NIH Blueprint for Neuroscience Research

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Beyond the Symptom: The Biology of Fatigue
September 27 – 28, 2021

Fatigue in Acute to Chronic Disease

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Disclaimer and Disclosures

Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure

This certifies that I, Josh Fessel, have no financial relationship that is relevant to the subject matter of this presentation.

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The Challenge of Fatigue

- "How am I doin'? Doc, I tell ya, I'm not."
- Fatigue vs. fatigability
  - Fatigue as subjective sensations, fatigability as objectively measured performance changes[1]
- Dimensions of fatigue
  - Initiation/activation energy vs. stamina
  - Physical, mental, emotional energy – others?
- Lack of standardization in clinical practice and in research
  - Parallels to "dizziness" or "altered mental status"

1. Kluger BM, Krupp LB, & Enoka RM. *Neurology* 2013;80:409–416

The Challenge of Fatigue

- Complaint/report of fatigue should probably trigger more focused questioning
- Clinically, some causes of fatigue may require a longer diagnostic and/or therapeutic journey
  - People may need time to recall important details
  - Trust may need to be built
- May be true of research focusing on fatigue as well
  - Balancing depth of detail against participant burden and against cost

1. Kluger BM, Krupp LB, & Enoka RM. *Neurology* 2013;80:409–416

COVID-19 as of 9 September 2021, 19:30 GMT -05:00

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

Last Updated at (M/D/YYYY)
9/6/2021, 1:21 PM

Total Cases	Total Deaths	Total Vaccine Doses Administered
220,957,255	4,571,729	5,480,646,636

28-Day Cases	28-Day Deaths	28-Day Vaccine Doses Administered
17,963,504	273,411	979,103,694

Cases | Deaths by Country/Region/Sovereignty

US
28-Day: 4,181,179 | 31,529
Totals: 39,973,912 | 648,714

India
28-Day: 1,057,667 | 12,443
Totals: 33,027,621 | 440,752

Iran
28-Day: 970,678 | 16,659
Totals: 5,156,986 | 111,257

United Kingdom
28-Day: 912,423 | 2,923
Totals: 7,051,345 | 133,598

Brazil
28-Day: 725,107 | 20,477
Totals: 20,890,779 | 583,628

Malaysia
28-Day: 582,295 | 7,470
Totals: 1,862,187 | 18,491

France
28-Day: 549,812 | 2,974
Totals: 6,921,986 | 115,413

Russia
28-Day: 549,734 | 21,787
Totals: 6,929,862 | 184,672

Japan
28-Day: 543,303 | 1,074
Totals: 1,583,617 | 16,409

Thailand
28-Day: 524,029 | 6,651
Totals: 1,294,522 | 13,042

Turkey
28-Day: 516,406 | 4,912
Totals: 6,412,247 | 57,000

Indonesia
28-Day: 462,989 | 28,765
Totals: 4,133,433 | 136,473

Mexico
28-Day: 456,567 | 18,720

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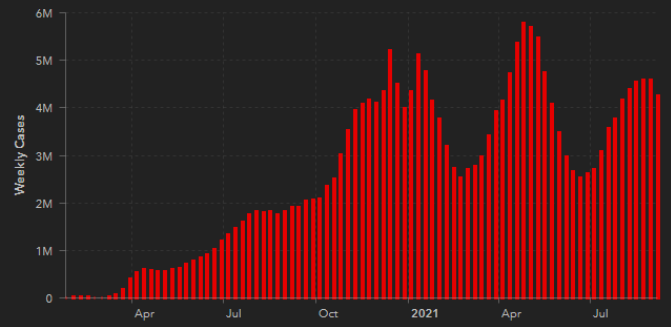

