Towards making Ireland the best place in the world to grow old

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Staidéar Fadaimseartha na hÉireann um Dhul in Aois

The Irish Longitudinal Study on Ageing

Associations between entropy in cardiovascular/ neurovascular measures and frailty

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The Irish Longitudinal Study on Ageing

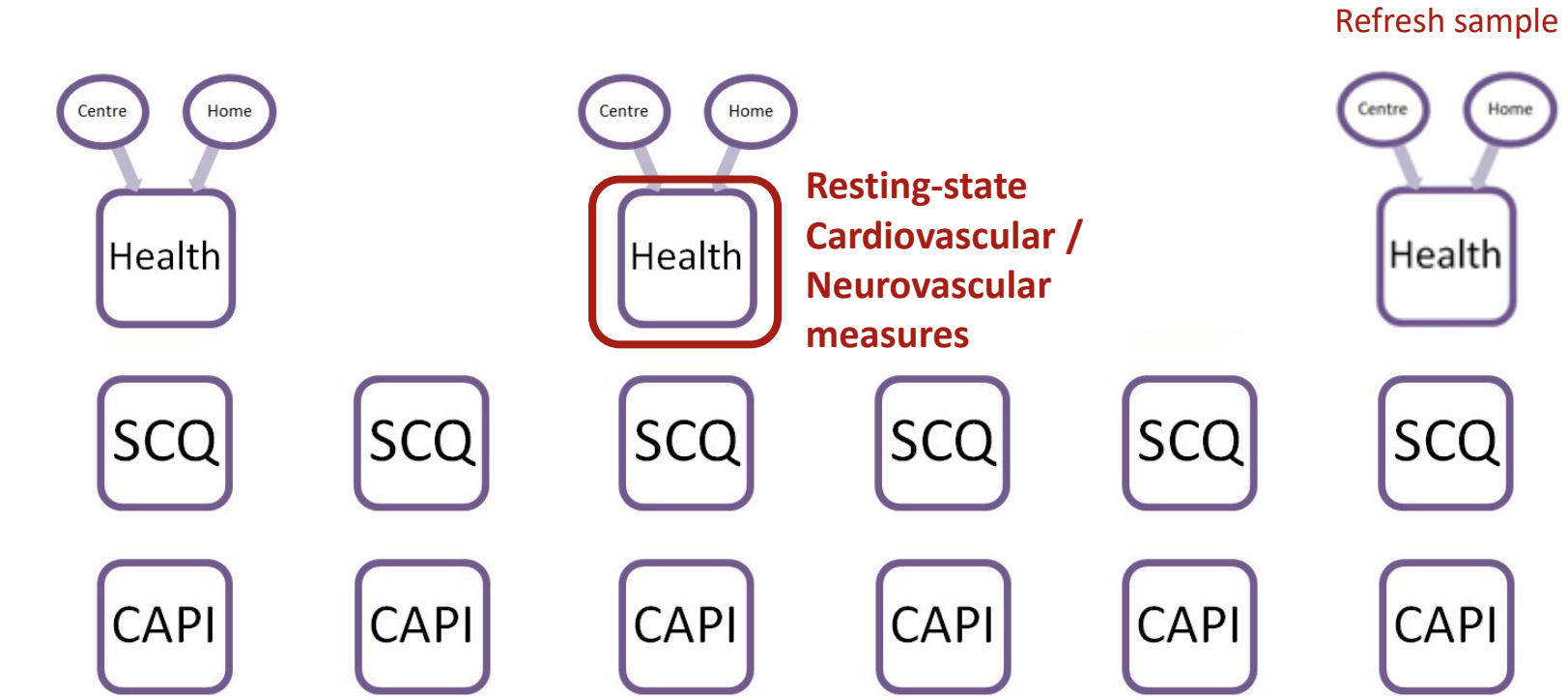
- Nationally representative sample

- Over 8,500 participants

- Running for 10+ years (est. 2009)

The most comprehensive study of ageing ever conducted in Ireland

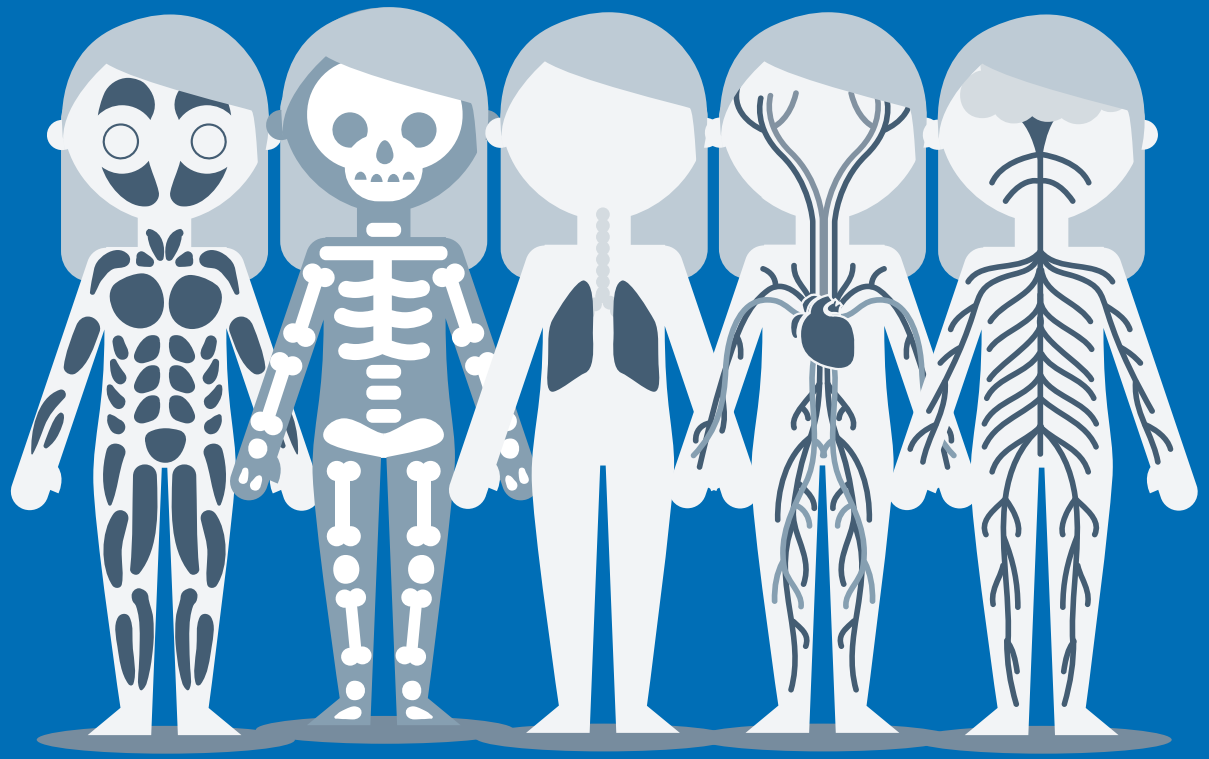
Data collection every 2 years for interview, every 4 - 6 years for health assessment



