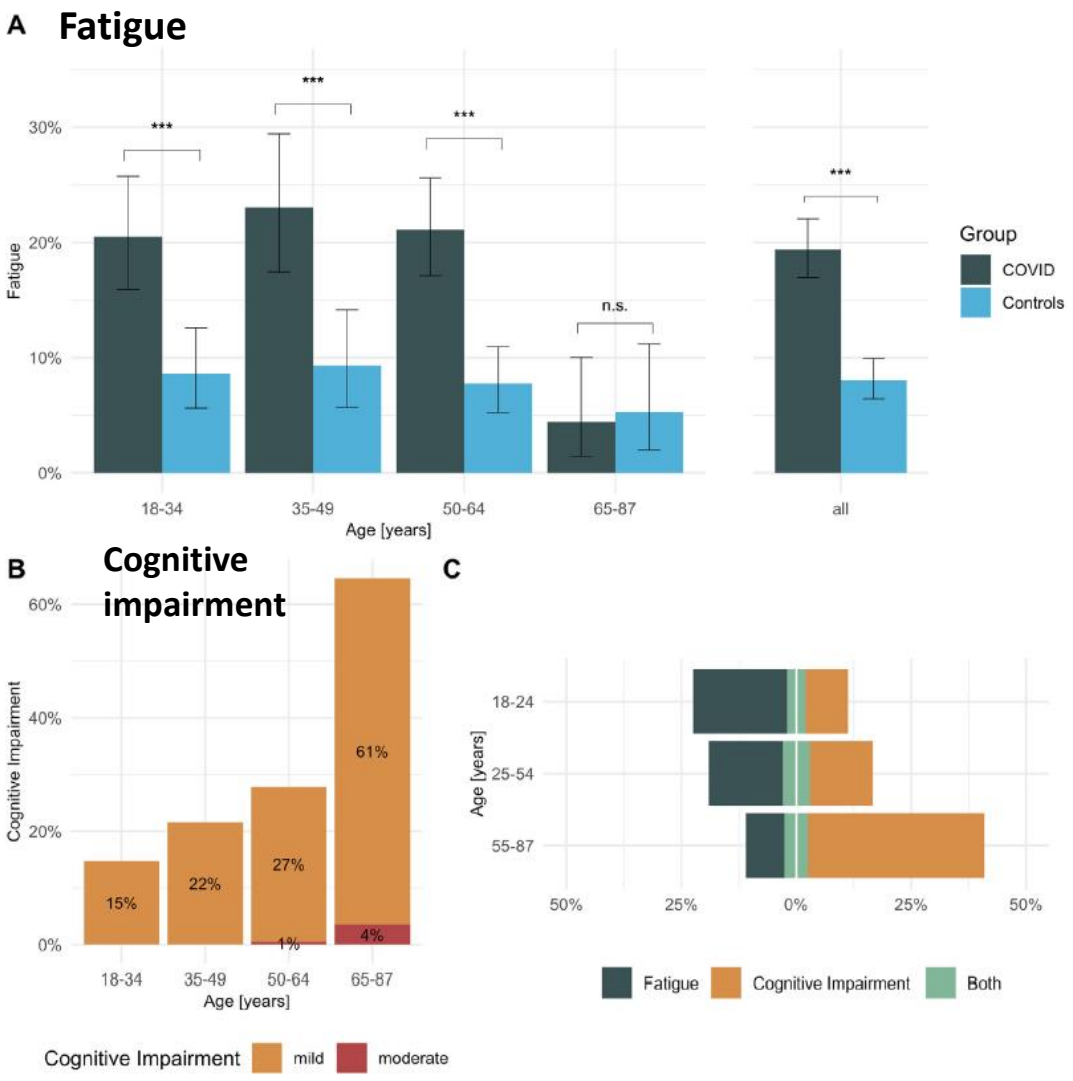
Different pathophysiological mechanisms leading to neurological and neuro-psychiatric long COVID



Castanares-Zapatero Annals of Med vol 54 p. 1473, 2022

Fatigue and cognitive impairment > 6 mo after COVID-19: A prospective multicentre study in Germany Nov 20-Sept 21



Fatigue more common in younger patients,
Cognitive impairment more common in older patients.
Both fatigue and cognitive impairment in 4-6 % of patients

Factors associated with **fatigue:**
- female gender,
- younger age,
- history of depression
- number of acute COVID symptoms

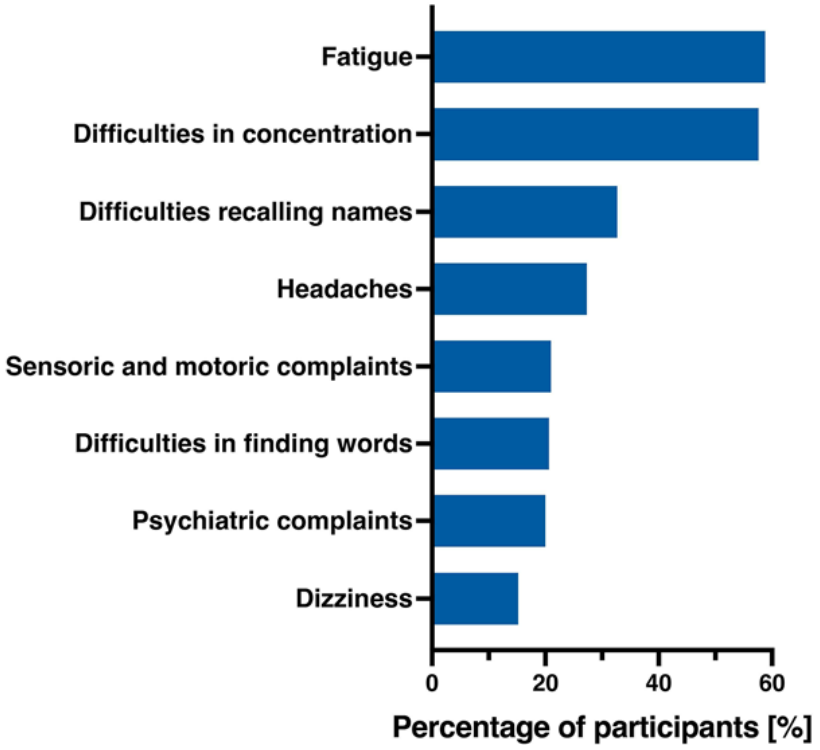
Factors associated with **cognitive impairment**:
- male gender,
- older age,
- shorter education
- history of neuropsychiatric disease

Tim Hartung eClinicalMedicine Sept 2022

Post-COVID-19 Syndrome is Rarely Associated with Damage of the Nervous System: Prospective cohort of 171 patients with neuro-psych long-COVID complaints

Table 1 Demographics, severity of COVID-19, and medical history of patients

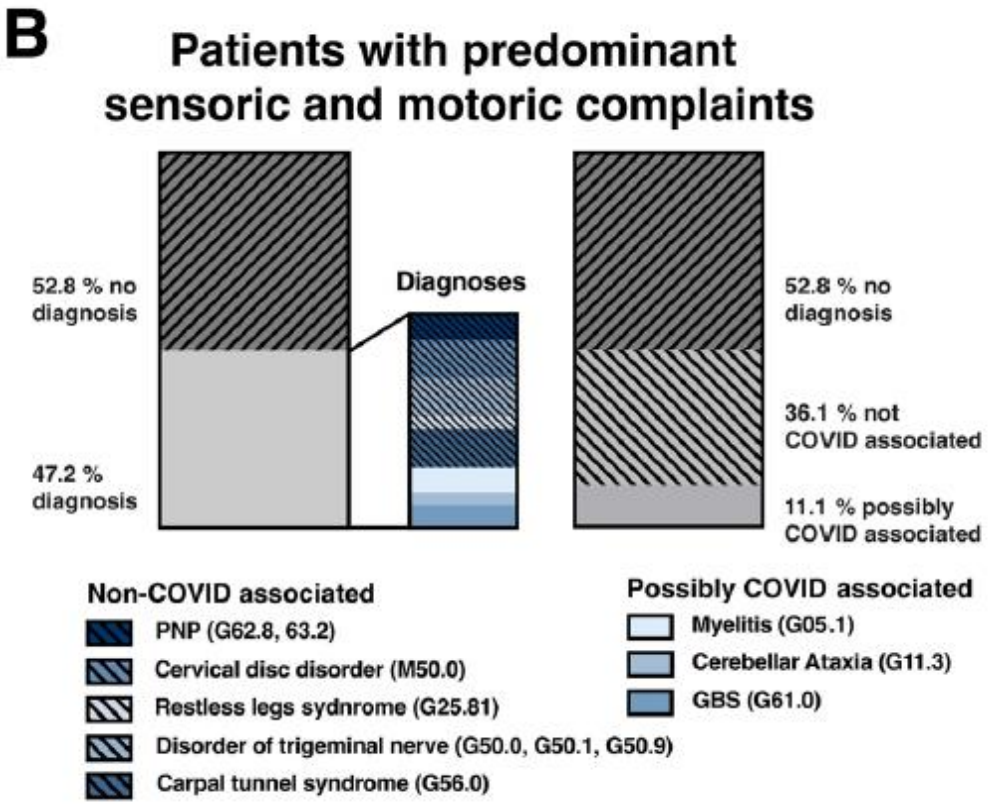
Demographics	
Participants	171
Age, years	45.2 ± 12.7 (18–74)
Female	66.7%
Severity COVID	%
Mild	34.5
Moderate	64.9
Severe	0.6

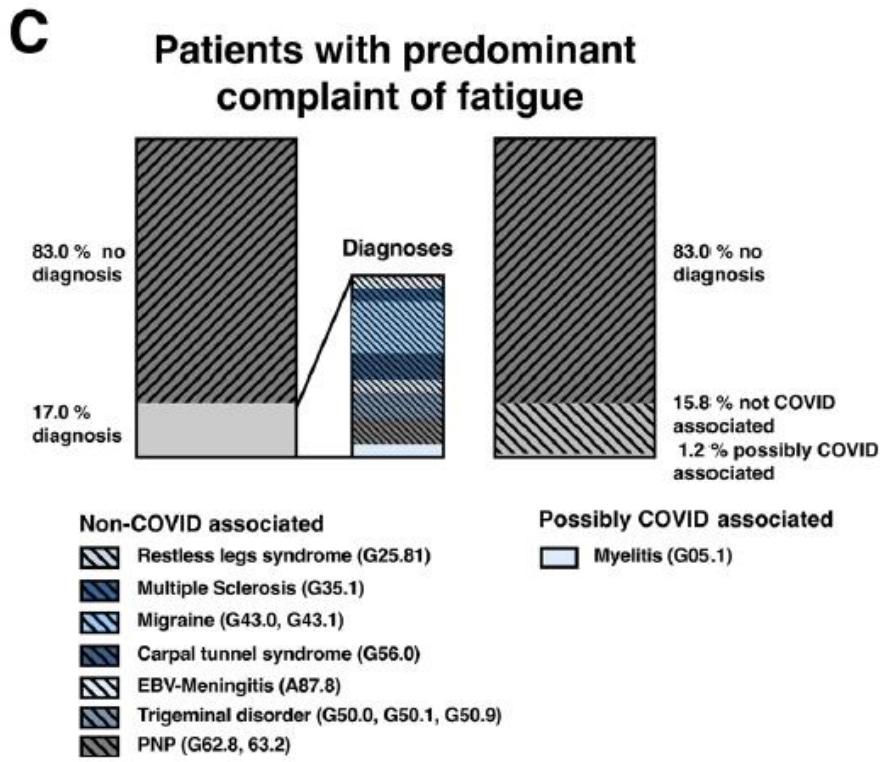


Medical history	%
Previous cardiovascular condition (arterial hypertension (86%), myocardial infarction (4%), other heart diseases (10%))	28.3
Previous neurological conditions (Migraine (44%), stroke (16.3%), MS (4.1%), PNP (8.2%), CPS (8.2%), epilepsy (4.1%), post-infectious fatigue (2%), others (12.2%))	29.0
Previous psychiatric preconditions (Depression (66.7%), anxiety disorder (20.1%), post-traumatic stress disorder (3.3%), somatic disorder (3.3), adjustment disorder (3.3%), borderline disorder (3.3%))	19.0

Michael Fleischer Neurol Ther Aug 2022

Post-COVID-19 Syndrome is Rarely Associated with Damage of the Nervous System: prospective cohort of 171 patients with neuro-psych long-COVID complaints