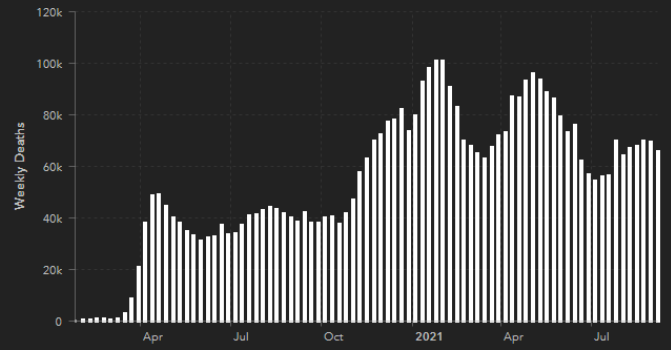

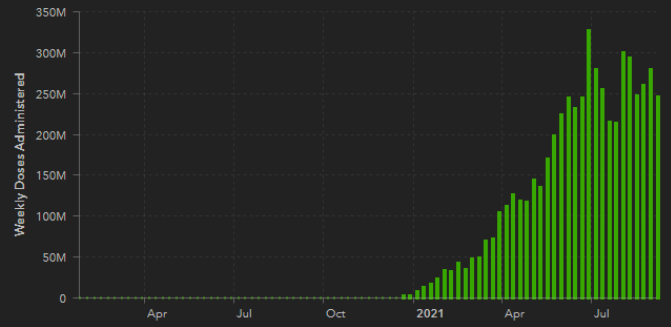

Admin0 | Admin1 | Admin2 | 28-Day | Totals | Incidence | Case-Fatality Ratio | Global Vaccinations | US Vaccinations | Terms of Use | Weekly | Daily

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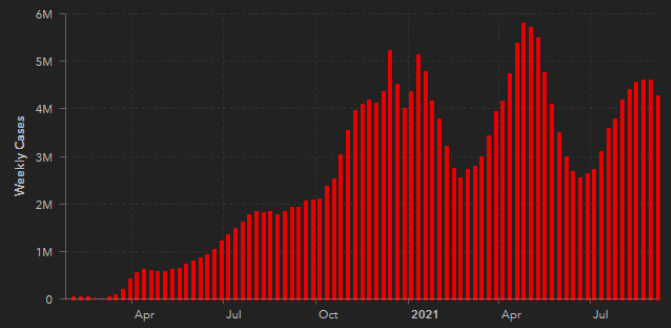
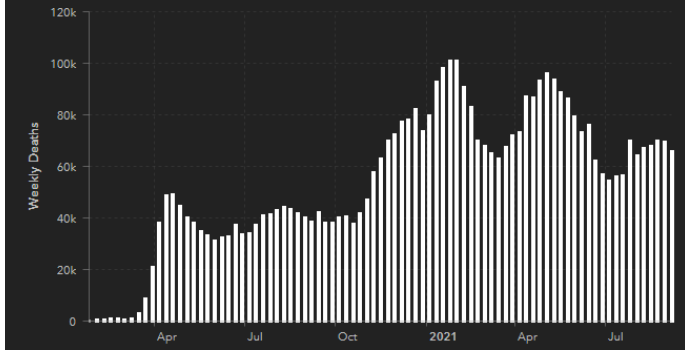
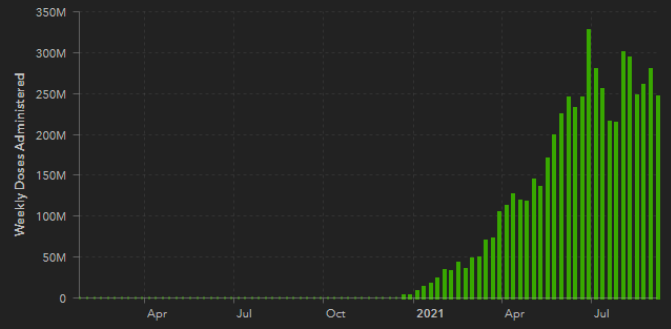
Indonesia	462,989	28,765	4,133,433	136,473
Mexico	456,567	18,720		