CAPI: computer-assisted personal interview
SCQ: self-completion questionnaire
Health: TILDA health assessment

Frailty **is a biologically driven decrease in reserve and resistance to stressors**

It results from *collective declines across multiple physiological systems*



Frailty **causes increased vulnerability to adverse outcomes such as mortality, institutionalisation, falls, and hospitalisation[1-4]**

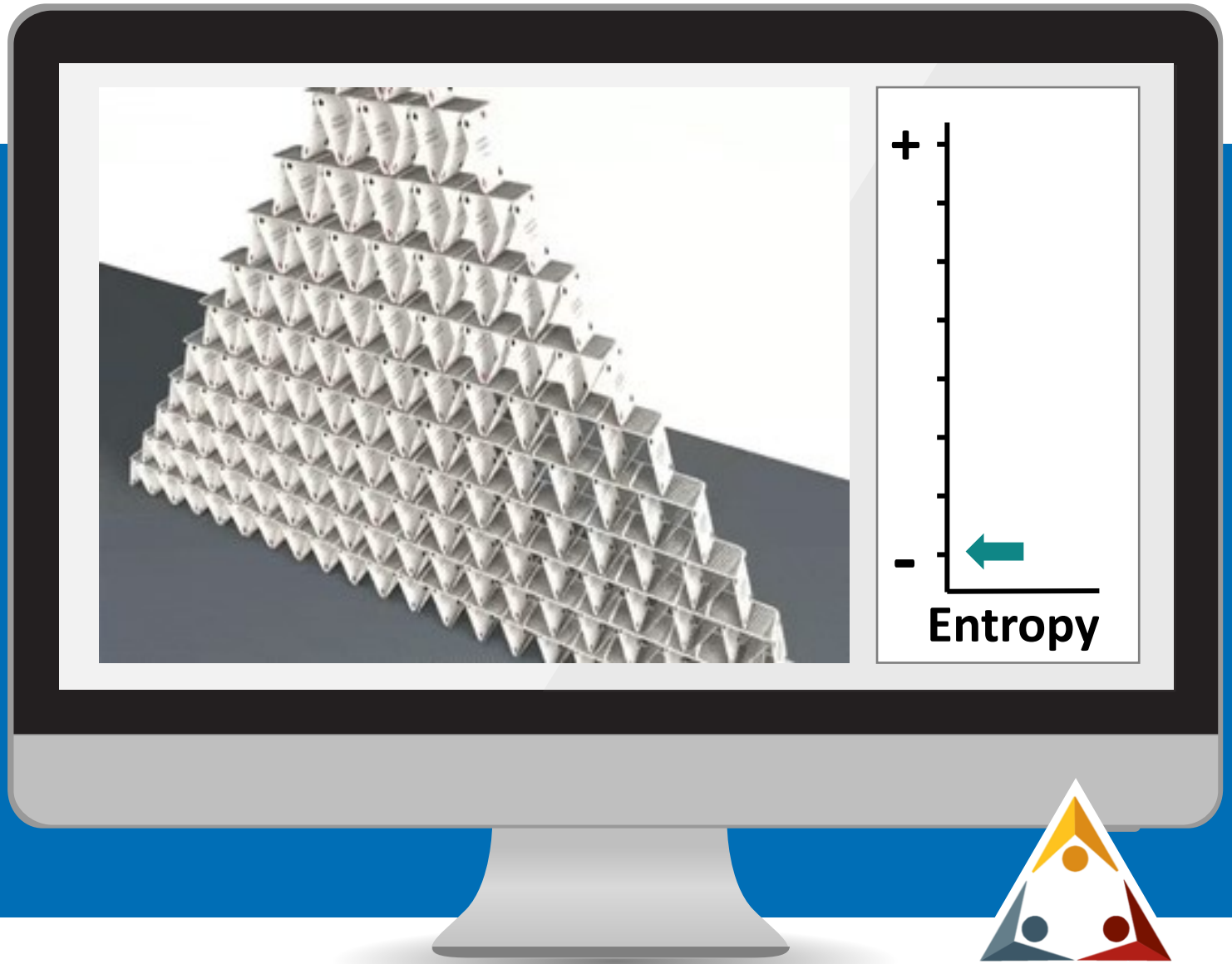
It is important to detect frailty early - *before* it manifests as a visible disability

Research has shown that interventions can delay and even reverse frailty, especially when it presents in the early stages[4,5]

[1] Fried L. et al. *J Gerontol A Biol Sci Med Sci* 2001 [2] Rockwood, K. et al. *Lancet* 1999
[3] Speechley, M. & Tinetti, M., *J Am Geriatr Soc* 1991 [4] Winograd, C. H., *J Am Geriatr Soc* 1991
[5] Dent, E. et al. *Lancet* 2019 [6] Travers, J. et al. *Br J Gen Pract* 2019,