PNP = polyneuropathy; GBS = Guillain Barré Syndrome

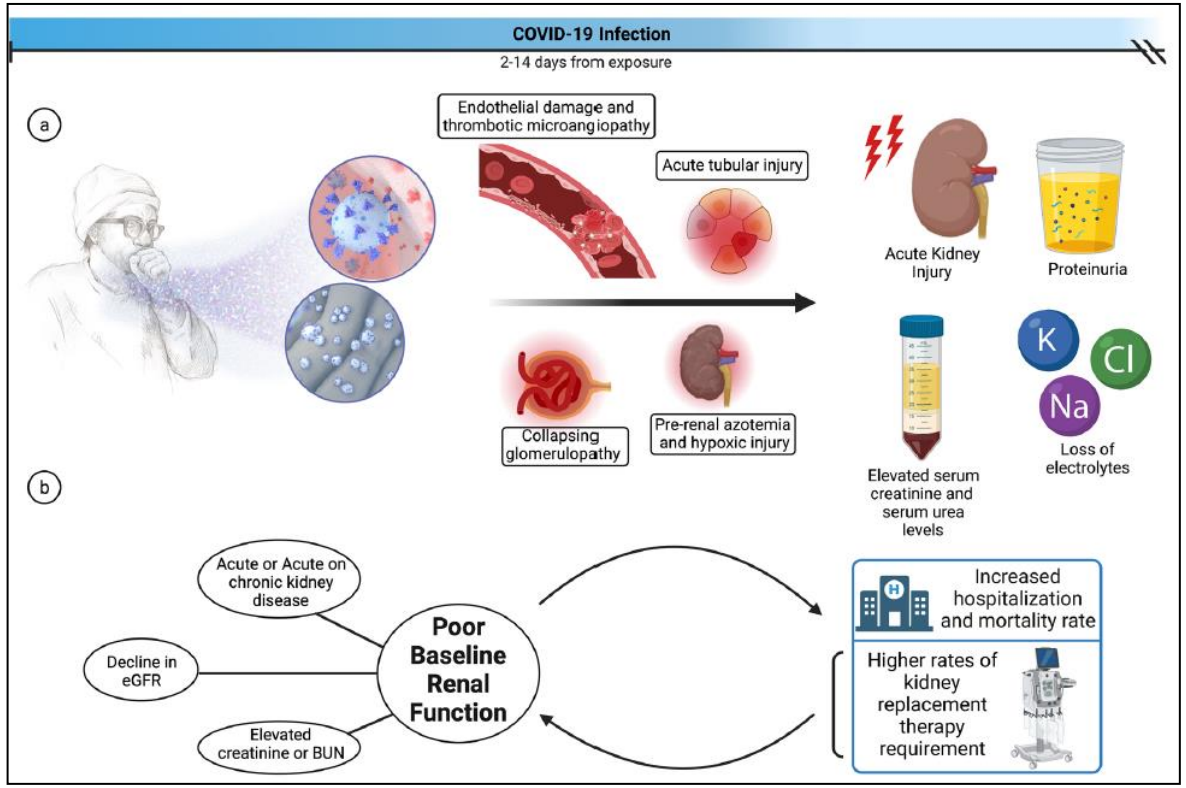
Michael Fleischer Neurol Ther Aug 2022

Pathophysiology hypotheses and associations:

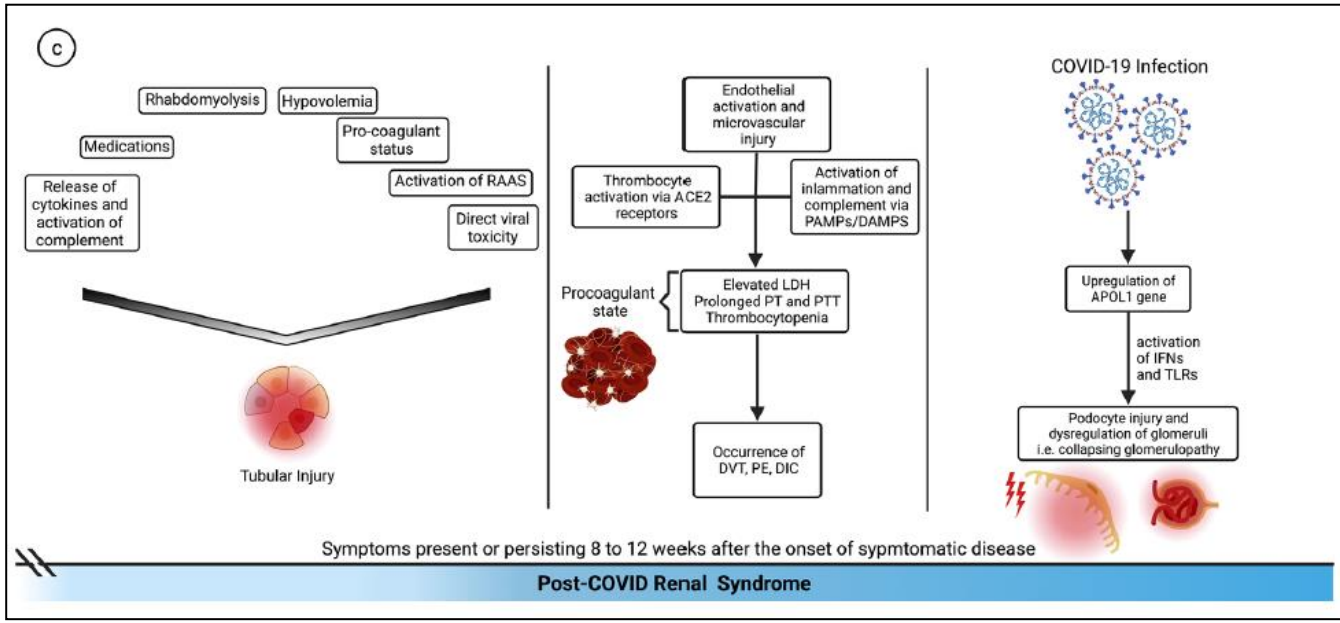
- General
- Pulmonary
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- **Kidney**
- Diabetes
- Gastro-intestinal disorder

Post-acute COVID-19 syndrome and kidney diseases

Acute phase



Chronic phase



1) In acute phase: chronic kidney disease and development of acute kidney injury (AKI) →high mortality and morbidity rates.
2) In the 6-to-12-month follow-up period: a decline in renal function has been observed even in patients without AKI in acute phase.
3) There are no guidelines regulating the follow-up period or therapeutic alternatives.

Sidar Copur J Nephrology (2022) vol 35 p795–805

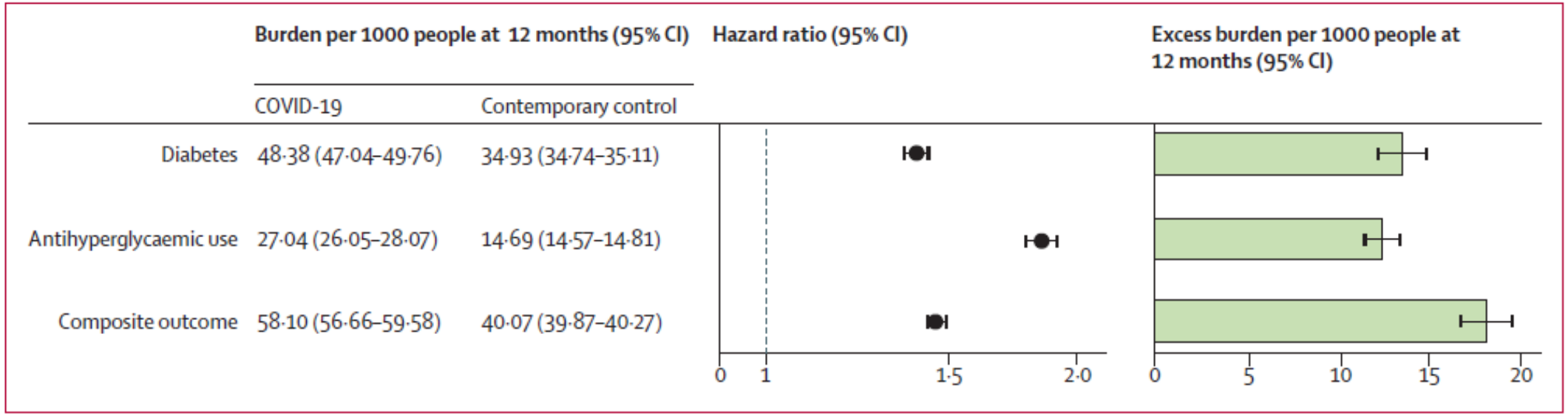
Pathophysiology hypotheses and associations:

- General
- Pulmonary
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- Kidney
- **Diabetes**
- Gastro-intestinal disorder

Risks and burdens of incident diabetes in long COVID: a cohort study

Cohort of US Department of Veterans Affairs:

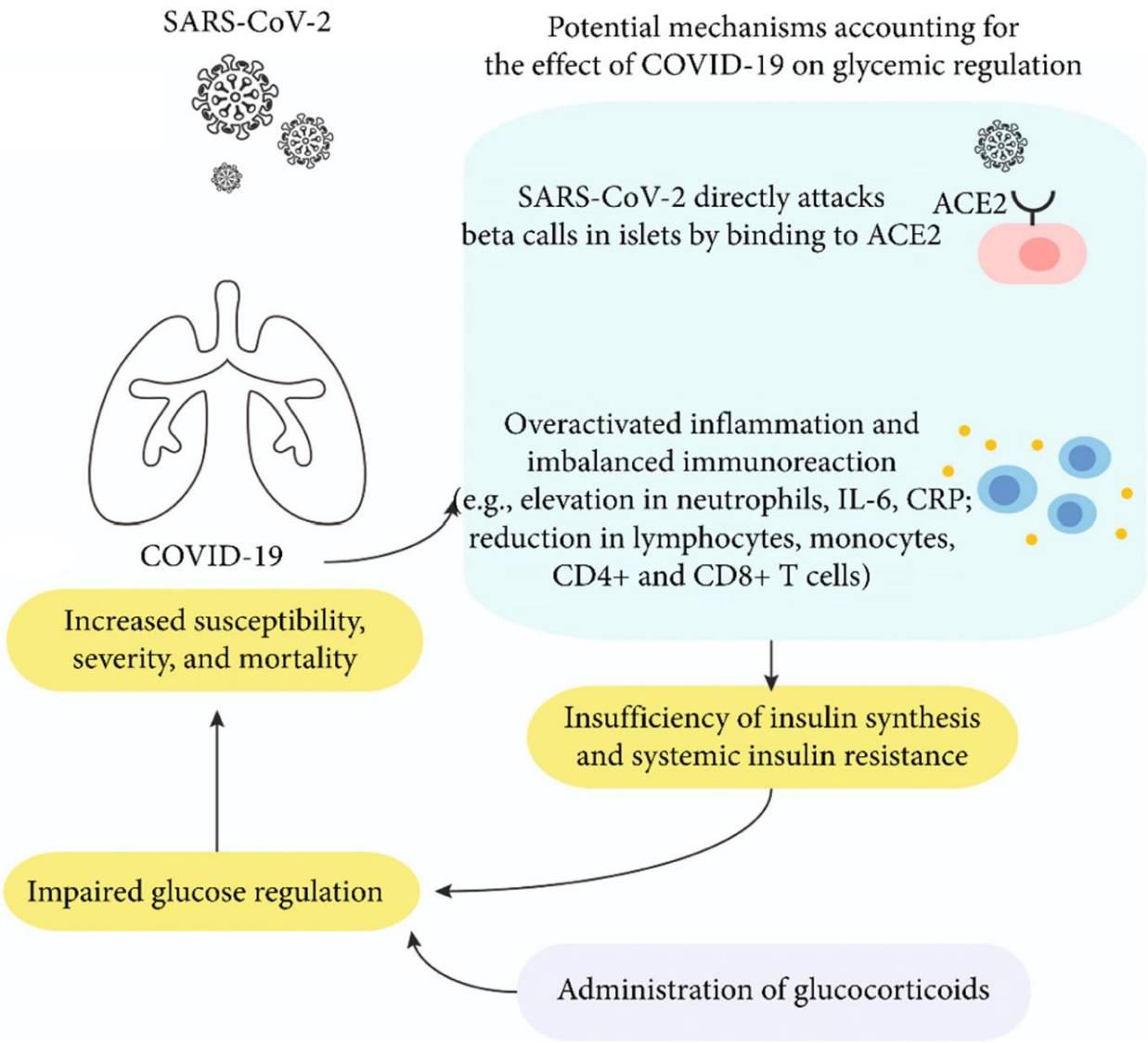
- 181 280 participants with a positive COVID-19 test between March 1, 2020, and Sept 30, 2021
- Two control groups: contemporary (n=4 118 441) and historical 2018-19 (n = 4 286 911)



Conclusion: Increased risks and 12-month burdens of incident diabetes and antihyperglycaemic drug use

Yan Xie *Lancet Diabetes Endocrinol* 2022; 10: 311–21

Mechanisms leading to increased risk of hyperglycemia and diabetes in SARS CoV2 Infection



Ali Rizvi J Diabetes and its complications Oct 2022

Pathophysiology hypotheses and associations:

- General
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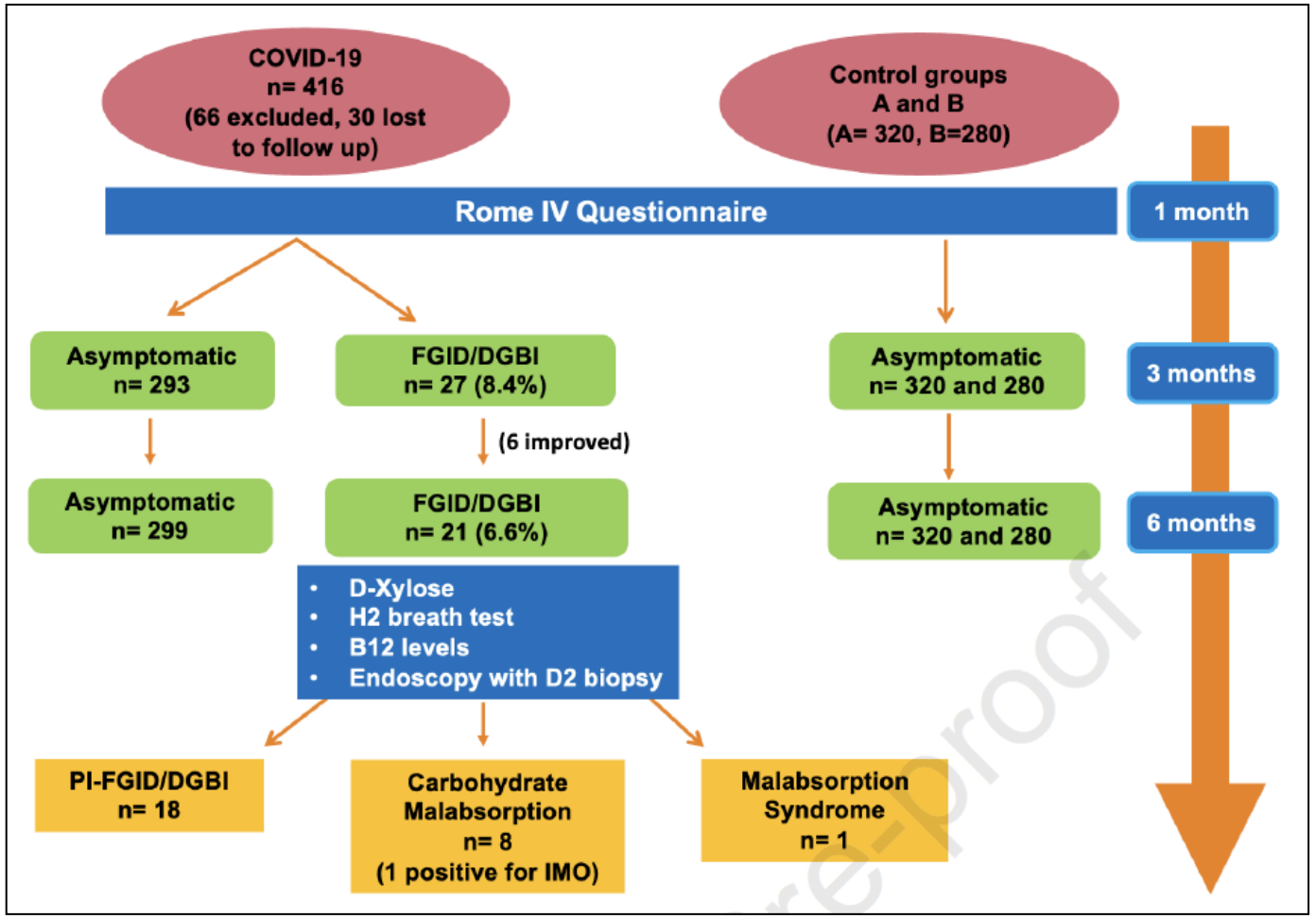
- Diabetes
- **Gastro-intestinal disorder**

Long-term gastrointestinal sequelae following COVID-19: A controlled prospective follow-up cohort study



IMO = Intestinal methanogen overgrowth

PI-FGID/DBI = post infection functional gastro-intestinal disorders /disorders of gut-brain interaction

= irritable bowel syndrome, functional diarrhea, functional dyspepsia, functional constipation, abdominal bloating

Predictive factors:

- COVID severity
- GI symptoms during acute phase

Rithvik Golla Clinical Gastroenterology and Hepatology Oct 2022

Voorzichtig besluit over patho-fysiologische mechanismen van long COVID

1) Slechts weinig evidentie over persisterende infectie, behalve bij personen met immuundeficiëntie

2) Gevolg van coagulo-pathie tijdens acute fase en aanhoudende inflammatie (met laag cortisol) tijdens chronische fase

→ Sterkste argumenten voor structurele gevolgen **cardio-pulmonair, renaal en endocrien**:
longfibrose; geleidingsstoornissen en cardio-myocytaire dood; glomerulaire en tubulaire schade; diabetes

→ Meer argumenten voor indirecte functionele effecten van microthrombi en inflammatie op **zenuwstelsel:** -
- Functionele cardio-pulmonaire klachten als inspannings-intolerantie, hartkloppingen; pijn op de borst
- Anosmie en ageusie
- Neurologische, neuro-psychische en neuro-cognitieve klachten
- Gastro-intestinale klachten

Long COVID: Aanpak in de tweede lijn

Thérèse Lapperre

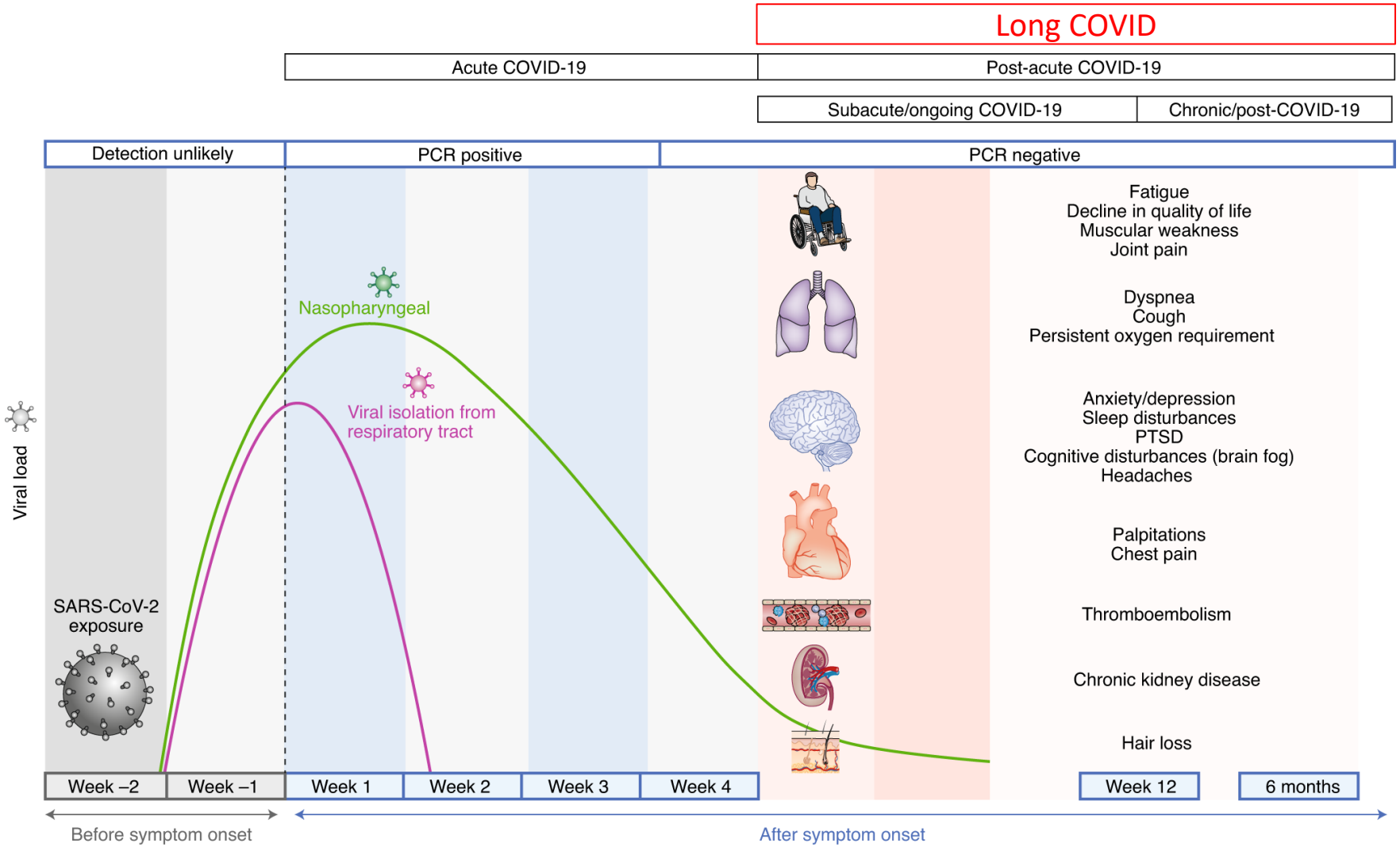
Longarts

8-12-22

Content:

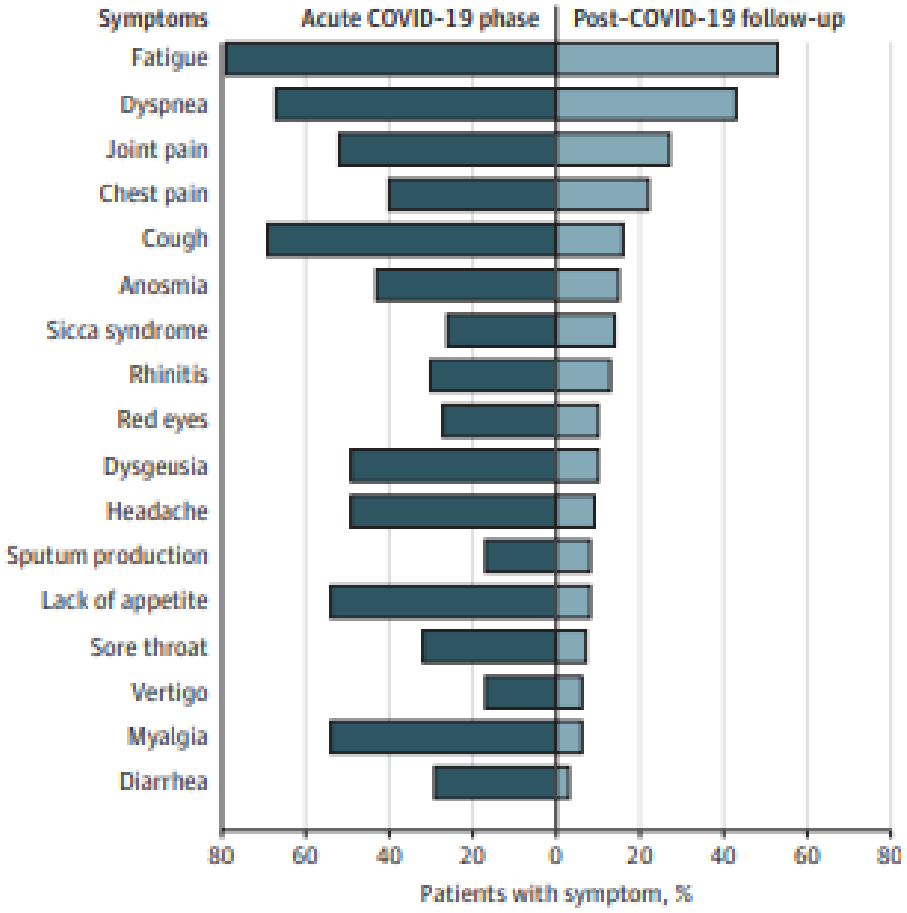
- Casuistiek
- COVID raadpleging UZA
- Long COVID richtlijnen (NICE guideline)
- PuRe-COVID trial

Timeline of post-acute COVID-19



Nalbandian, Nature Med 2021

Symptoms following COVID-19



N=180

2 months post COVID-19

- 62% feels not returned to full health after 2 months
- Reduced 6-min walking distance in about 25% of pts

Carfi, JAMA 2020;
Townsend, Ann ATS 2020

University of Antwerp UZA

Holistic assessment

For people with ongoing symptomatic COVID-19 or suspected post-COVID-19 syndrome who have been identified as needing an assessment, use a holistic, person-centred approach. Include a comprehensive clinical history and appropriate examination that involves assessing physical, cognitive, psychological and psychiatric symptoms, as well as functional abilities.

Include in the comprehensive clinical history:

- *history of acute COVID-19 (suspected or confirmed)*
- *the nature and severity of previous and current symptoms*
- *timing and duration of symptoms since the start of acute COVID-19*
- *history of other health conditions*
- *exacerbation of pre-existing conditions.*

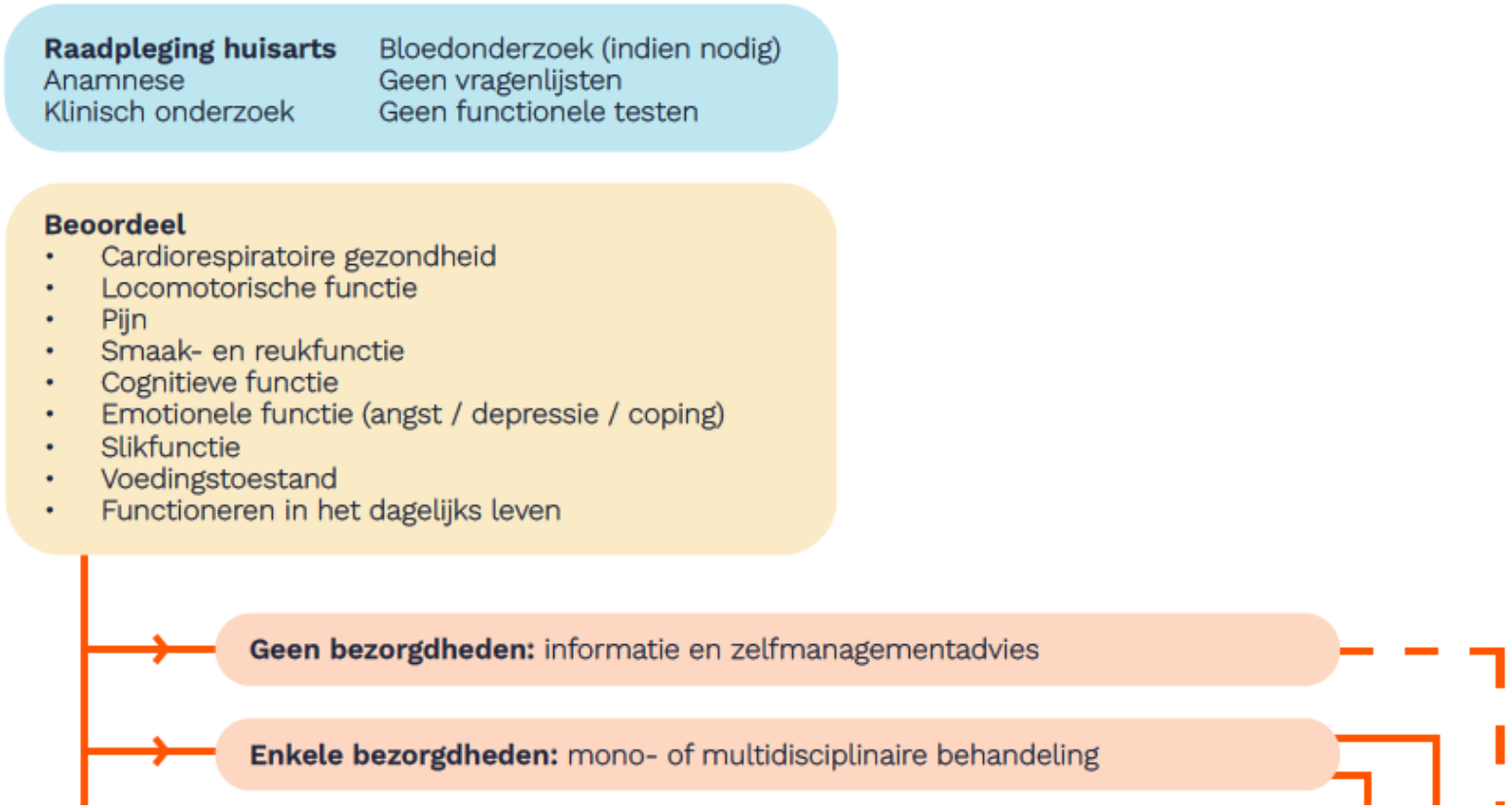
Holistic assessment

- **Impact of symptoms on daily life and activities**
- **Cognitive symptoms: use validated screening tool**
- **Tests and investigations tailored to signs and symptoms**
  - Routine blood tests (FBC, kidney and liver fx, CRP, ferritin, BNP, HBA1C, thyroid fx) (evt d-dimer)
  - Chest X-ray
  - Exercise tolerance tests (e.g. sit-to-stand test + sat + HR)
  - Postural symptoms: lying and standing BP + HR