- Most people survive acute COVID-19 at present
- For many COVID-19/SARS-CoV-2 survivors, symptoms can linger for weeks or months after the acute illness
  - For some, the lingering symptoms are worse than those of the acute illness
- Fatigue is one of the most commonly reported and most problematic sequelae of acute SARS-CoV-2 infection
- A problem that affects even 1% of people with COVID-19 represents a global affected population of over 2.2 million people… as of September 9, 2021
  - Estimate was 1.2 million in March 2021







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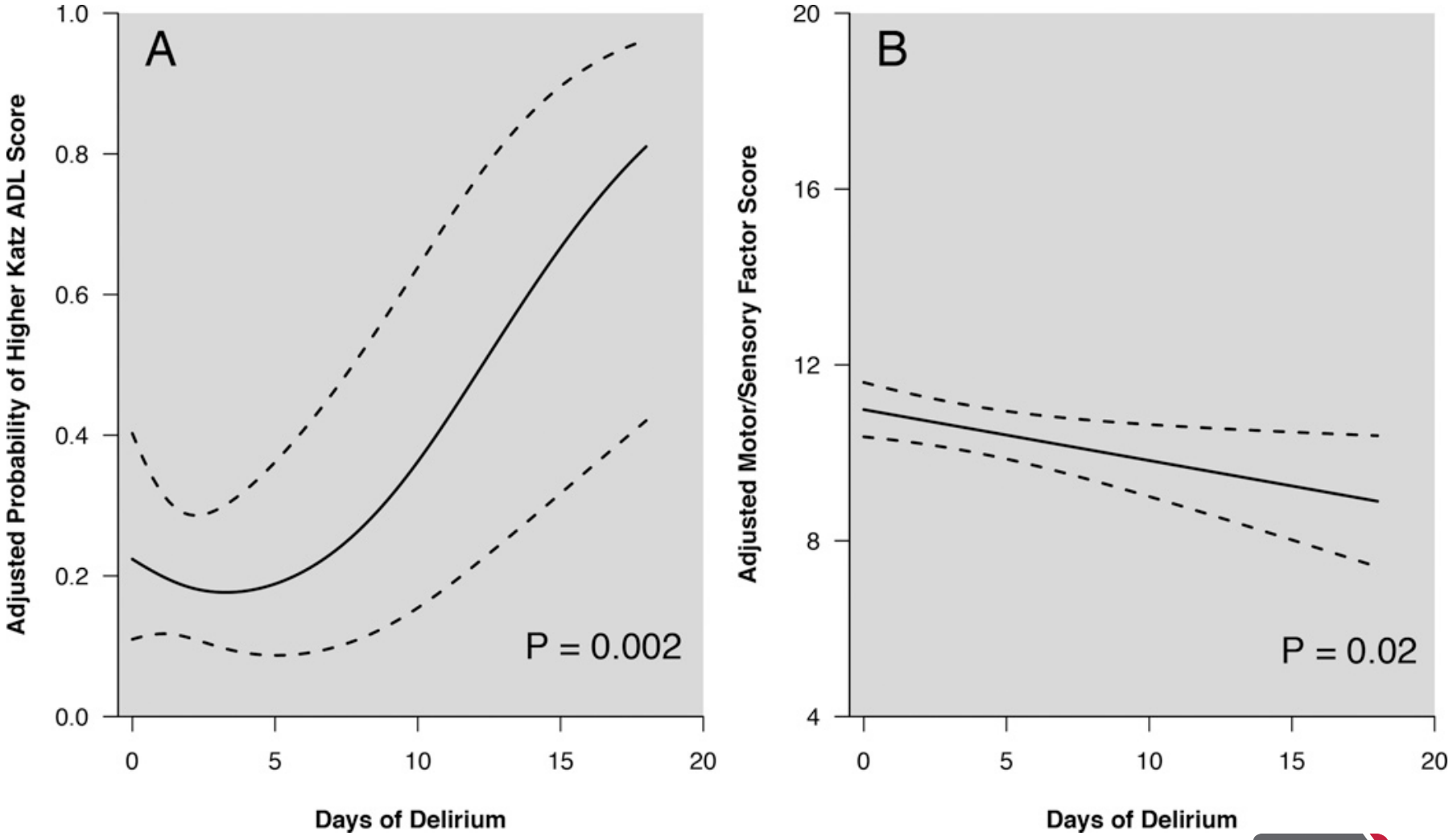
Fatigue and Acute Disease