Entropy is a measure of the amount of ‘disorder’ in a closed system

Higher Entropy indicates *Greater* Disorder



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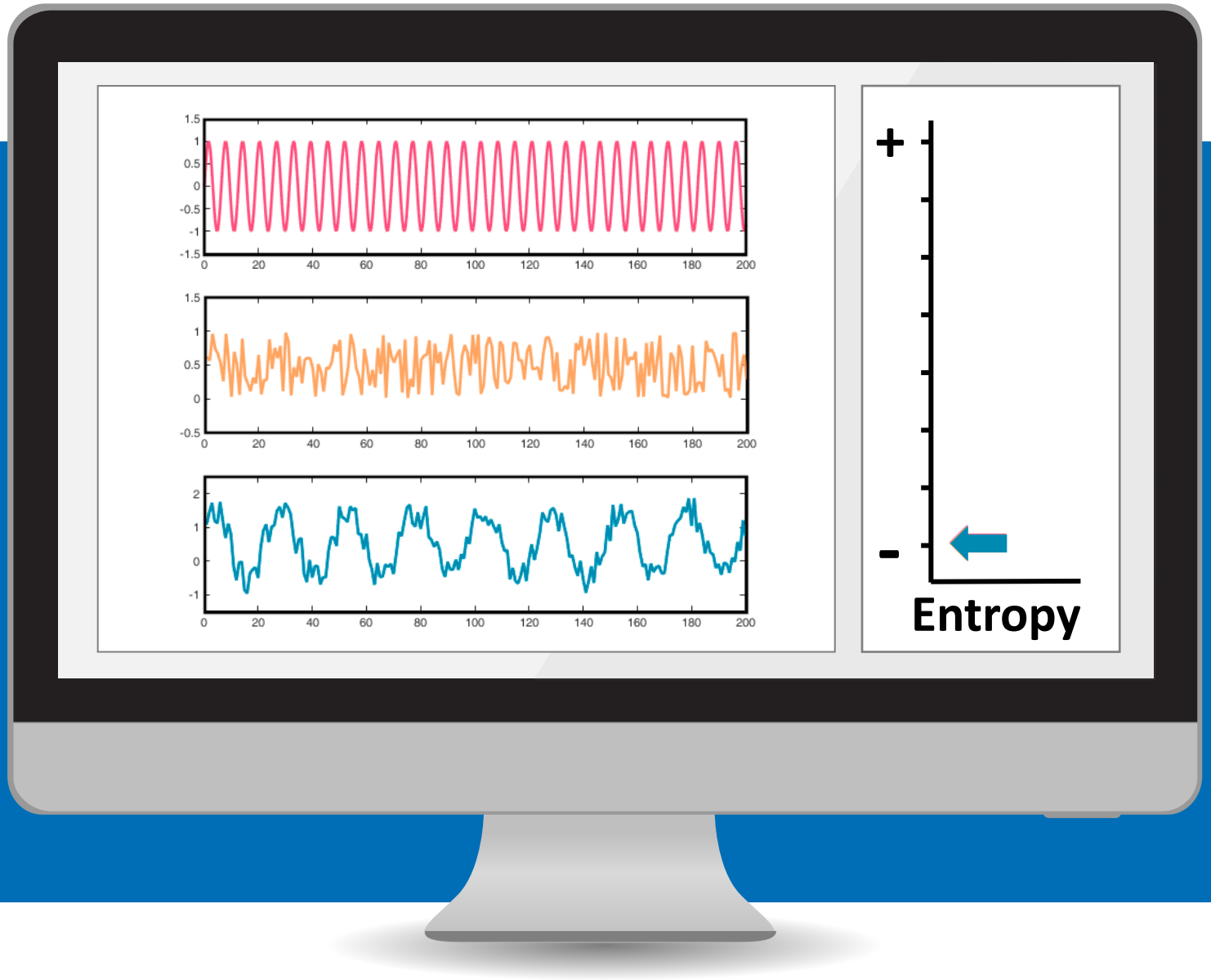
Entropy **can be used to quantify disorder in physiological signals**

In this study we used two methods:

Approximate Entropy (ApEn)

and

Sample Entropy (SampEn)

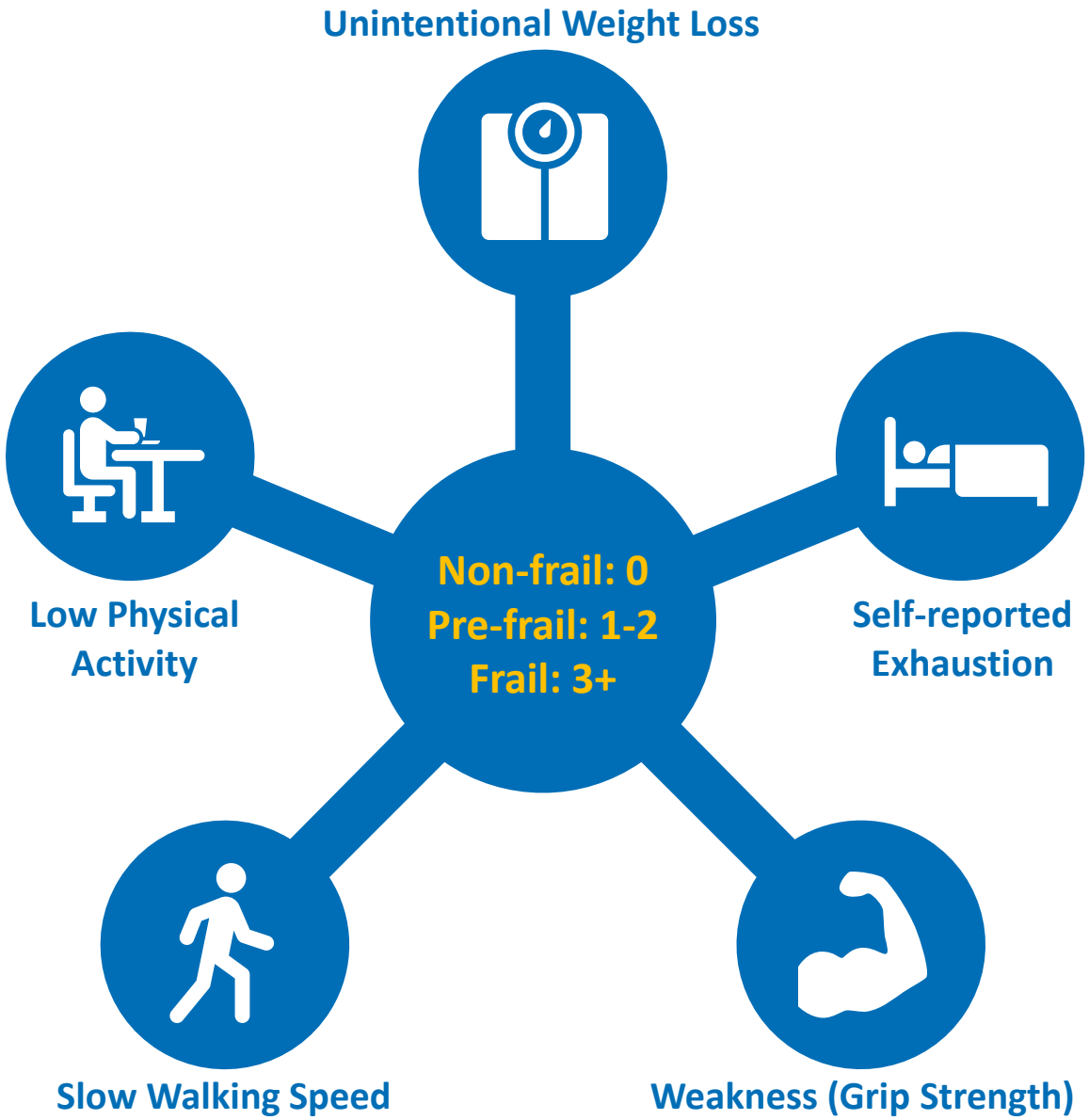


Can we detect subtle signs of frailty in the neurocardiovascular system using signal entropy?..