NICE Guideline 2022
Belgische richtlijn: https://ebpnet.be/nl/ebsources/6691 (1/12/22)

Belgische richtlijn long COVID: Eerste lijn

- **Opvolging en revalidatie van patiënten met aanhoudende klachten na COVID-19 in de eerste lijn**



Belgische richtlijn: https://ebpnet.be/nl/ebsources/6691 (1/12/22)

Belgische richtlijn long COVID: Eerste lijn

Evaluatie met discipline-specifieke instrumenten

Kinesitherapeut
Fysiek trainingsprogramma
Ademhalingsoefeningen
Ademspiertraining

Ergotherapeut
Beheersing van dagelijkse activiteiten
Energiemanagement

Diëtist
Bevorderen van de voedingstoestand
Voedingsadvies

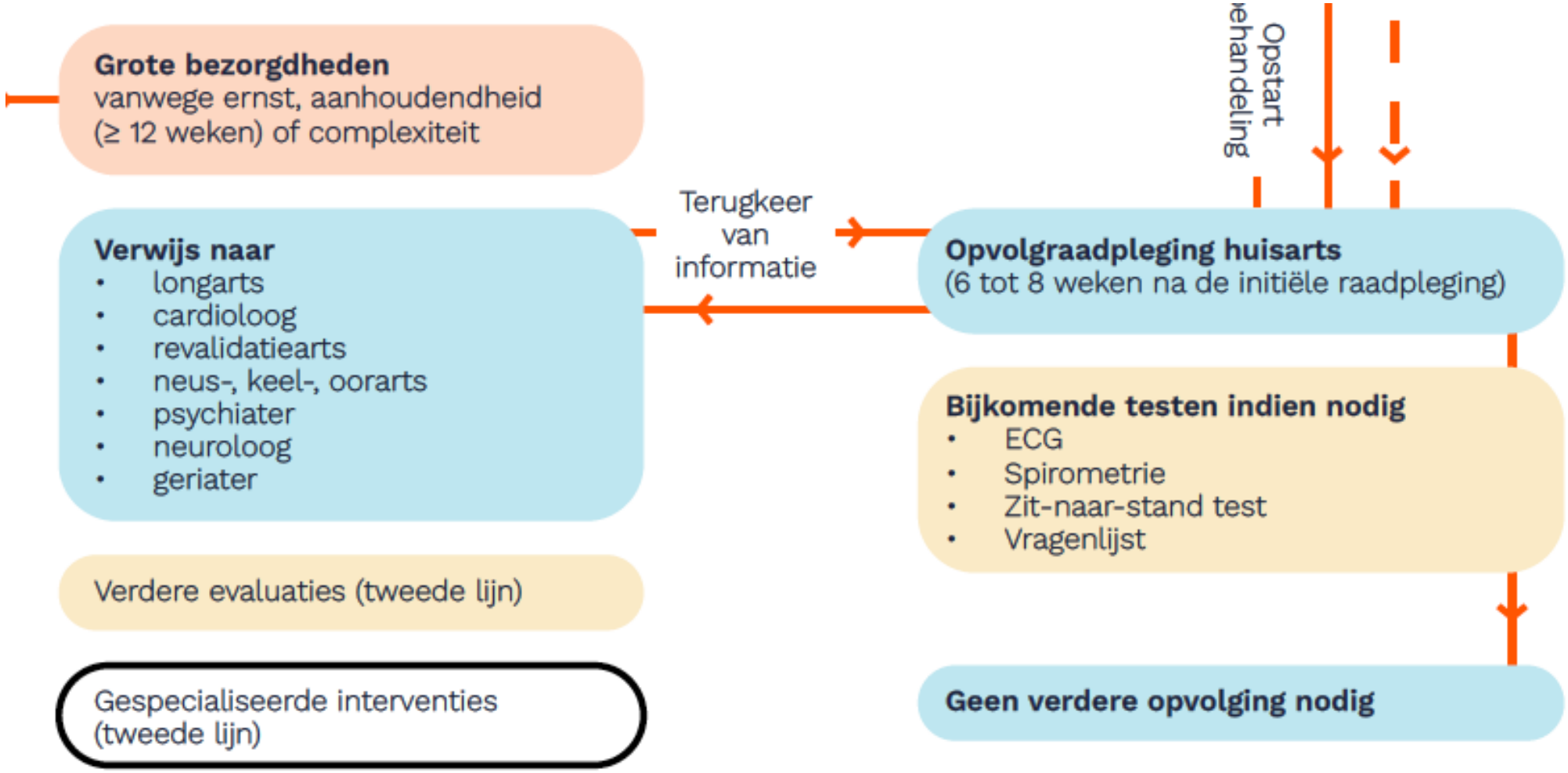
Logopedist
Behandeling van stem-, hoest-, kauw- en slikproblemen

Psycholoog
Behandeling van angst, depressie, PTSS, slapeloosheid

Maatschappelijk werker
Hulp bij psychosociale problemen

Belgische richtlijn: https://ebpnet.be/nl/ebsources/6691 (1/12/22)

Belgische richtlijn long COVID: Eerste lijn



Belgische richtlijn: https://ebpnet.be/nl/ebsources/6691 (1/12/22)

Urgent referral

Refer people with ongoing symptomatic COVID-19 or suspected post-COVID-19 syndrome urgently to the relevant acute services if they have signs or symptoms that could be caused by an acute or life-threatening complication, including (but not limited to):

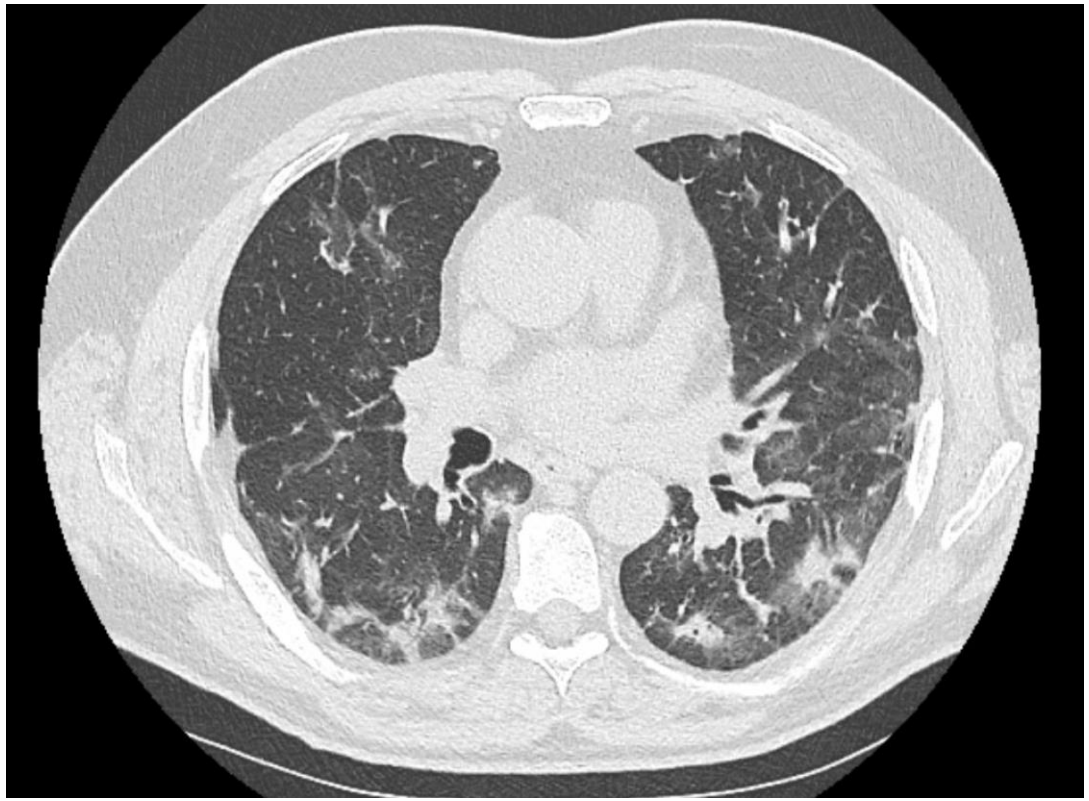
- hypoxaemia or oxygen desaturation on exercise
- signs of severe lung disease
- cardiac chest pain
- paediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 (PIMS-TS).

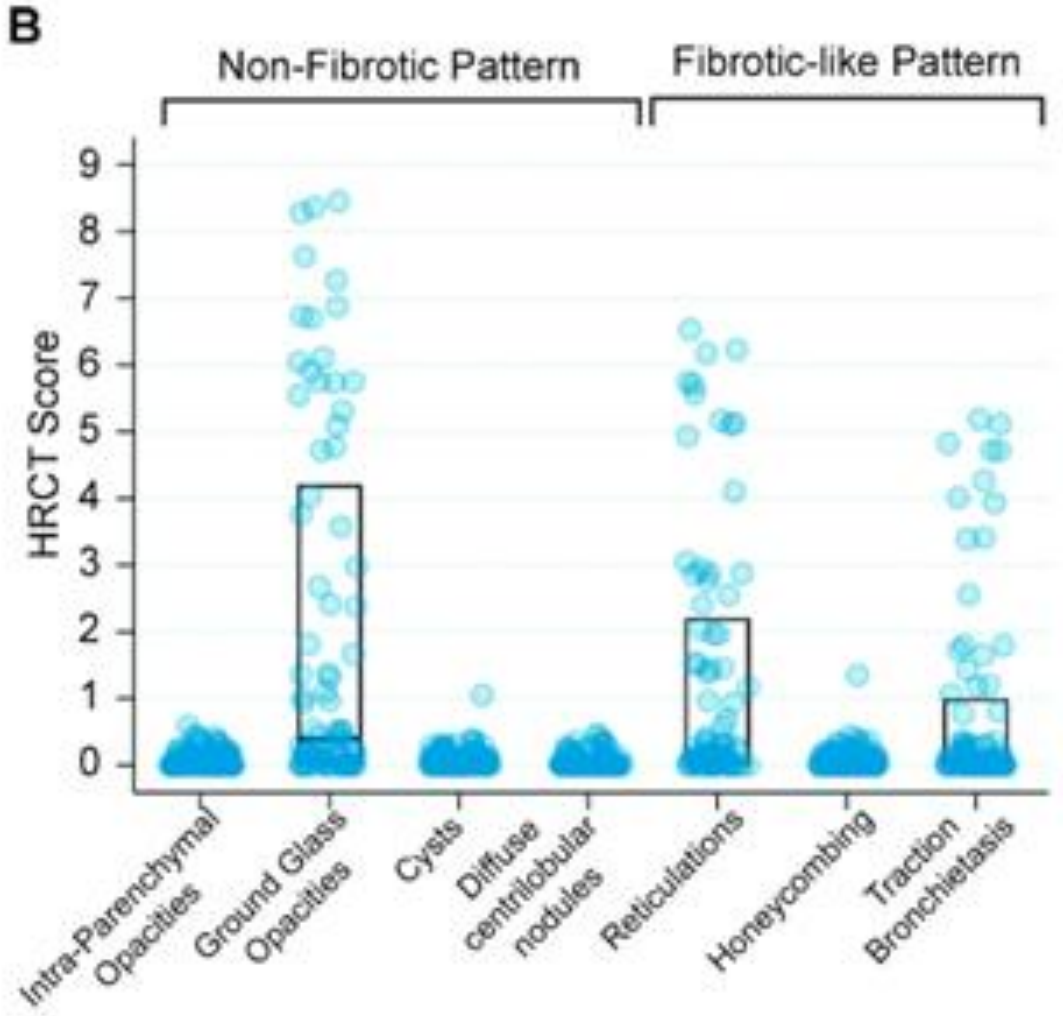
NICE Guideline 2022

COVID raadpleging UZA Pneumologie

- **Populatie:**
  - Evaluatie na opname voor COVID-19 (2 mnd na opname)
  - Verwijzingen ivm persisterende klachten (respiratoir, vermoeidheid, verlies energie)
- **Standaard:**
  - Vragenlijst: CAT score
  - Longfunctie: spirometrie, bodyplethysmography, diffusiecapaciteit
  - 6-minutenwandeltest met saturatie meting
  - Beeldvorming: RX-thorax of CT-thorax
- **Op indicatie:**
  - Arteriële bloedgas, uitsluiten astma (provocatietest)
  - Verwijzing: cardioloog, neuroloog, slaapcentrum,…

