# Long COVID

## Pathophysiology

### Exercise

* Lower VE/VCO2 slope (32.1 severe vs 32.9 normal; p = 0.068) (Cherneva et al., 2025)
* No difference in VE/VCO2 (Kersten et al., 2022)
* No difference in VE or VO2 (Samaranayake et al., 2023)
* No difference in VO2 at AT (Kersten et al., 2022)
* No difference in PetCo2
  + (Frizzelli et al., 2022)
* Lower max heart rate
  + (Contreras et al., 2023)
* Lower o2 delivery / utilization
  + Only 2 subjects demonstrated Respiratory Limitation (RL) (Baratto et al., 2021)
  + Lower SaO2 (Baratto et al., 2021)
  + 19.6 versus 17.1 (Baratto et al., 2021)
  + Lower A-VO2 difference with lower peripheral oxygen extraction, (Baratto et al., 2021)
  + Cardiac output
    - No difference in absolute values, but COVID has lower percentage of predicted values (Baratto et al., 2021)
  + No sign of ventilatory impairment, impaired o2 pulse and oxygen uptake capacity (Evers et al., 2022, p. 8)
* Earlier anaerobic threshold
  + Impaired fat metabolism from mitochondria 🡪 higher mean lactate [@deBoerDecreasedFattyAcid]
    - Not associated with COVID symptoms [@deBoerDecreasedFattyAcid]
  + (Frizzelli et al., 2022)
* Low OUES
  + Frizzelli et al., 2022)

### Muscular Strength

* No difference in grip strength
  + (Baker et al., 2023)
* No difference in neuromuscular transmission
  + (Baker et al., 2023)

### Pulmonary

* Lower SpO2 in PCS with fatigue
  + (Baker et al., 2023)

### Cardiac

* No difference in LVEF
  + (Baratto et al., 2021)
* Mildly dilated right ventricle
  + 40 mm vs 35 mm diameter (Baratto et al., 2021)
* Abnormal left or right ventricular strain
  + 1/3 (Baratto et al., 2021)
* Higher cardiac output and PAP at rest, similar total pulmonary resistance (TPR) (Baratto et al., 2021)

### Autonomic Nervous System (ANS)

* No difference in resting heart rate
  + 78 vs 77 (Contreras et al., 2023)
  + (Santos-de-Araújo et al., 2024)
* ANS not associated with dyspnea, fatigue, sleep, or most forms of neurocognitive dysfunction (concentration, memory) (Ladlow et al., 2022)
  + Was associated with poor attention
* ANS is associated with more lactate at rest (Ladlow et al., 2022)
* ANS is associated with higher VE/VCO2 (Ladlow et al., 2022)

## Mediators

### Respiratory

* Respiratory strength and endurance is not associated with VE/VCO2 or Breathing Reserve (Severin, 2022)
* MIP is not lower among OSA vs non-OSA (Rehling et al., 2017)

### Dyspnea

* Improvements in dyspnea are not associated with improvements in fatigue
  + r= 0.122 (insignificant) (Harenwall et al., 2022)
* Dyspnea is associated with reduced VO2 max
  + (Debeaumont et al., 2021)

### Vascular

* Lower EQI (EQI < 2) is NOT associated with:
  + - Sleep (Charfeddine et al., 2021)
* Improvement in endothelial function is NOT associated with improvements in fatigue, dyspnea, brain fog (Charfeddine et al., 2022)
  + Endothelial drug does NOT improve fatigue, dyspnea, brain fog

### Pulmonary

* SpO2 did not correlate with dyspnea severity
  + Long COVID (Paradowska-Nowakowska et al., 2023)

## Symptoms

### Fatigue

* Improvements in fatigue are associated with improvements in QOL
  + r = -0.371; p < 0.001 (Harenwall et al., 2022)

# Descriptive Statistics

## Age

* Age is associated with:
  + higher rates of fatigue
    - CFQ (Harenwall et al., 2022)
  + reduced activity tolerance
    - Borg scale (Paradowska-Nowakowska et al., 2023)
  + reduced FMD
    - [@riouReducedFlowMediatedDilatation2021]
  + more severe cognitive impairment
    - [@rabaiottiEffectsMultidisciplinaryRehabilitation2023]
    - less risk of cognitive impairment
      * (Bonner-Jackson et al., 2024)
* Age was not associated with:
  + Dyspnea
    - p = 0.372 (Paradowska-Nowakowska et al., 2023)
    - (Craparo et al., 2022)
  + Brain Fog
    - (Craparo et al., 2022)
  + Sensory Disorder