Research Question:

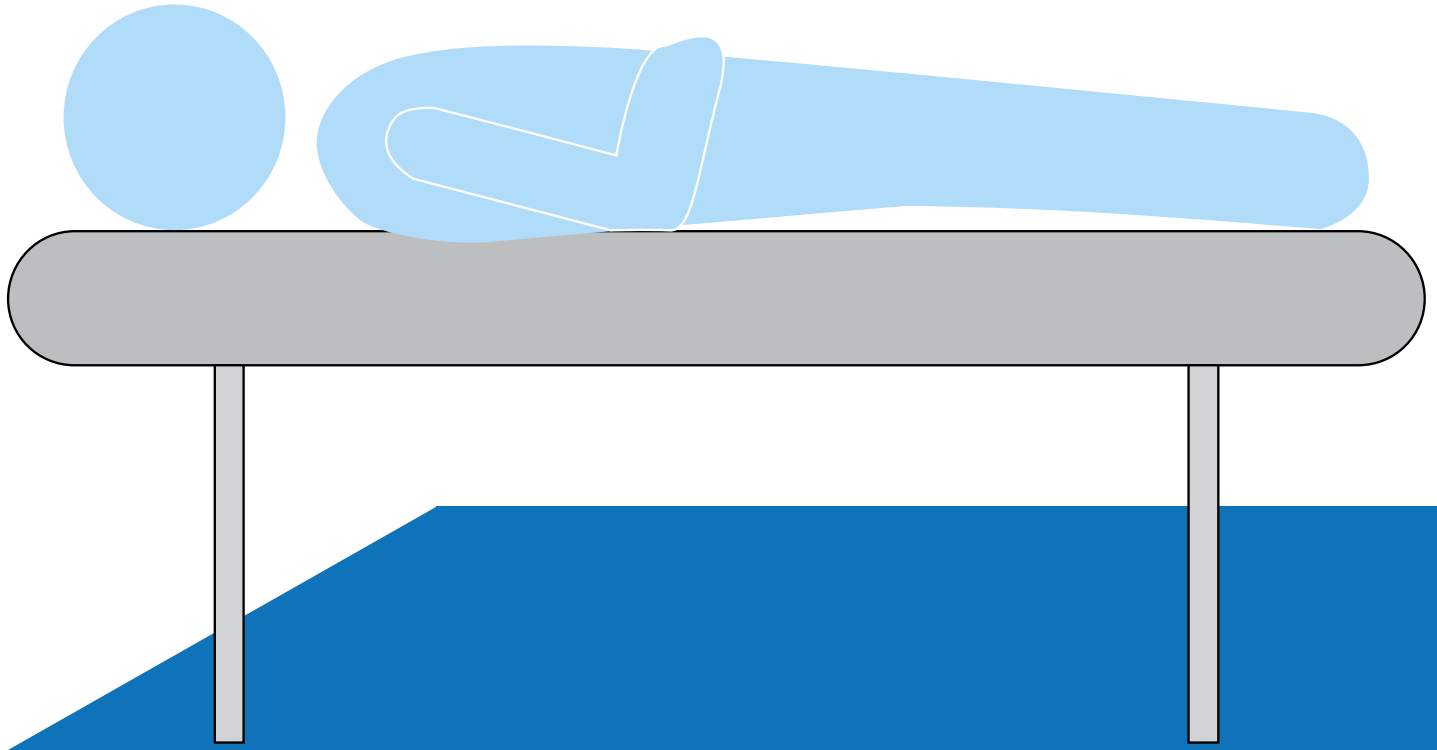
Is cardiovascular and neurovascular signal entropy associated with pre-disability frailty status?

Fried's Frailty Phenotype used: 5 Components



Active Stand Protocol

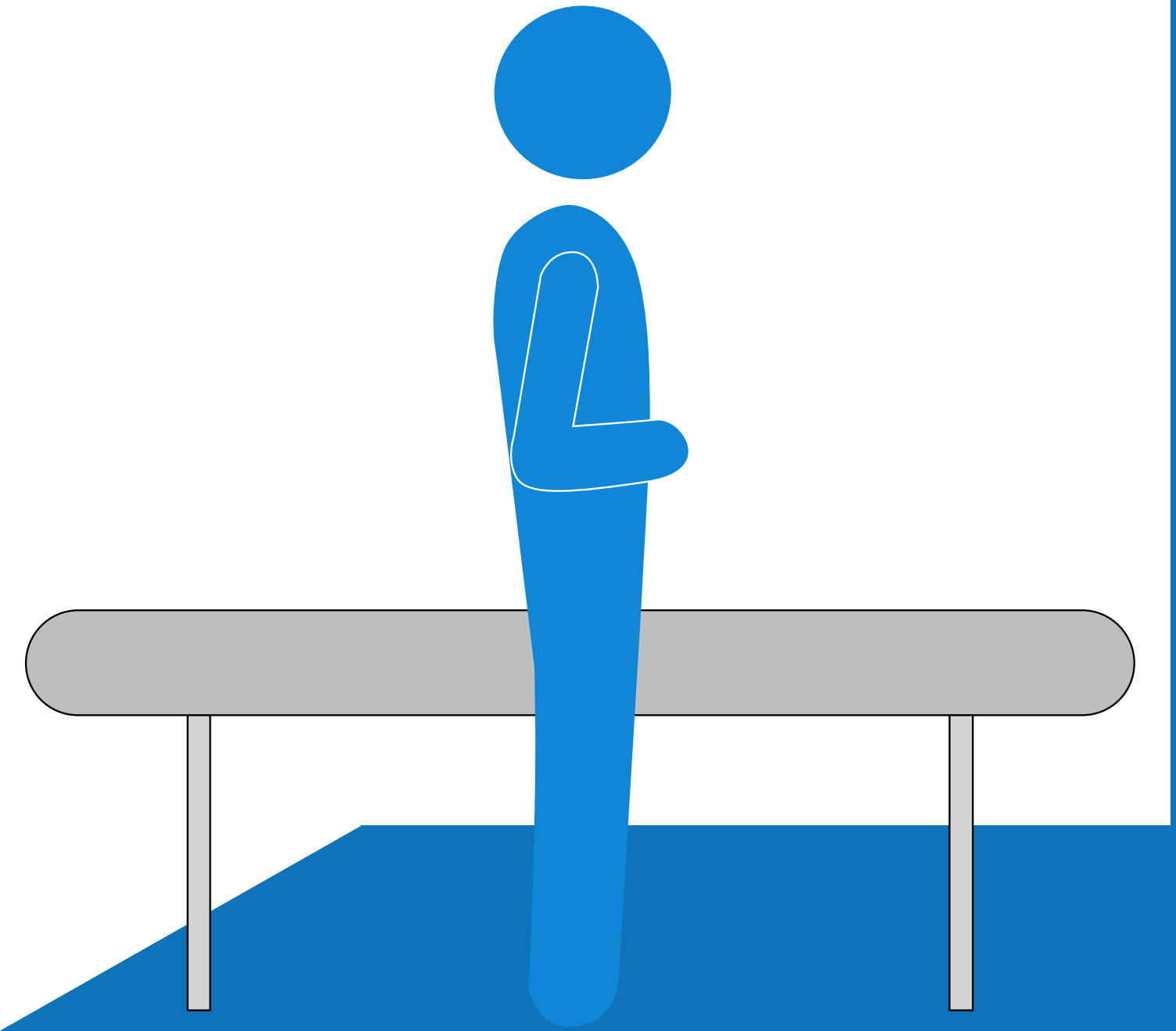
‘Rest’ - Participants laid supine for ~10 minutes