Post COVID-19 folow-up pulmonary sequelae





University of Antwerp UZA

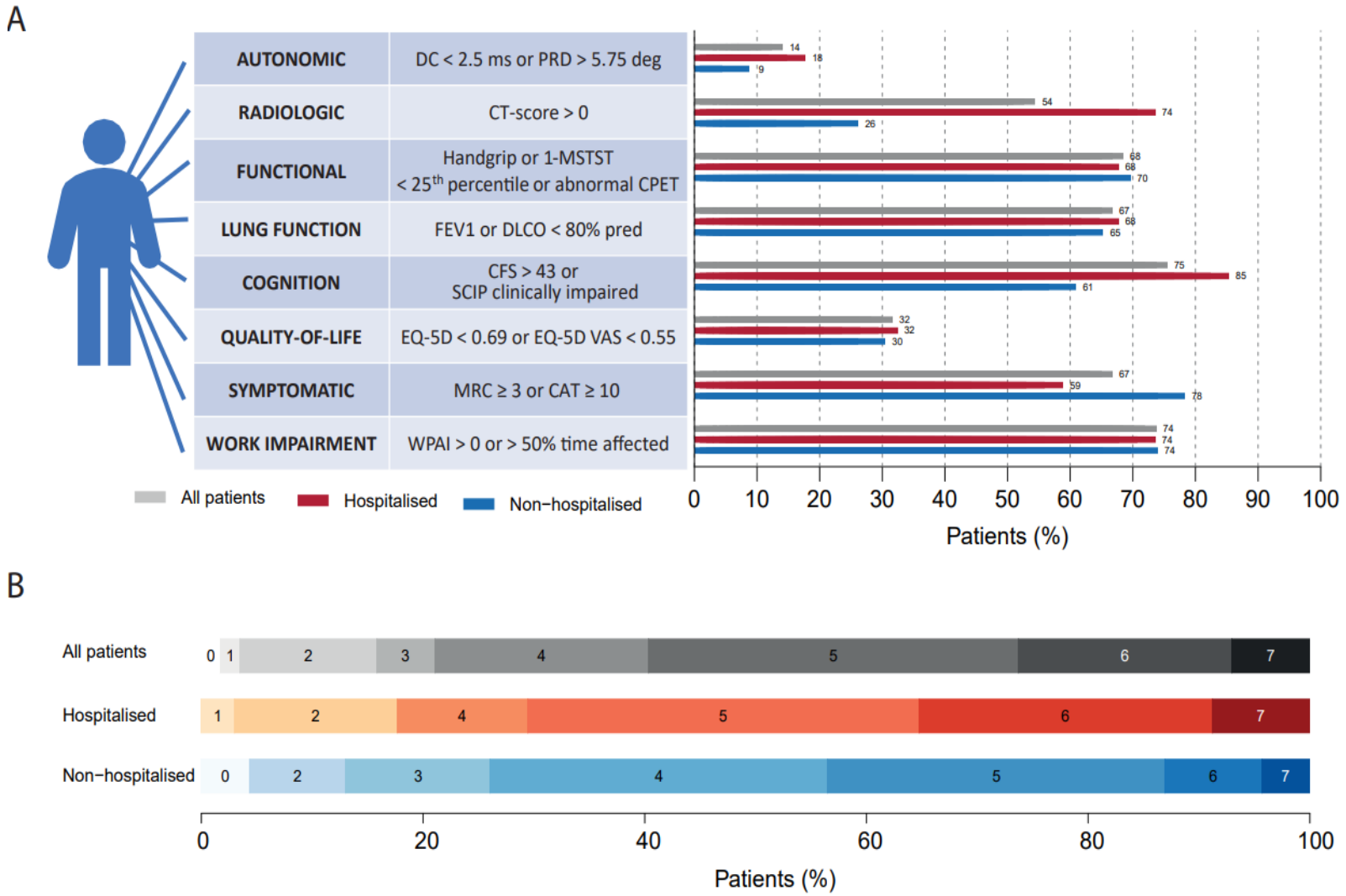
Associated with severity acute COVID-19

McGroder, Thorax 2021

Belang specialistische evaluatie: casuistiek UZA

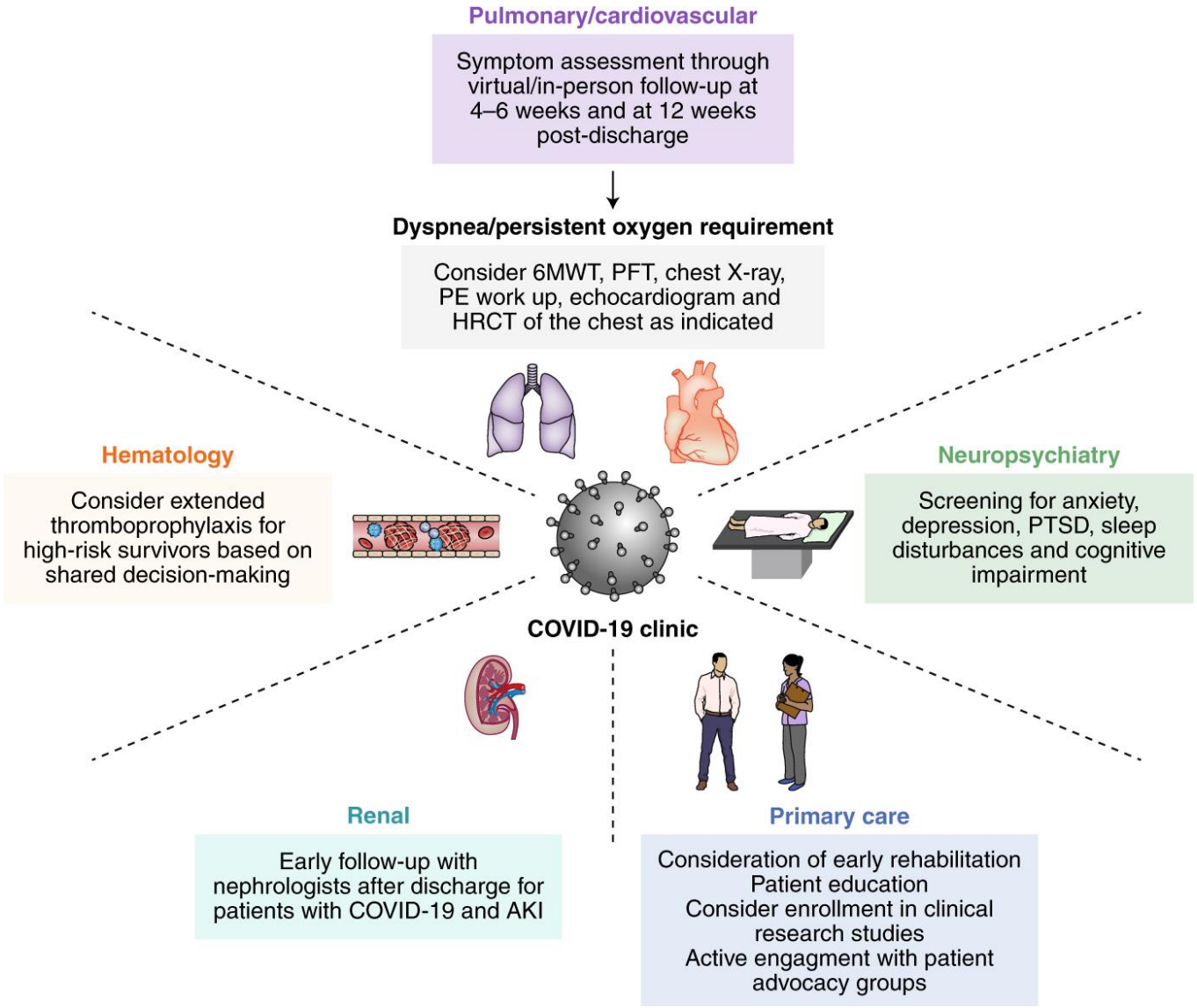
1. Post-infectieuze pulmonale sequellen en fibrose met restrictieve longfunctie
2. Respiratoire insufficientie tgv diafragma dysfunctie met nood aan chronische ventilatie (NIV)
3. Onbehandelde astma comorbiditeit
4. Extrathoracale luchtwegobstructie door intubatieletsel
5. …

IMPACT study: hospitalised and non-hospitalised pts



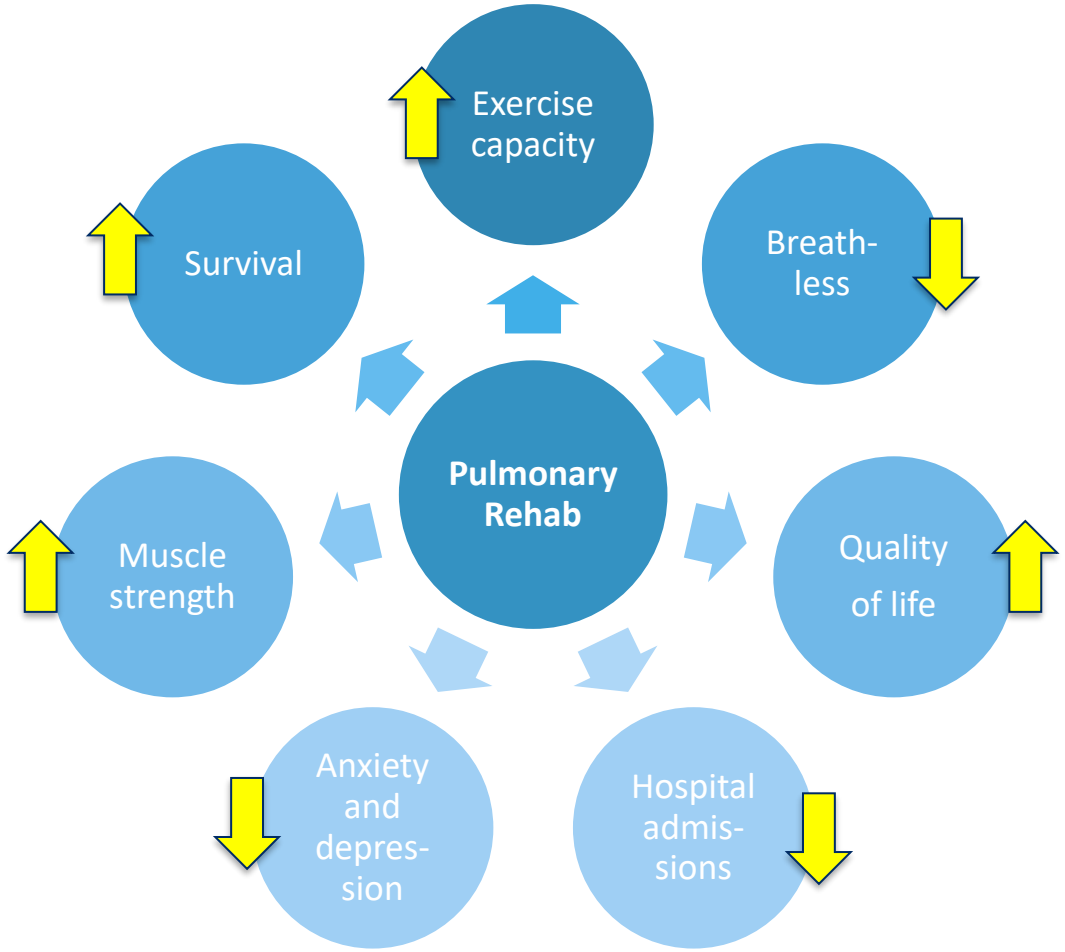
Johnsen, ERJ Open 2021

Interdisciplinary management of post-acute COVID-19



Nalbandian, Nature Med 2021

Benefits of Pulmonary Rehabilitation in COPD



Effects in Long COVID?

Multidisciplinary rehabilitation

Provide integrated, multidisciplinary rehabilitation services, based on local need and resources. Healthcare professionals should have a range of specialist skills, with expertise in managing fatigue and respiratory symptoms (including breathlessness). Additional expertise may be needed depending on the age and symptoms of the person. The core team could include, but not be limited to, the following specialist areas:

- occupational therapy
- physiotherapy
- clinical psychology and psychiatry
- rehabilitation medicine.

Certainty of the Evidence

The panel concluded that lower-certainty evidence from patient experience paired with consistent panel expertise show that the overall benefits of the intervention are clearly greater than the disadvantages.

In the absence of conclusive evidence on specific service delivery components, the panel considered that recommendations should take the form of general principles.

Limitaties huidige interventies long COVID

- **Geen evidence base voor (non-)farmacologische interventies**
- **Revalidatie**
  - Geen nationale richtlijn inhoud (1e lijn) revalidatie behandeling
  - Heterogene aanpak kine's
  - Impact post-exertional malaise (PEM)
  - Responders en non-responders
- **Alternatieve geneeskunde**

Key recommendations for research

1 Interventions for post-COVID-19 syndrome

What are the most clinically effective interventions (including social prescribing and structured community support) for managing post-COVID-19 syndrome?