(Craparo et al., 2022)

## Gender

* Females are more likely to experience long COVID
  + [@charfeddineLongCOVID192021]
  + 63.6% (versus 41.1%) (Barbagelata et al., 2022)
  + Higher proportion of females (73.3%) versus controls (59.1%) (Bonner-Jackson et al., 2024)
  + Higher proportion of females (71%) versus controls (58%) (Contreras et al., 2023)
* Females are more likely to experience brain fog
  + (Orfei et al., 2022)
  + (Nordvig et al., 2023)
* Females are more likely to experience dyspnea
  + (Craparo et al., 2022)
* Females are more likely to experience more than 1 long COVID symptom
  + (Craparo et al., 2022)
* Males are more likely to experience brain fog
  + 42.3% of males (u = 6.45) versus 29.1% of females (u = 5.66) [@vyasMildCognitiveImpairment2022]
* Females have better respiratory values than men:
  + FEV1 / FVC
    - (Paradowska-Nowakowska et al., 2023)
* Females have better lung health than men
  + XRAYS/CT
    - (Paradowska-Nowakowska et al., 2023)
* Females have better exercise capacity
  + 6MWT
    - (Paradowska-Nowakowska et al., 2023)
* Females have worse exercise tolerance
  + Borg scale
    - (Paradowska-Nowakowska et al., 2023)
* Females have healthier hearts
  + LVEF
    - (Paradowska-Nowakowska et al., 2023)
* Females are more likely to report the following long COVID symptoms:
  + Myalgia
    - (Paradowska-Nowakowska et al., 2023)
  + Palpitations
    - (Paradowska-Nowakowska et al., 2023)
  + Increased or unstable blood pressure
    - (Paradowska-Nowakowska et al., 2023)
  + Impaired concentration
    - (Paradowska-Nowakowska et al., 2023)
  + Memory deterioration
    - (Paradowska-Nowakowska et al., 2023)
  + Worsened mood
    - (Paradowska-Nowakowska et al., 2023)
  + Sleep disorder
    - (Paradowska-Nowakowska et al., 2023)
  + Hair loss
    - (Paradowska-Nowakowska et al., 2023)
  + Dizziness
    - (Paradowska-Nowakowska et al., 2023)

CPET

* Higher proportion of women in the O2 delivery / utilization group (62.5%) compared to dysfunctional breathing group (46.7%) or the respiratory limitation group (17.9%)

## Ethnicity

* Black race was associated with lower likelihood of cognitive impairment

(Bonner-Jackson et al., 2024)

# IMT

## Outcomes

### Cardiac

* IMT does not improve LVEF
  + (Trevizan et al., 2021)
* IMT does not improve BNP
  + (Trevizan et al., 2021)