Active Stand Protocol

‘Rest’ - Participants laid supine for ~10 minutes

‘Challenge’ - Participants asked to stand (unassisted) as fast as possible

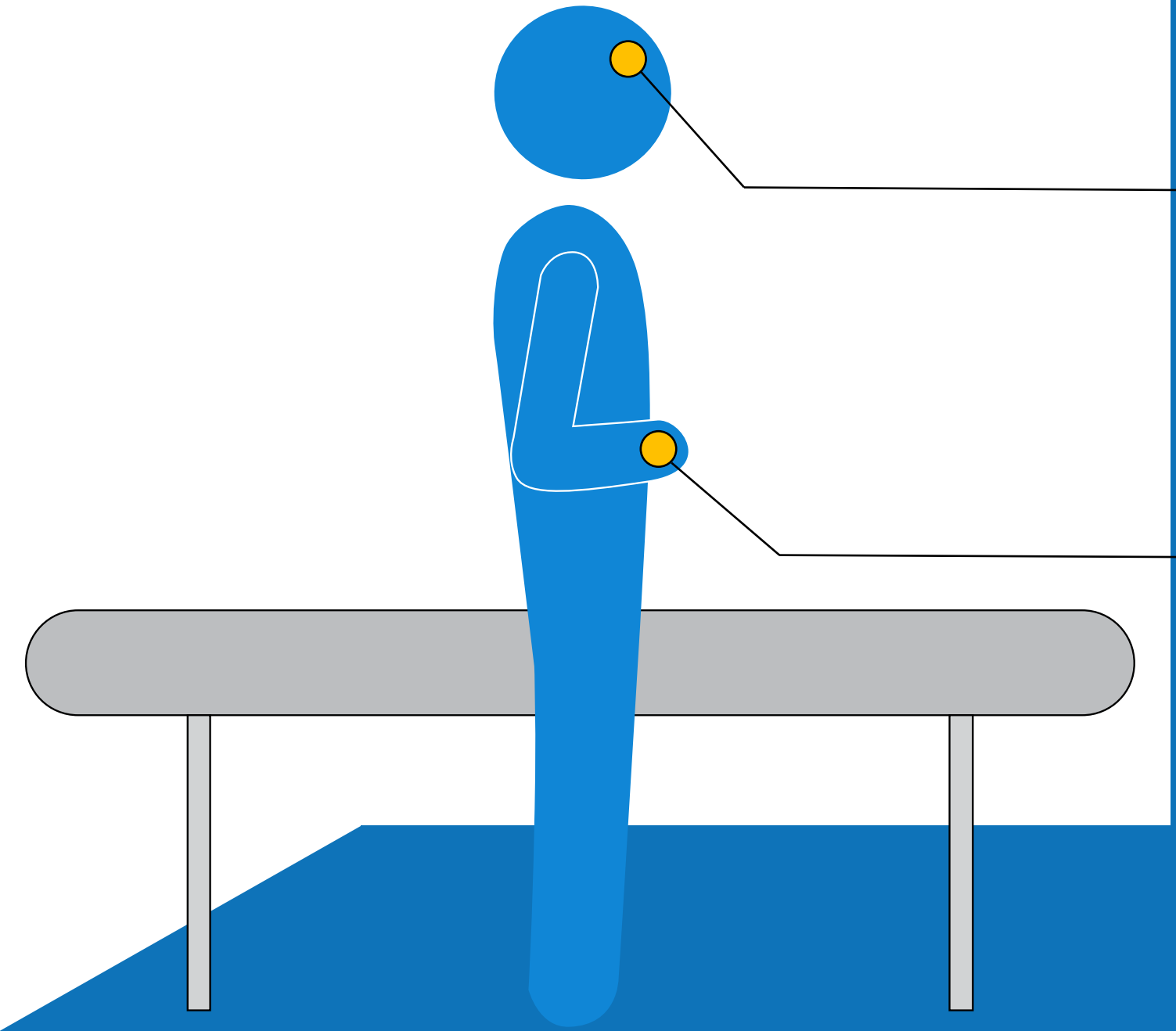


Active Stand Protocol

‘Rest’ - Participants laid supine for ~10 minutes

‘Challenge’ - Participants asked to stand (unassisted) as fast as possible

‘Recovery’ - Participants remained standing for 3 minutes



Continuously Monitored:

Near Infrared Spectroscopy (NIRS)

- Oxygenated and deoxygenated haemoglobin concentrations (O2Hb, HHb)
- Tissue Saturation Index (%TSI) (Frontal lobe, ~2cm below the scalp)

Finometer

- Beat-to-beat blood pressure (sBP, dBP, MAP)
- Heart rate (HR)

Methods

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Approximate Entropy (ApEn)[1] and Sample Entropy (SampEn)[2] Analysis

- MATLAB (R2019a; The MathWorks Inc., Massachusetts, USA)
- Data down-sampled to 5Hz (1 minute windows)
- m = 2, τ = 1 (@ 5Hz), and optimal r derived via multiple iterations (ApEn)[3] / r = 0.15 (SampEn)

$$\mathrm{ApEn}(m,r,N) \coloneqq \frac{1}{(N-m+1)} \sum_{i=1}^{N-m+1} \log \frac{C_i^m(r)}{C_i^{m+1}(r)}$$

$$\mathrm{SampEn}(m,r,N) \coloneqq \log\left(\sum_{i=1}^{N-m} C_i^m(r)\right) - \log\left(\sum_{i=1}^{N-m-1} C_i^{m+1}(r)\right)$$