Does effectiveness vary for different population groups (for example, sex, age, socioeconomic group, black, Asian and minority ethnic group communities or people with a learning disability)?

Do any symptoms of post-COVID-19 syndrome predict the need for specialist intervention?

Are there clusters of symptoms that identify response to interventions in post-COVID-19 syndrome?

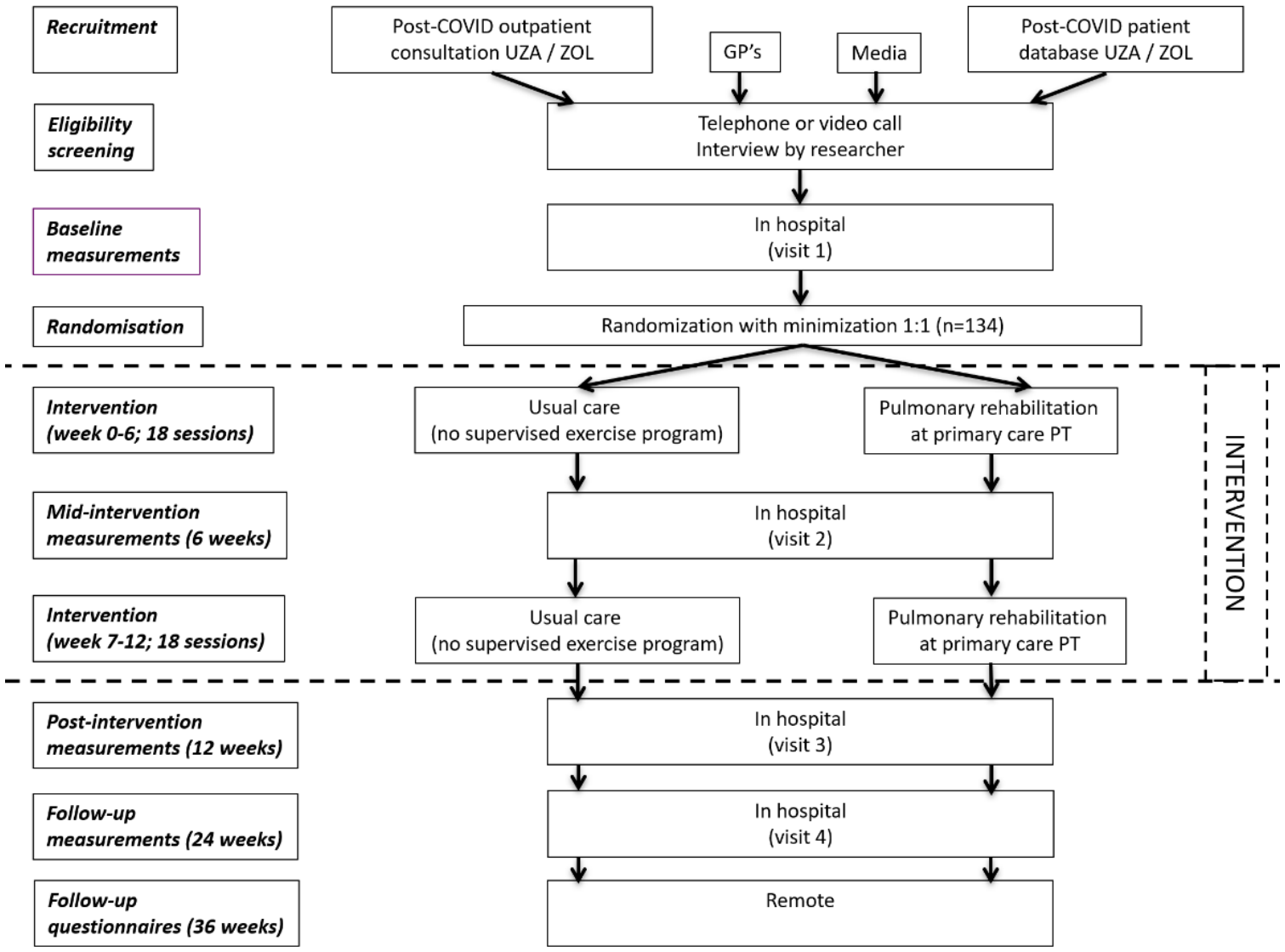
What is the clinical effectiveness of different service models of multimodality/multidisciplinary post-COVID-19 syndrome rehabilitation in improving patient-reported outcomes (such as quality of life)?

What is the clinical effectiveness of exercise interventions for people with post-COVID-19 syndrome? Does effectiveness vary for different population groups (for example, sex, age, socioeconomic group, black, Asian and minority ethnic group communities or people with a learning disability)?

Does early exercise rehabilitation assist in improving symptoms of post-COVID-19 syndrome?

PuRe-COVID: Aims

- **Primary aim:**
  - To assess the effect of a ***pulmonary rehabilitation*** (PR) program in primary care on ***exercise capacity*** (6MWD) in patients with long COVID.
- **Secondary aims:**
  - To assess the effect of a PR program, delivered in primary care, in patients with long COVID, on respiratory ***symptoms***, fatigue, quality of life, and physical activity in daily life as measured by ***activity tracker***.
  - To identify ***predictors of response*** to a primary care PR program.
  - The ***longer-term effects*** of a 12-week primary care PR program on exercise capacity and symptom burden in patients with long COVID after 24 weeks (exercise capacity and symptoms) and 36 weeks (symptoms only) follow-up.



PuRe-COVID: Study Design

- Rehabilitation by primary care physiotherapist
- 36 sessions
- Intervention: 5 phases
- Composed of:
  - Exercise capacity training
  - Muscle strength training
  - Breathing exercises
  - Education
  - Coaching

PuRe-COVID: Inclusion and exclusion criteria

- **Inclusion criteria:**
  - Post COVID-19 (positive COVID-19 PCR, official pharmacy performed antigen test, self-performed test confirmed by a physician during the acute COVID-19 or positive antibodies before vaccination)
  - Persistent COVID related symptoms that were not present pre-COVID
  - Symptomatic: dyspnea on exertion, loss of energy, fatigue or sleep impairment (based on questionnaires: mMRC, CAT, CIS fatigue, PCFS)
- **Exclusion criteria:**
  - Impossible to participate in pulmonary rehabilitation
  - Completed ≥9 sessions of physiotherapy in total for long COVID
  - Significant comorbidities (e.g. malignancy, transplant patients)

PuRe-COVID: Measurements

	Baseline	Mid-intervention	Post-intervention	Follow-up 1	Follow-up 2
Time (weeks)	0	6 *	12 *	24 *	36
Visit no.	1	2	3	4	5
Questionnaires					
• CAT	X	X	X	X	X
• mMRC	X	X	X	X	X
• CIS	X	X	X	X	X
• PCFS	X	X	X	X	X
• Patient interview	X	X	X	X	X
• Nijmegen	X	X	X	X	X
• HADS	X	X	X	X	X
• WPAI	X	X	X	X	X
• EQ-5D-5L	X	X	X	X	X
Pulmonary function: Spirometry + DCO + TLC	x #		X	X	
Physical functioning					
• MIP/MEP	X	X	X	X	
• Handgrip strength	X	X	X	X	
• 6MWT	X (2x)	X	X	X	
• Activity tracker	X	X	X	X	
Pulmonary evaluation: Rx-thorax / CT-thorax	X #				

Primary endpoint →

University of Antwerp UZA

PuRe-COVID: Casus

- **Voorgeschiedenis:**
  - Sportieve 26 jarige dame, verpleegkundige, liep in september 2021 nog marathon
  - Blanco medische voorgeschiedenis, geen medicatie
  - Volledig gevaccineerd
- **11/11/2021: COVID-19 infectie (+ PCR test)**
  - Geen ziekenhuisopname, wel erg ziek tijdens acute infectie
- **16/05/2022: Inclusie PuRe-COVID**
  - Vermoeidheid, slechter slapen, druk op de borstkas + hoofdpijn tijdens inspanning, moeite met diep ademhalen, dyspneu, tintelende vingers, zeer emotioneel (huilen bij inclusie gesprek)

PuRe-COVID casus: baseline metingen

RX normaal

CAT: 19

mMRC: 1

CIS: 39

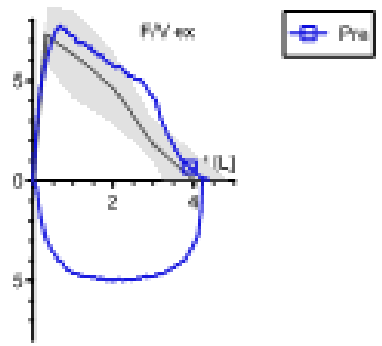
PCFS: 2

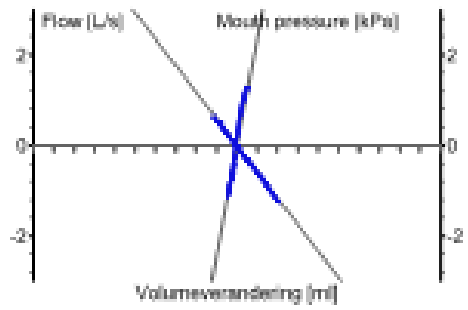
6MWD: 654 m (98%pred)

- Fatigue: 2 → 2
- Dyspneu: 0 → 3

		Voorsp	Best	%Pred
MIP Piek	**kPa**	7.05	10.46	148.3
MIP Gemiddeld	**kPa**	7.05	9.39	133.1
MEP Piek	**kPa**	9.02	12.25	135.8
MEP Gemiddeld	**kPa**	9.02	11.56	128.1

Datum onderzoek	16.05.22	Pred.	Gemeten	%Pred	Z-score	Gemeten	%Pred	% Verschil
SPIROMETRIE/FLOW-VOLUME								
FVC	L	4.01	4.34	108	0.86			
FEV 1	L	3.41	3.85	113	1.08			
FEV 1 % VC MAX	%	86	89	103	0.48			
PEF	L/s	7.25	7.74	107	0.54			
MFEF 75/25	L/s	3.83	5.17	135	1.46			
FEF 75	L/s	1.77	2.63	149	1.20			
LONGVOLUMES (Bodyplethysmografie)								
RV	L	1.19	0.99	83	-0.48			
ITGV	L	2.69	2.79	104	0.19			
TLC	L	5.35	5.27	98	-0.12			
RV % TLC	%	22	19	84	-0.53			
LUCHTWEGWEERSTAND								
R tot	kPa/(L/s)	0.300	0.169	56				
SR tot	kPa*s	0.962	0.524	54				
DIFFUSIECAPACITEIT								
DLCO SB	mmol/(min*kPa)	7.69	6.88	90	-0.81			
VA-SB	L	5.02	4.98	99	-0.05			
DLCO/VA	mmol/(min*kPa*L)	1.54	1.38	90	-0.77			





University of Antwerp UZA

6-wk follow-up

Kine verloopt goed: rustige opbouw (15x geweest)

CAT: 12 (-7)

mMRC: 1 (=)

CIS: 33 (-6)

PCFS: 2 (=)

6MWD: 674m (99%predicted) (+20m)

Fatigue: 1 → 1

Dyspneu: 0 → 2

		Voorsp	Best	%Pred
MIP Piek	kPa	7.05	10.54	149.4
MIP Gemiddeld	kPa	7.05	9.14	129.5
MIP	cmH2O	71.93	93.17	129.5
MEP Piek	kPa	9.02	14.47	160.4
MEP Gemiddeld	kPa	9.02	13.98	155.0
MEP	cmH2O	92.00	142.58	155.0

12-wk follow-up

Kine afgerond (35 sessies), voelt zich veel beter.

CAT: 2 (-17)

mMRC: 0 (-1)

CIS: 12 (-17)

PCFS: 0 (-2)

6MWD: 692m (101%predicted) (+38m)

Fatigue: 0 → 1

Dyspneu: 0 → 0

		Voorsp	Best	%Pred
MIP Piek	kPa	7.05	11.92	169.0
MIP Gemiddeld	kPa	7.05	10.27	145.6
MIP	cmH2O	71.93	104.71	145.6
MEP Piek	kPa	9.02	12.17	134.9
MEP Gemiddeld	kPa	9.02	11.47	127.1
MEP	cmH2O	92.00	116.93	127.1

24-wk follow-up

Voelt zich een heel ander mens, terug energie en niet meer emotioneel, nog niet op niveau van voor COVID-19.

CAT: 3 (-16)

mMRC: 0 (-1)

CIS: 14 (-15)

PCFS: 0 (-2)

6MWD: 754m (+100m)

Fatigue: 1 → 1

Dyspneu: 0 → 0,5

		Voorsp	Best	%Pred
MIP Piek	kPa	7.01	12.17	173.6
MIP Gemiddeld	kPa	7.01	10.77	153.7
MIP	cmH2O	71.46	109.81	153.7
MEP Piek	kPa	8.96	18.69	208.6
MEP Gemiddeld	kPa	8.96	17.53	195.7
MEP	cmH2O	91.36	178.78	195.7

Conclusions

- **Long COVID is a heterogenous condition.**
- **Long COVID symptoms require a holistic, person-centered, evaluation.**
- **Multidisciplinary management and rehabilitation may improve long COVID symptoms, though evidence from RCTs is urgently needed.**
- **The PuRe-COVID trial will provide evidence on the the effect of primary care pulmonary rehabilitation on exercise capacity in patients with long COVID** (www.purecovid.be).