- Extremely common symptom
- Many contributing causes
  - Acute inflammation, pain, sleep disturbance, hypoxia, hypercapnia, electrolyte disturbances, nitrogenous waste metabolites, nutritional disruption, effects of treatments, etc.
- Challenging to assess in acute setting
  - Hard to disentangle specific causes
  - Features of acute illness can complicate assessment and interpretation of fatigue
    - Fatigue vs. decreased LoC vs. encephalopathy vs. delirium vs. other

Fatigue and Acute Disease

- Often assumed that:
  - addressing cause of acute illness will address most associated clinical features, including fatigue
  - there will be a complete return to pre-illness baseline, including with respect to fatigue
- Assumptions may not be correct
- May be missing opportunities to intervene in the acute phase
- Example of critical illness delirium may be illustrative

ICU Delirium and Longer-Term Disability



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2. Brummel NE et al. *Crit Care Med*. 2014 Feb; 42(2): 369–377.

ICU Delirium and Longer-Term Disability

Multivariable models for delirium duration (N=304)

Model 1: Effect of Use of Opioids or Benzodiazepines Controlling for Dementia, Use of Haloperidol, and Baseline Health Status[†]		
Risk factor for Delirium Duration	Rate Ratio (95% CI)	P-value[*]
Benzodiazepine or opioid use	1.64 (1.27-2.10)[§]	<0.001
Control Variables		
Dementia (IQCODE >3.3)	1.19 (1.07-1.33)	0.002
Haloperidol	1.35 (1.21-1.50)	<0.001
APACHE II Score (minus the Glasgow Coma Scale)	1.01 (1.00-1.02)	0.02
Model 2: Modification of Effect of Use of Opioids or Benzodiazepines by Dementia Status: Controlling for Use of Haloperidol and Baseline Health Status[†]		
Risk factor for Delirium Duration	Rate Ratio (95% CI)	P-value[*]
Effect of benzodiazepines or opioids when dementia is absent	2.42 (1.65-3.55)	<0.001
Effect of benzodiazepines or opioids when dementia is present	1.08 (0.78-1.50)	0.64
Model 3: Modification of Effect of Use of Haloperidol by Dementia: Controlling for Use of Opioids or Benzodiazepines and Baseline Health Status[†]		
Risk factor for Delirium Duration	Rate Ratio (95% CI)	P-value[*]
Effect of haloperidol when dementia is absent	1.47 (1.29-1.69)	<0.001
Effect of haloperidol when dementia is present	1.15 (0.96-1.37)	0.14

Abbreviations: IQCODE-Informant Questionnaire on Cognitive Decline in the Elderly, APACHE-Acute Physiology and Chronic Health Evaluation.

[†]The deviance divided by the degrees of freedom for the three models are respectively 0.95, 0.92, and 0.93, providing no evidence of overdispersion.

[*]P-values are calculated for the Likelihood Ratio Chi-square statistic.

[§]Bootstrapped results for this model coefficient yielded a slightly larger but significant confidence interval: RR, 1.67, 95% CI, 1.17, 2.27.

- Use of benzodiazepines or opioids associated with longer duration of first episode of ICU delirium
- Bigger effect when baseline dementia and haloperidol use controlled for
  - Rate ratio 2.42

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3. Pisani MA et al. *Crit Care Med*. 2009 Jan; 37(1): 177–183.