Statistical Analysis

- STATA (v15.1; StataCorp, Texas, USA)

[1] Pincus et al. *J Clin Monit* 1991 [2] Richman & Moorman Am J *Physiol Heart Circ Physiol* 2000 [3] Chon et al. *IEEE Eng Med Biol* 2009

Demographics

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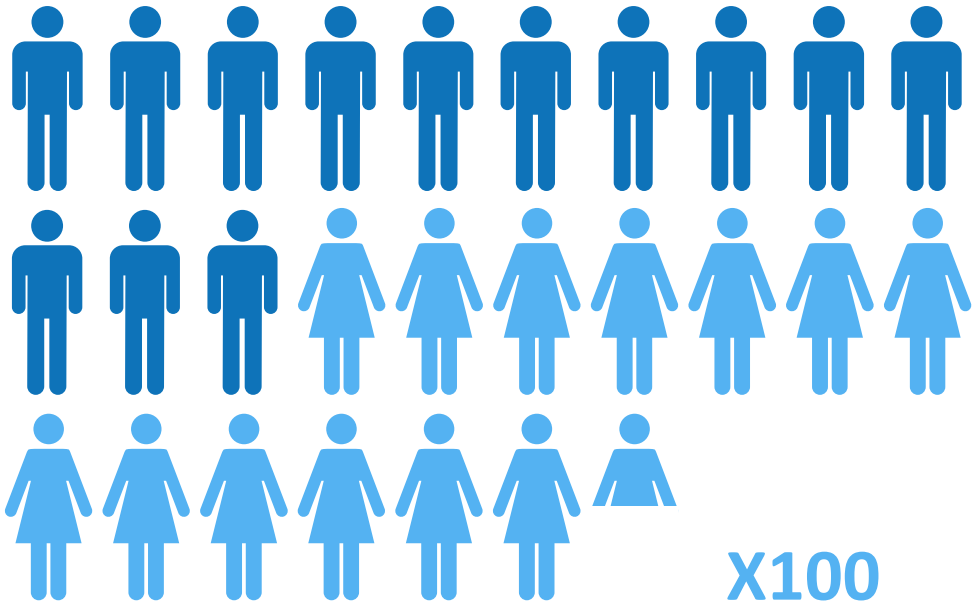
Finometer: sBP, dBP, MAP, HR