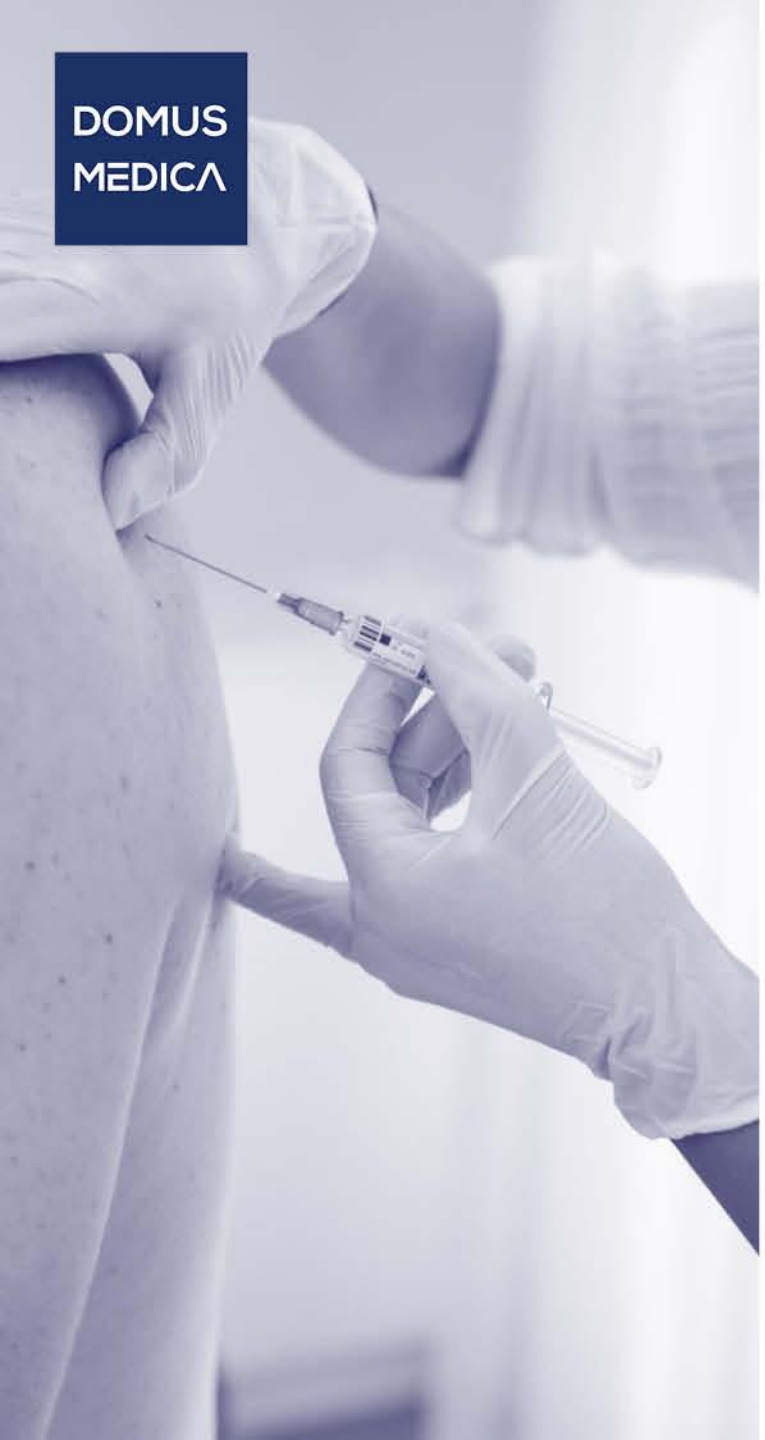
Thank you

Zorgtraject Post-Covid

Dr. Stefan Teughels
Medisch Directeur Domus Medica
Lid Transversale werkgroep Riziv Post-covid

Inleiding

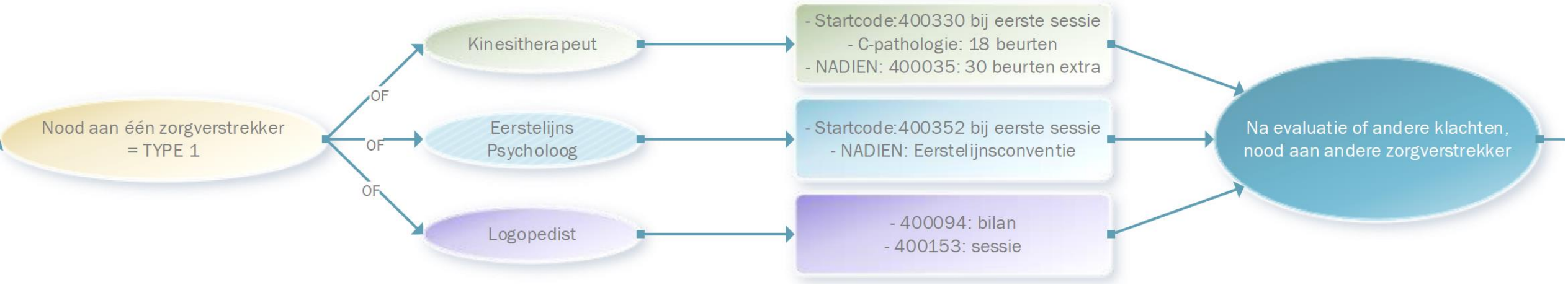
- Zorgtraject (cfr DM/CNI)
- Doel: toegankelijkheid zorg verbeteren voor postcovid patiënten door tegemoet te komen aan de vastgestelde zorgnood per patiënt
- Belangrijk kader voor behandeling in de 1ste lijn
- Transversale projecten (1 v/d 15)
- Looptijd 1 jaar:
  - 1/7/22-30/6/23 (afh van start tot max 30/6/24)
  - Nadien evaluatie en kader voor andere pathologieën
- Parallel met ontwikkeling richtlijn
- Terugbetaling diëtist, ergotherapie, neuropsychologie (sinds 1/12)



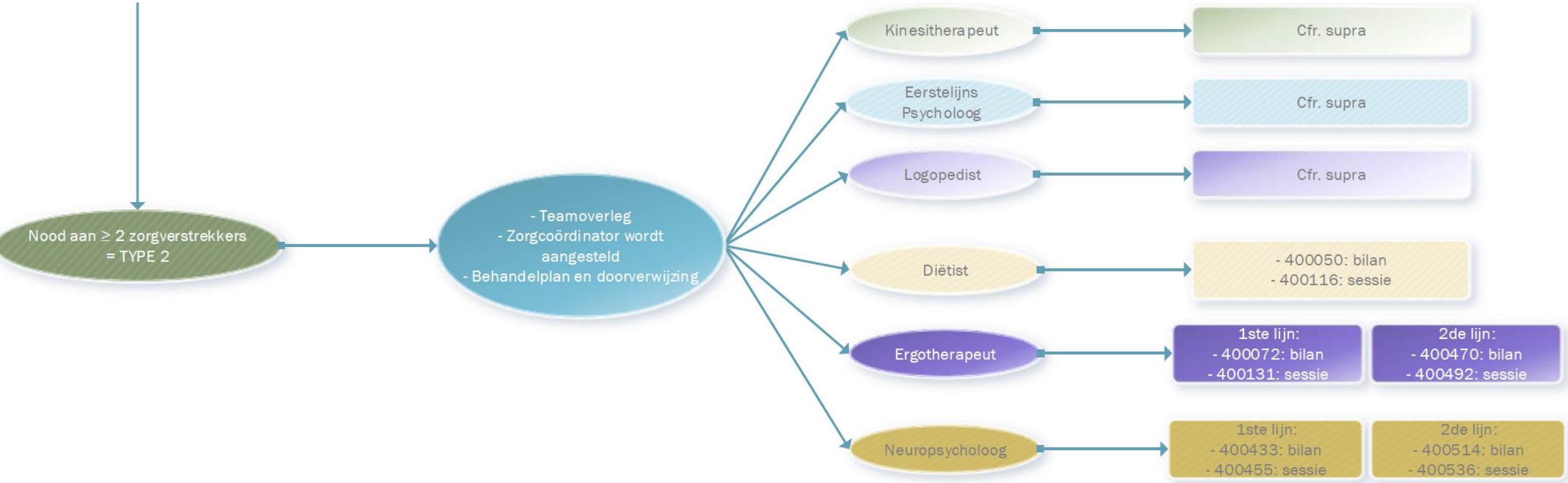
Wie?

- Diagnose Post-covid19 WHO (in afwachting duidelijke richtlijnen):
  - *'**Post**-COVID-19-aandoening komt voor bij personen met een voorgeschiedenis van **waarschijnlijke of bevestigde** SARS-CoV-2-infectie, meestal 3 maanden vanaf het begin van COVID-19 met symptomen die minstens 2 maanden aanhouden en niet verklaard kunnen worden door een alternatieve diagnose.*
  - *Symptomen kunnen nieuw opgetreden zijn na het initieel herstel van een acute COVID-19-episode, of aanhouden na de initiële episode. Symptomen kunnen ook fluctueren in de tijd of terugkomen na verloop van tijd.'*
- Het zorgtraject Post-COVID-19 wordt ten vroegste gestart 12 weken na de eerste symptomen van acute COVID-19 en/of 12 weken na positieve test voor COVID-19.
- Diagnose gesteld door huisarts of via verslag specialist

Zorgtraject type 1: monodisciplinaire zorg

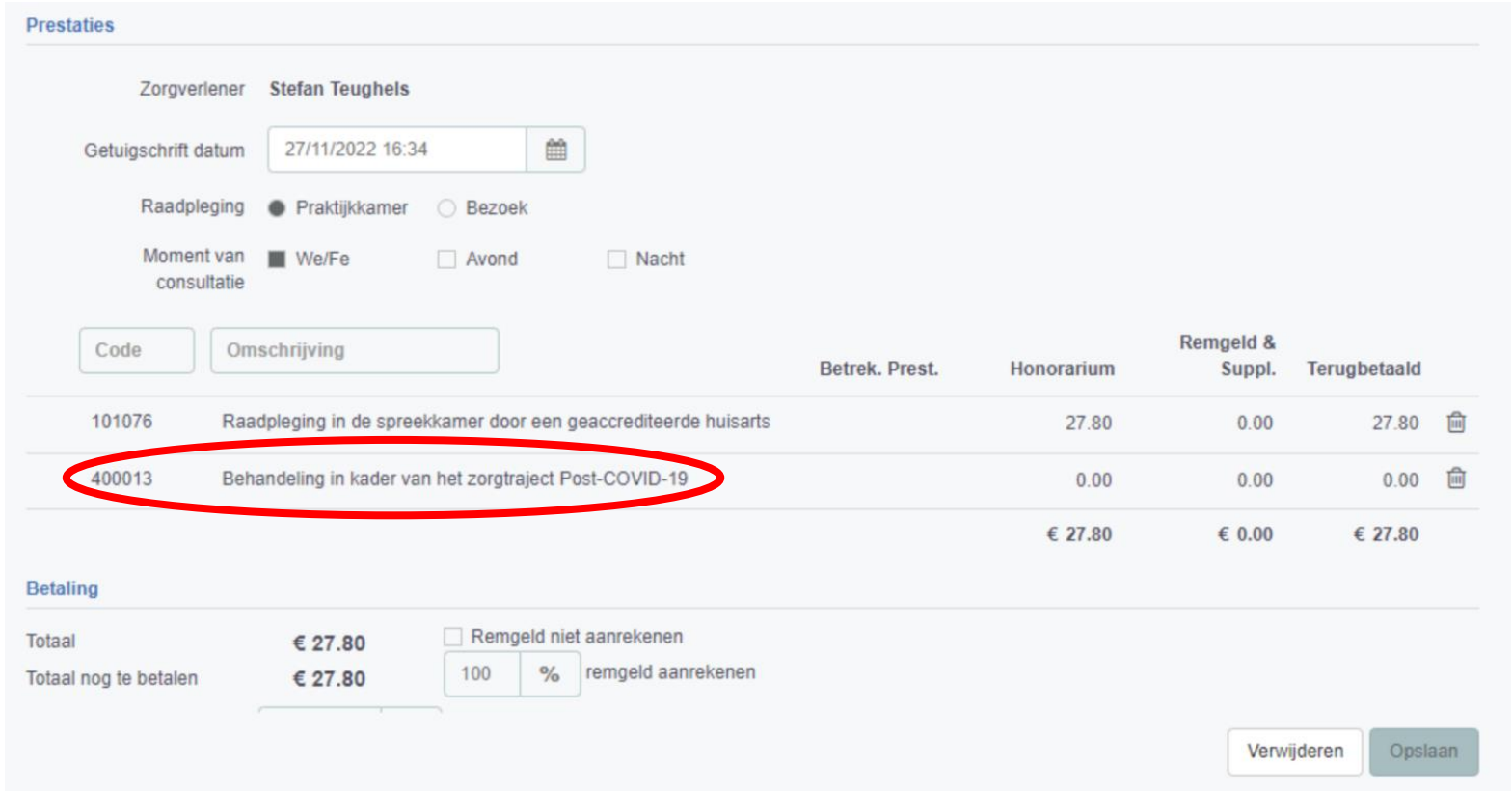


Zorgtraject type 2: multidisciplinaire zorg



Start zorgtraject

- Toetreding via pseudocode 400013
- GMD arts/groepering/Medisch Huis



Start zorgtraject

- Opmaak behandelplan op basis van een assesment (anamnese, KO, TO 1ste en 2de lijn) in functie van gepersonaliseerde doelstellingen en informatieverstrekking aan de patiënt

- Verwijzing naar gepaste zorgverlener(s): op voorschrift vermelden “Post-Covid revalidatie”

- Belangrijk! Raadpleging in kader traject progressieve tewerkstelling voor overleg met
  - Adviserend arts Ziekenfonds
  - Terug naar werk coördinator
  - Arbeidsarts