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Might there be parallels for fatigue in acute illness and acute-to-chronic transitions?

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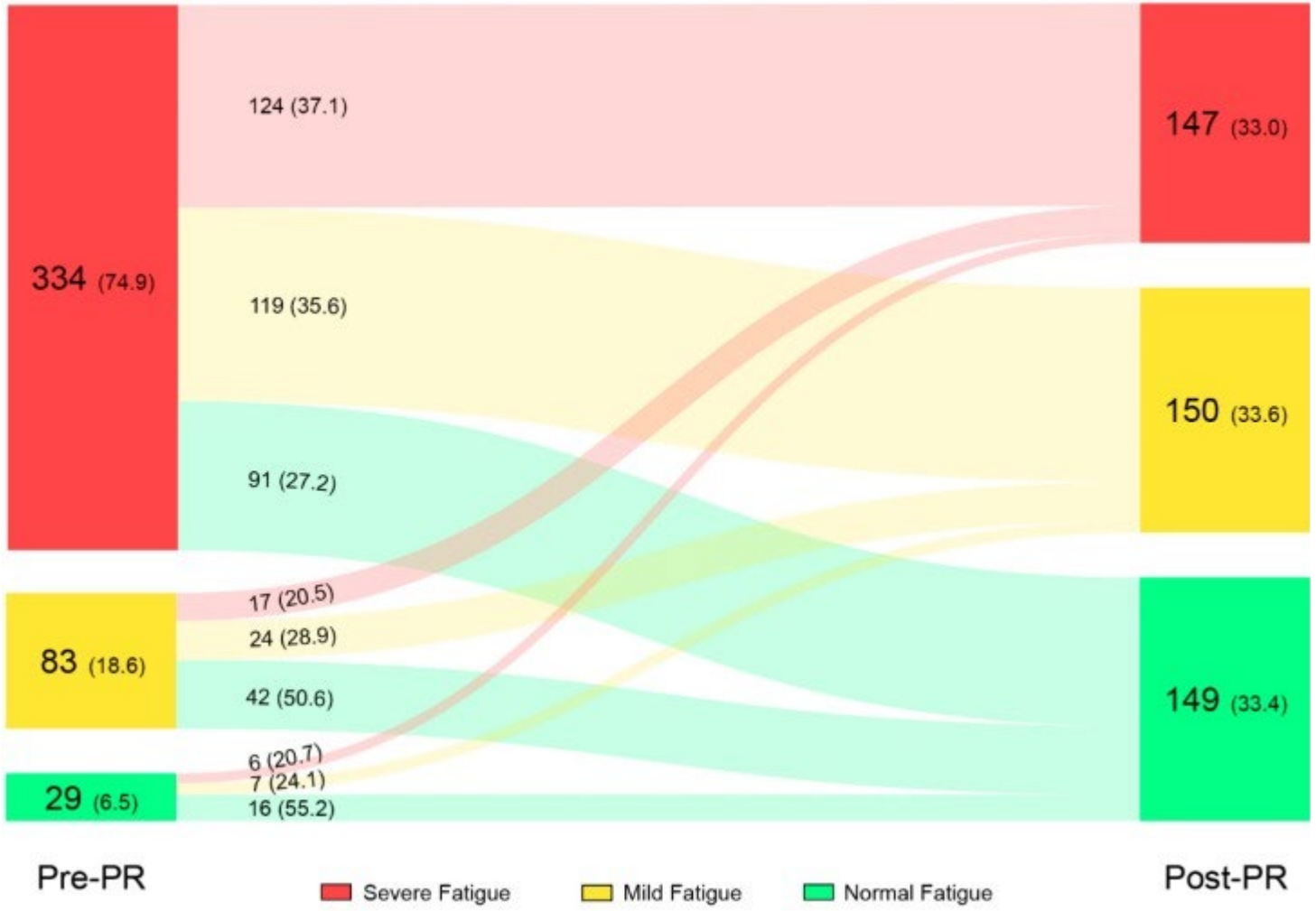
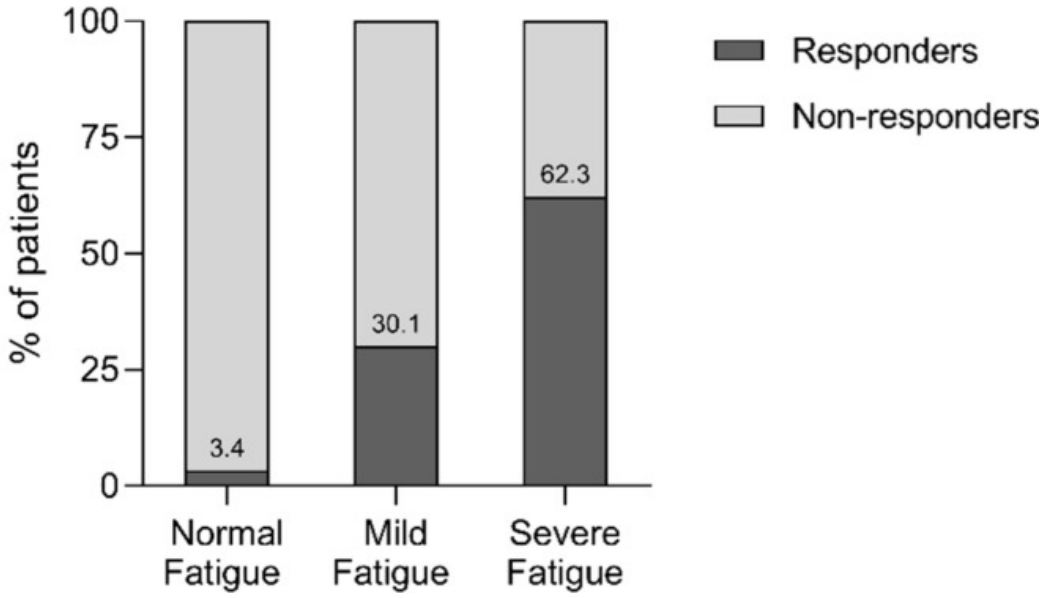
Fatigue and Chronic Disease