N **= 2,645**

Age = 64.3 ± 7.7 years

53% Female

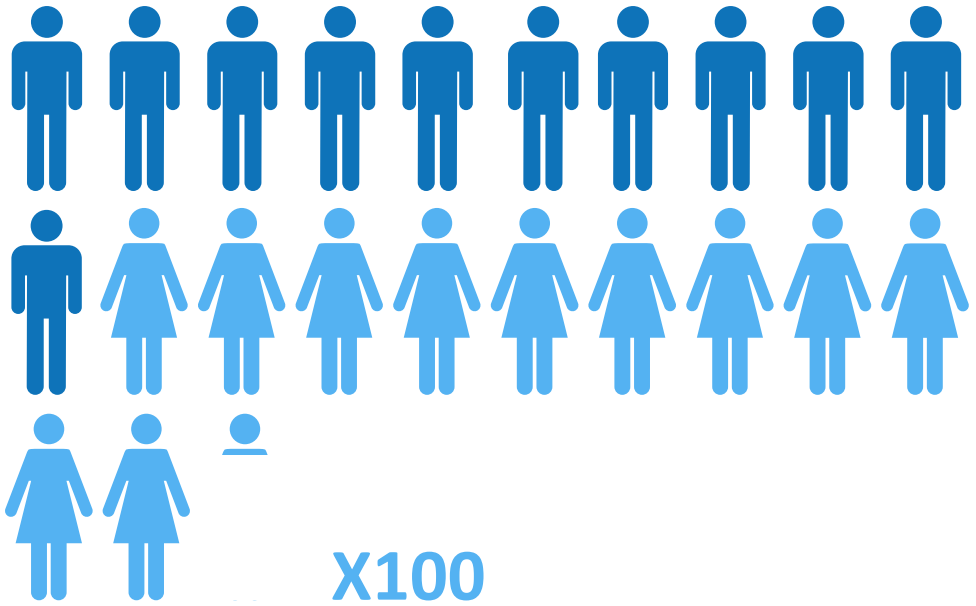


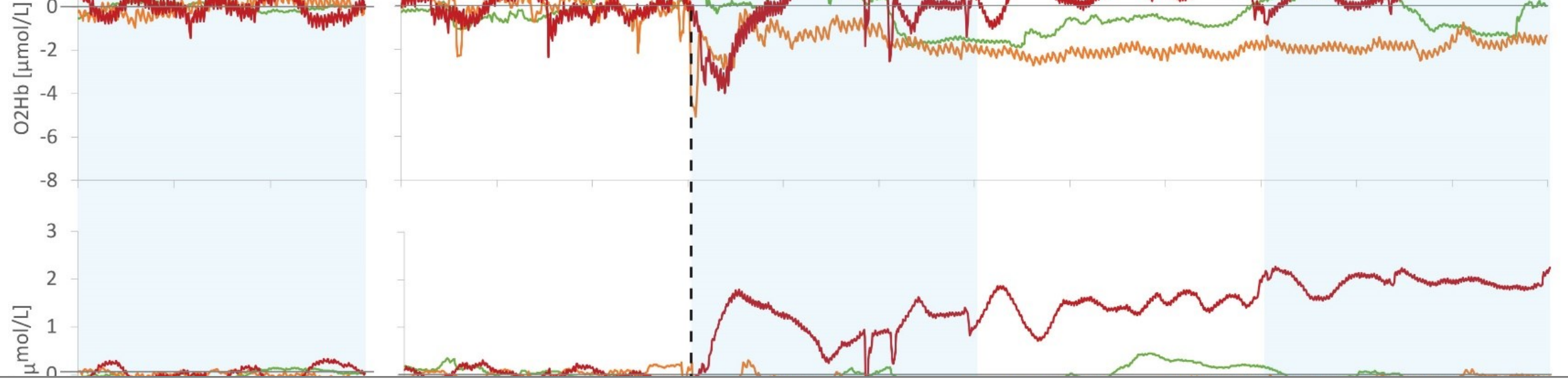
NIRS: TSI, O2Hb, HHb

N **= 2,225**

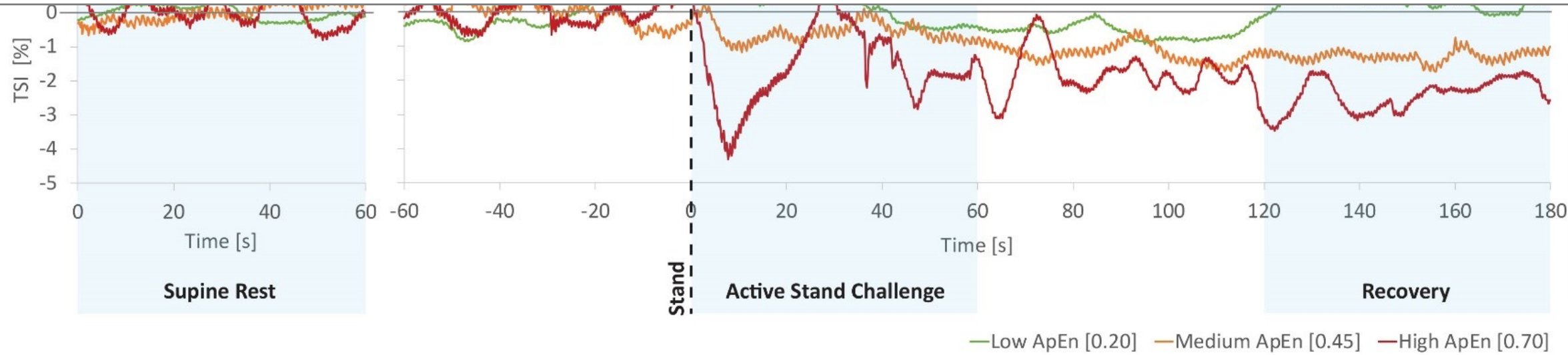
Age = 64.3 ± 7.7 years

52% Female





Shown here are example data from 3 participants with 'low', 'medium', and 'high' entropy in resting state systolic BP signals



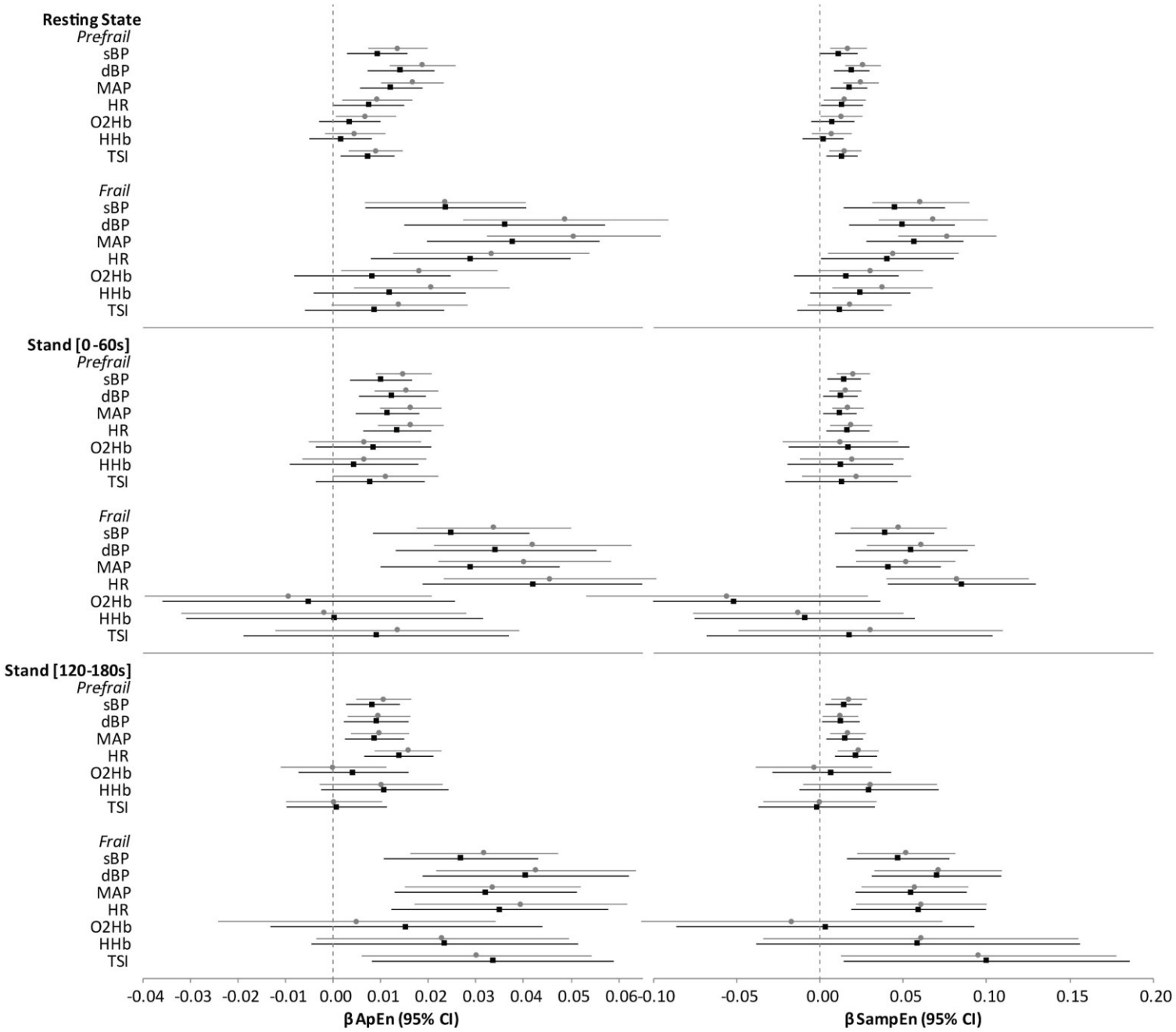
Main Findings

Significantly higher entropy in BP and HR signals for both Pre-frail and Frail individuals (vs. Non-frail)

Higher entropy for Frail vs. Pre-frail

Higher HR entropy results for 'Challenge' and 'Recovery' vs. 'Rest' data

Higher entropy in TSI for Frail individuals during 'Recovery'



** vs. non frail; 'Fully Controlled' - controlling for age, sex, education, antihypertensive medication, diabetes, cardiovascular conditions, smoking, alcohol, and depression*

Discussion

Strengths

- Largest study to date (N = 2,225/2,645)
- First study to examine frontal lobe oxygenation entropy (as measured using NIRS) with the physical frailty phenotype
- Rich data available as part of TILDA meant that models could be comprehensively controlled
- Rich, continuously and simultaneously measured neurovascular and cardiovascular data allowed for the assessment of several physiological measurements, recorded within the same experimental paradigm.