Overzicht max. aantal beurten per zorgverlener

- Kinesitherapeut:
  - 18 beurten
  - Nadien extra beurten (max. 30 per 6 maanden/60 per jaar)

- Diëtist:
  - Intake 60 minuten
  - Behandelsessies 30 minuten max. 7/jaar

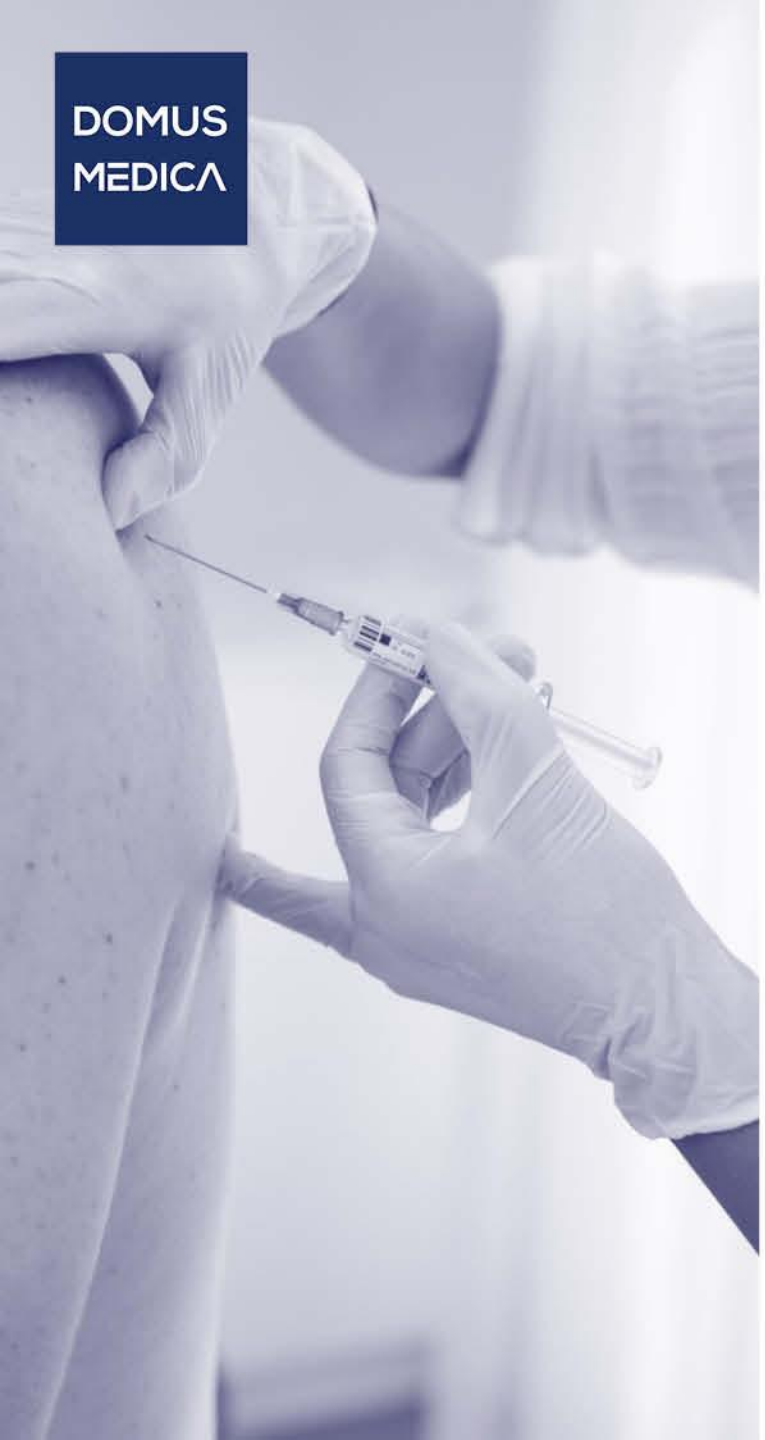
- Ergotherapeut:
  - Observatiebilan 60 minuten
  - Behandelsessies 60 minuten max. 14/jaar en max. 2 per dag
  - Ook in 2de lijn mogelijk

Overzicht max. aantal beurten per zorgverlener

- Logopedist
  - Intake 60 minuten
  - Behandelsessies 30 min. Max. 7/jaar
  - Kan virtueel

- Psycholoog
  - Eerstelijnspsycholoog in kader overeenkomst 26/7/2021 tussen riziv en netwerk geestelijke gezondheid betreffende de financiering van de psychologische functies in de eerste lijn

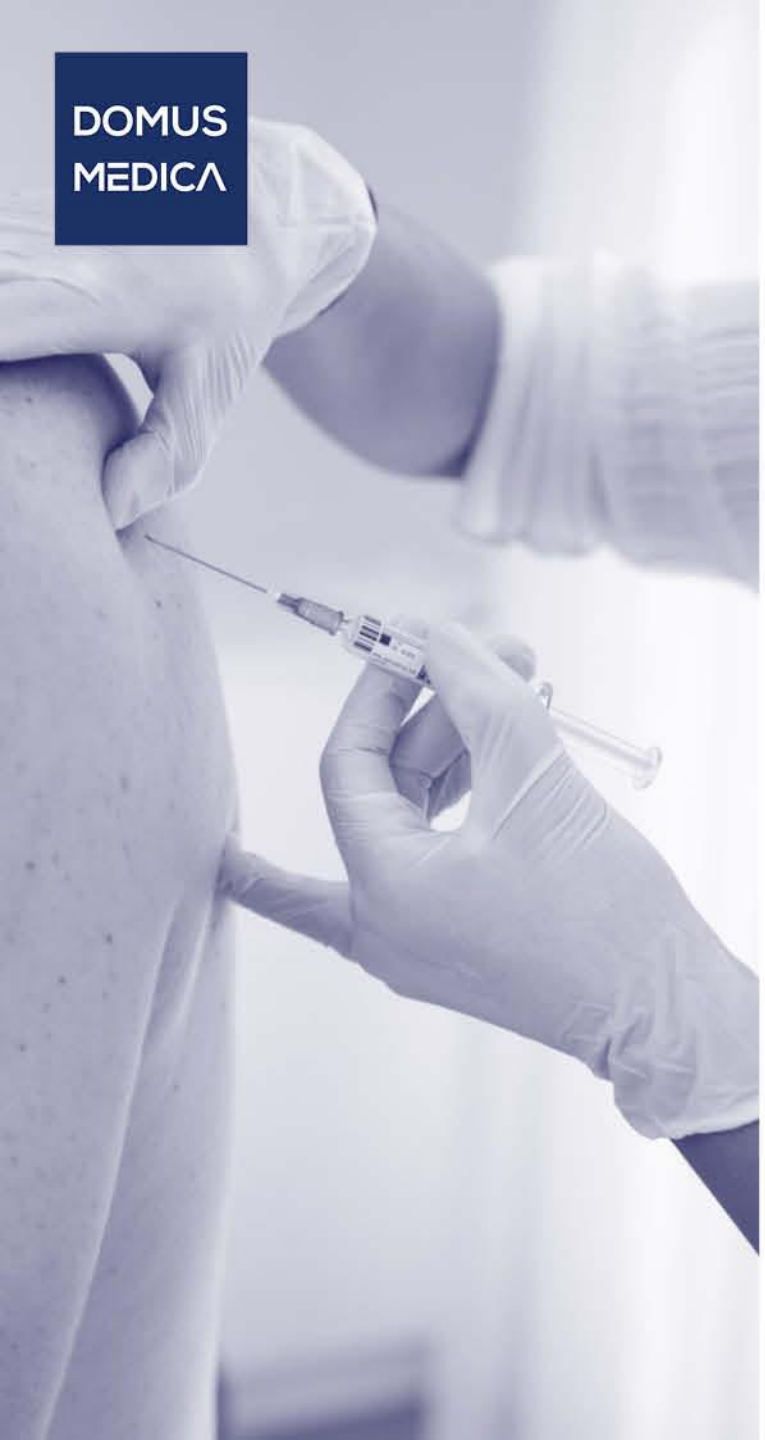
- Neuropsycholoog:
  - Observatiebilan 180 minuten
  - Behandelsessies 60 minuten 10x/jaar
  - Kan virtueel
  - Ook in 2de lijn mogelijk



Zorgcoördinatie vanaf type 2

- Wie?
  - Huisarts, andere zorgverleners
  - Kan gedelegeerd worden aan (praktijkverpleegkundige, coördinator, …)
- Forfaitair honorarium van 120 euro (ncl 400175) (1x/jaar)
- Taken:

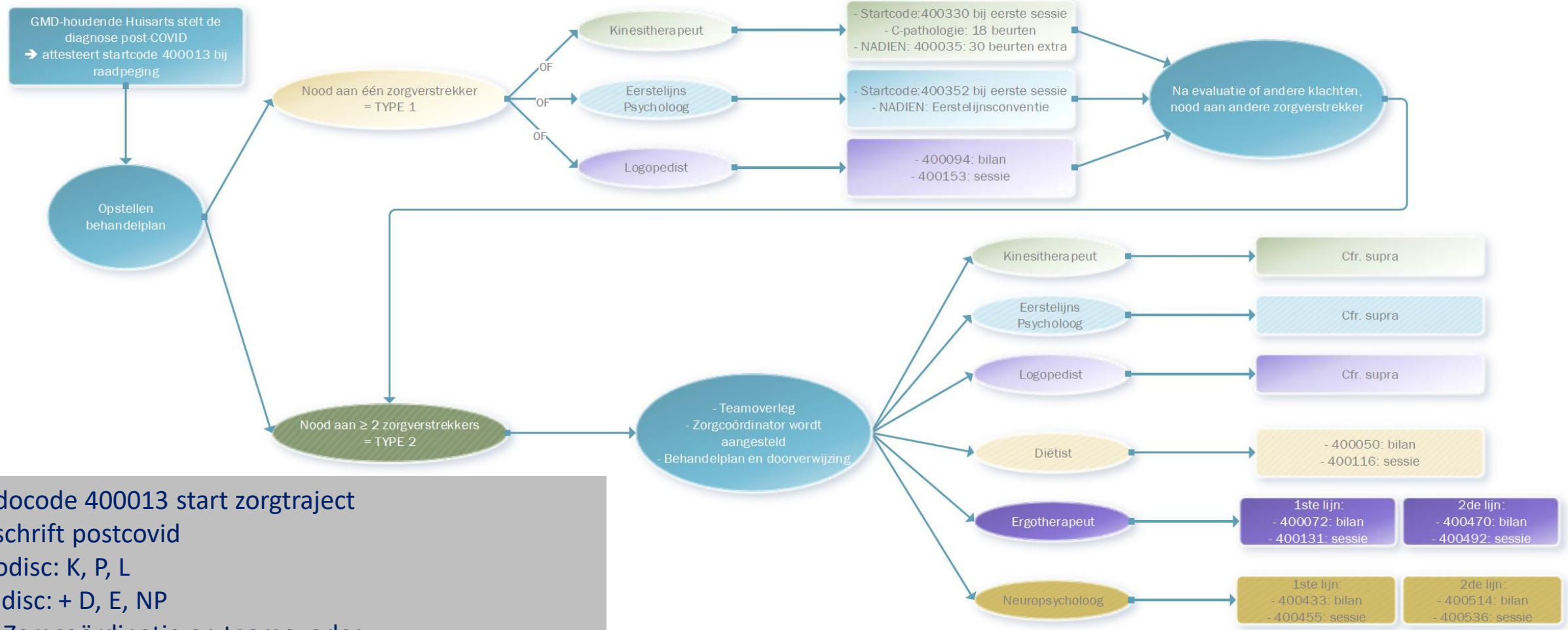
1° de ontwikkeling van het partnerschap met de andere eerstelijnszorgverleners, de neuropsycholoog en ergotherapeut uit tweede lijn en/of de arts-specialist;
2° de tijdige verwijzing naar de arts-specialist;
3° de planning, coördinatie en opvolging van het behandelplan;
4° de communicatie en organisatie met de betrokken zorgverleners;
5° het ondersteunen van de patiënt in het overleg en bewaken dat de patiënt voldoende beluisterd wordt (bv. formuleren gepersonaliseerde doelstellingen)
6° het overleg met adviserend arts / arbeidsarts in het kader van eventuele reïntegratie verzorgen
7° de opmaak van het verslag na elk overleg



Zorgcoördinatie-teamoverleg

- Organiseren teamoverleg
- Aanwezig:
  - Huisarts, andere zorgverleners, patiënt, (specialist)
  - Indien patiënt niet aanwezig bespreekt HA/ZC het behandelplan met hem/haar
  - Deelnamehonorarium van 20 € (ncl 400190)
- 1ste teamoverleg:
  - Bepalen wie zorgcoördinator is
  - Bespreken behandelplan en –afspraken en gepersonaliseerde doelstellingen volgens bestaande beschikbare richtlijnen
- Volgende overleggen bespreking en vervollediging
- Min 2x/6 maanden (max. 3 vergoed per 6 maanden)
- Laatste overleg kan beslist worden evt. 1malig verlenging 6 maanden
- Indien verdere behandeling niet meer nodig: beëindiging ZT
- Indien geen verbetering of verergering kan naar 2de lijn verwezen worden
- Teamoverleg fysiek, virtueel, hybride

Zorgtraject type 1 en 2



Pseudocode 400013 start zorgtraject
Voorschrift postcovid
Monodisc: K, P, L
Multidisc: + D, E, NP

Zorgcoördinatie en teamoverleg
Deelname teamoverleg code 400190

Voorjaar 2023

EINDE

1 LIVE UPDATE

2 Update Flash ONLINE!