- Fatigue is extremely common in a wide variety of chronic diseases
- Can manifest during recovery and rehabilitation from acute illness, even if not a prominent feature of the acute illness itself
- Wide variety of contributing causes
  - Chronic inflammation, sleep disturbance, nutritional disturbance, chronic organ dysfunction, pain, muscle loss, polyneuropathy, etc.
- Often approach is to try to improve underlying condition(s), hoping fatigue and other associated symptoms will improve

Chronic Fatigue – What Helps Depends on Context



Pulmonary rehab reduces fatigue in people with COPD…



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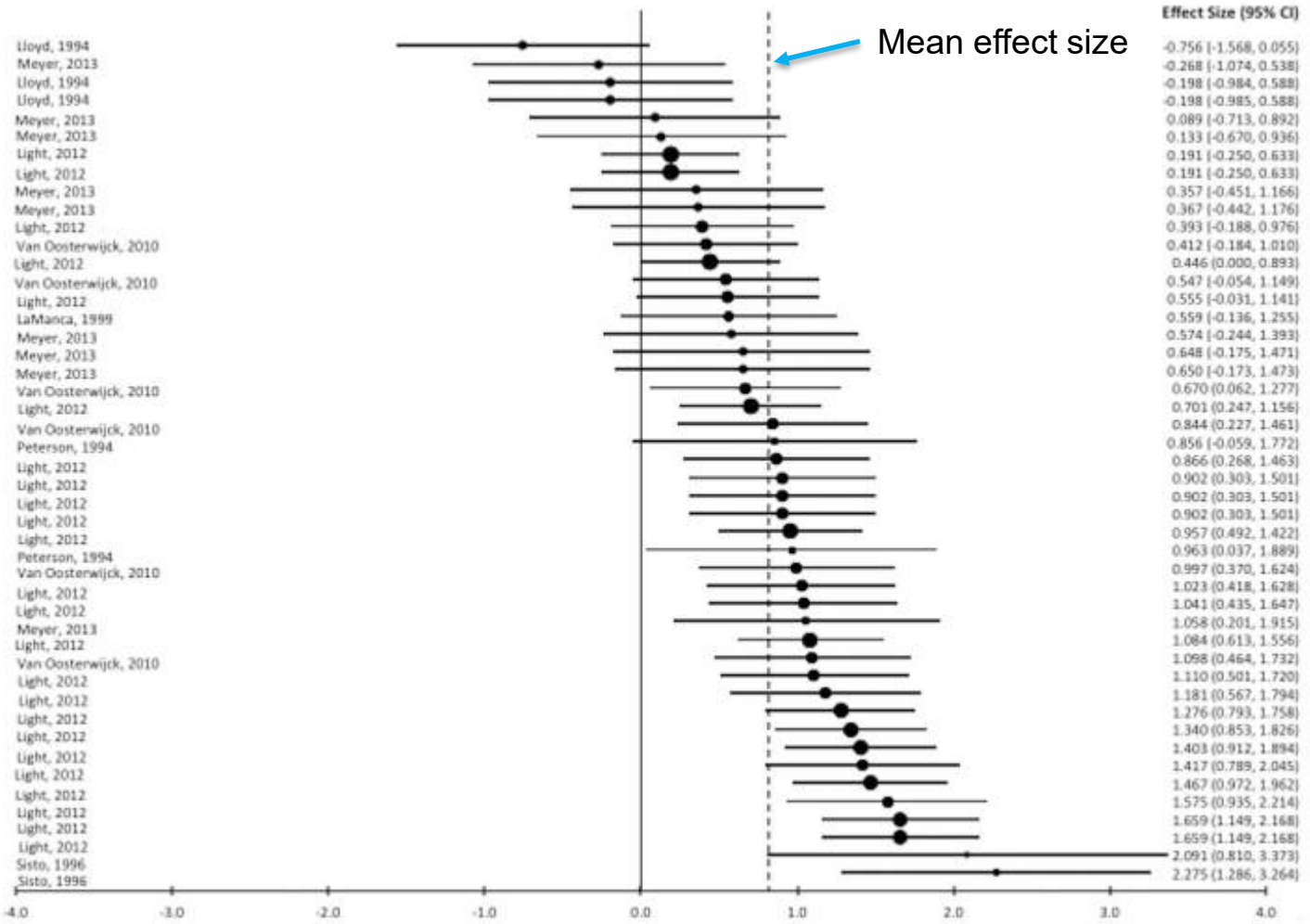
4. Van Herck M et al. *J Clin Med*. 2019 Aug 20;8(8):1264. doi: 10.3390/jcm8081264

Chronic Fatigue – What Helps Depends on Context



… but physical activity can actually make fatigue ***worse*** for people with ME/CFS/SEID.

- Studies are variable
- Post-exertional malaise is variable
- Despite variability, PEM findings have held up in subsequent meta-analyses
  - e.g., Wormgoor MEA & Rodenburg SC, *J Transl Med* 2021

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5. Loy BD et al. *Med Sci Sports Exerc*. 2016 Oct;48(10): 2003-2012.

Summary

- Fatigue is a very common feature of acute and chronic diseases
  - Causes/contributing factors may differ
  - Greater understanding of particulars of fatigue may improve both research and clinical care
- Opportunities to intervene in acute setting?
- Effective treatments for fatigue can be highly context-dependent
- I am ***not*** a fatigue expert, and I look forward to learning a lot from this workshop!