### Respiratory

* + Reduced EMGdi / EMG dimax (Langer et al., 2018)
* No change in phrenic nerve conductance
  + [@schaefferEffectsInspiratoryMuscle2023]
* No change in diaphragm EMG [@schaefferEffectsInspiratoryMuscle2023]
* No change in diaphragm thickness
  + (Benli et al., 2024)
  + (Spiesshoefer et al., 2024)
* Dyspnea
* IMT reduces dyspnea
  + Long COVID (McNarry et al., 2022)
  + MRC, TDI (Langer et al., 2018)
  + TDI [@schaefferEffectsInspiratoryMuscle2023]
  + DSI [@abodonyaInspiratoryMuscleTraining2021]
  + Long COVID, improved mmRC (3 to 2) and CRQ dyspnea domain (Spiesshoefer et al., 2024)
  + CHF, mMRC (Tanriverdi et al., 2023)
  + (Katayıfçı et al., 2022)
  + COPD meta-analysis SGRQ, TDI total, mMRC (Ammous et al., 2023)
* IMT does not reduce dyspnea
  + mMRC (Jimeno-Almazán et al., 2023) ## Inhalation
* IMT improves MIP
  + (Katayıfçı et al., 2022)
  + (Alwohayeb et al., 2018)
  + (Freeberg et al., 2023)
  + CKD (Campos et al., 2018)
  + CHF (Trevizan et al., 2021)
  + (Chen et al., 2023)
  + Long COVID (McNarry et al., 2022)
  + (Langer et al., 2018)
  + [@azeredoInspiratoryMuscleTraining2022]
  + (Del Corral et al., 2023), p. 5)
  + mean change: 21.43 meta-analysis [@chenCanInspiratoryMuscle2023]
  + [@schaefferEffectsInspiratoryMuscle2023]
  + CHF (Tanriverdi et al., 2023)
  + Long COVID, +79.4 versus +17.3 (Palau et al., 2022)
* IMT improves inspiratory muscle endurance
  + (Del Corral et al., 2023), p. 5)
  + CHF, ITL (Tanriverdi et al., 2023)
* IMT improves MIP but not above the MCID
  + COPD meta-analysis Mean: 14.57 cmH20 (Ammous et al., 2023)
* IMT improves S-index
  + (Yáñez-Sepúlveda et al., 2022)
* IMT improves SMIP
  + Long COVID (McNarry et al., 2022)
* IMT improves Fatigue Index Time (FIT)
  + Long COVID (McNarry et al., 2022)
* IMT does not improve TLC
  + RMT (Bisconti et al., 2018)
  + Long COVID (Spiesshoefer et al., 2024)

### Oxygen Saturation

* No improvement in SaO2 at nadir or baseline

[@krause-sorioInspiratoryMuscleTraining2021]

* IMT does not improve spO2

CKD (Campos et al., 2018)

* IMT not effective for improving oxygen saturation (spO2)
  + (Langer et al., 2018)

### Autonomic

* No change in LF/HF (Bisconti et al., 2018)
* IMT improves resting heart rate
  + (∆: −2.6 ± 2.9 bpm) (Yáñez-Sepúlveda et al., 2022)
  + CKD (Campos et al., 2018)
  + Long COVID (75 to 68) (Edgell et al., 2025)
* IMT does not improve HRV
  + RMT (Bisconti et al., 2018)

### Exercise Capacity

* No change in dyspnea during exercise
  + [@schaefferEffectsInspiratoryMuscle2023]
* IMT does not improve 6MWT
  + Long COVID, 6MWT, (Spiesshoefer et al., 2024)
* IMT does not improve respiratory rate during CPET
  + CKD (Campos et al., 2018)
* IMT not effective for improving peak workload (W)
  + (Trevizan et al., 2021)
* IMT not effective for improving VO2max / Peak VO2
  + (Trevizan et al., 2021)
* IMT not effective for improving ventilation (Ve)
  + (Langer et al., 2018)
  + [@schaefferEffectsInspiratoryMuscle2023]
* No change in ventilatory efficiency (VE/VCO2)
  + Long COVID (Palau et al., 2022)
* No change in VO2, VE, VE/VO2, RER
  + (Archiza et al., 2018)

### Quality of Life / Functional Capacity

* IMT improves QOL
  + (Katayıfçı et al., 2022)
  + CHF (Trevizan et al., 2021)
  + COPD (Ammous et al., 2023)
  + Long COVID (McNarry et al., 2022)
  + [@abodonyaInspiratoryMuscleTraining2021]
  + CHF, MLHFQ and SF-36 (physical functioning subscale score only)(Tanriverdi et al., 2023)
* IMT does not improve QOL
  + (Del Corral et al., 2023), p. 5)
  + meta-analysis [@chenCanInspiratoryMuscle2023]
  + Long COVID, EQ visual analogue scale (Palau et al., 2022)
* IMT does not improve functional status
  + PCFS (Jimeno-Almazán et al., 2023)
  + Long COVID, Mobility and self-care EQ subdomain (Palau et al., 2022)
* IMT does not increase physical activity
  + (Freeberg et al., 2023)
  + CHF (Tanriverdi et al., 2023)

### Sleep

* No improvement in AHI/RDA
  + [@krause-sorioInspiratoryMuscleTraining2021]

### Fatigue

* IMT does not reduce fatigue
  + ESS [@krause-sorioInspiratoryMuscleTraining2021]
  + FSS, CFS (Jimeno-Almazán et al., 2023)

### Strength

* IMT improves LE strength
  + 60 second sit-to-stand (Del Corral et al., 2023), p. 5)
* IMT does not improve UE strength
  + Grip HHDT (Del Corral et al., 2023), p. 5)
  + Bench 1RM and Grip HHDDT (Jimeno-Almazán et al., 2023)
* IMT does not improve LE strength
  + (Jimeno-Almazán et al., 2023)

### Working Memory

* IMT does not improve working memory
  + (Freeberg et al., 2023) ## Inhibitory Control
* IMT does not improve inhibitory control
  + (Freeberg et al., 2023)

### Attention

* IMT does not improve attention
  + (Freeberg et al., 2023)

### Language

* IMT does not improve vocabulary or oral reading recognition
  + (Freeberg et al., 2023)

### Executive Function

* IMT does not improve executive function
  + (Freeberg et al., 2023)

### Processing Speed

* IMT does not improve processing speed
  + (Freeberg et al., 2023)

### Psychological

* IMT does not improve mental health
  + SF-MH (Jimeno-Almazán et al., 2023)
* IMT does not reduce anxiety
  + GAD7 (Jimeno-Almazán et al., 2023)
* IMT does not reduce depression
  + PHQ9 (Jimeno-Almazán et al., 2023)
* IMT reduces depression and anxiety
  + Long COVID, depression anxiety EQ subdomain (Palau et al., 2022)
* IMT improves mental health
  + PAH -- NHP emotional regulations (Saglam et al., 2015)

### Musculoskeletal

* IMT reduces back pain
  + VAS [@ahmadnezhadInspiratoryMuscleTraining2020]
* IMT reduces “high-threshold” global strategy
  + Decreased RA, erector spinae activity [@ahmadnezhadInspiratoryMuscleTraining2020]
* IMT increases “low-threshold” local strategy
  + Increased TA, multifidus [@ahmadnezhadInspiratoryMuscleTraining2020]
* IMT does not improve balance
  + CHF, (Tanriverdi et al., 2023)
* IMT does not reduce myalgia
  + Long COVID, pain/discomfort EQ subdomain (Palau et al., 2022)

### Vascular

* IMT does not improve PWV
  + No acute change in response to single session (Tavoian et al., 2023)
  + [@Craighead2019InspiratoryMuscleStrength]
* No change in absolute % change, but significant improvement in shear rate (SR) and FMD normalized for shear (%FMD/SR) (Bisconti et al., 2018)
* Increased Diameter peak (Bisconti et al., 2018)
* Blood flow AUC response is 29% lower following RMT training (Bisconti et al., 2018)

## Placebo

justments every week following new MIP assessments. The SHAM group performed the same protocol using 15% of MIP as training load, which is known to elicit negligible training effects (Volianitis et al., 2001).

## Duration

* 12 weeks
  + (Miozzo et al., 2018)
  + (Sadek et al., 2022)
  + improvements initially became apparent at week 3 and continued to increase through week 12 (Winkelmann et al., 2009)
  + (Elshafey & Alsakhawi, 2022)
  + (Dos Santos et al., 2019)
  + [@azeredoInspiratoryMuscleTraining2022]
  + (Palau et al., 2022)
* 4 months
  + (Trevizan et al., 2021)
* 6 months
  + [@schaefferEffectsInspiratoryMuscle2023]
* 4 weeks
  + (Alwohayeb et al., 2018)
  + (Bhatnagar et al., 2021)
* 8 weeks
  + (Del Corral et al., 2023)
  + [@ahmadnezhadInspiratoryMuscleTraining2020]
  + (Langer et al., 2018)
  + (Campos et al., 2018)
  + (Tanriverdi et al., 2023)
* 5 days
  + (Benli et al., 2024)
* 2 weeks
  + [@abodonyaInspiratoryMuscleTraining2021]

Some previous research has found that the benefits of IMT can continue to increase for up to 13 weeks (Krause-Sorio 2021).

# Methods

## Ethics

### Informed Consent

For those who elected to participate in the study, the informed consent document was signed and stored in a locked cabinet accessible to IPL members.

## Analysis

### ANCOVA

Patients with lower baseline MIP are more likely to improve inspiratory strength and functional exercise performance (Gosselink et al., 2011).