Discussion

Clinical Advantages of NCV Entropy Measure

The methodologies presented herein were specifically designed to be highly transferable for use in a clinical setting

- 60s of data sufficient
- Resting-state - relatively quick and easy to measure
- Computationally fast – could provide an ‘at-the-bedside’ measure
- Easy to interrupt and track over time (single value measure)
- Quantitative and objective

Study Limitations and Future Direction

- Small N for Frail group
- Single signal scale investigated, multiscale?
- Cross-sectional design - Longitudinal tracking of entropy would be of interest to determine the clinical significance of these findings as well as causal direction of the relationship

Entropy in short length neurocardiovascular signals could provide a *clinically useful* marker of the multiple physiological dysregulations that *underlie physical frailty*

Fondúireacht Eolaíochta Éireann
Dá bhfuil romhainn
Science Foundation Ireland
For what's next

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Resources

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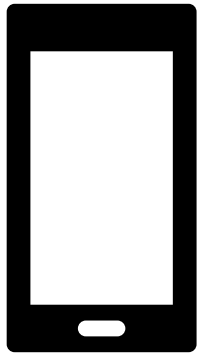
The Irish Longitudinal Study on Ageing

Knight, SP, Newman, L, O'Connor, JD, Davis, J, Kenny, RA, Romero-Ortuno, R. ***Associations between neurocardiovascular signal entropy and physical frailty***
doi: 10.3390/e23010004 *Entropy* 2021; 23(1),4



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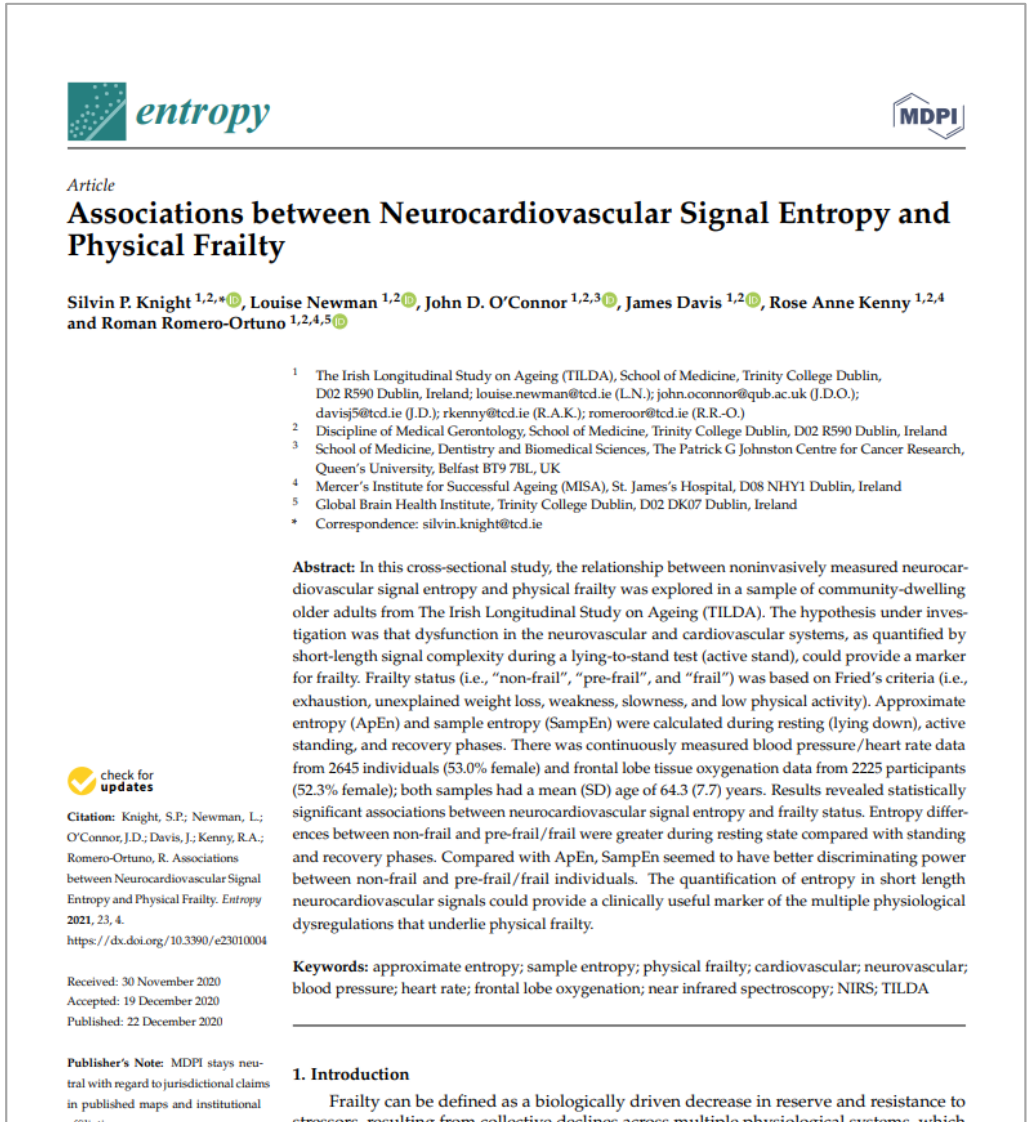

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Article

Associations between Neurocardiovascular Signal Entropy and Physical Frailty

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Abstract: In this cross-sectional study, the relationship between noninvasively measured neurocardiovascular signal entropy and physical frailty was explored in a sample of community-dwelling older adults from The Irish Longitudinal Study on Ageing (TILDA). The hypothesis under investigation was that dysfunction in the neurovascular and cardiovascular systems, as quantified by short-length signal complexity during a lying-to-stand test (active stand), could provide a marker for frailty. Frailty status (i.e., "non-frail", "pre-frail", and "frail") was based on Fried's criteria (i.e., exhaustion, unexplained weight loss, weakness, slowness, and low physical activity). Approximate entropy (ApEn) and sample entropy (SampEn) were calculated during resting (lying down), active standing, and recovery phases. There was continuously measured blood pressure/heart rate data from 2645 individuals (53.0% female) and frontal lobe tissue oxygenation data from 2225 participants (52.3% female); both samples had a mean (SD) age of 64.3 (7.7) years. Results revealed statistically significant associations between neurocardiovascular signal entropy and frailty status. Entropy differences between non-frail and pre-frail/frail were greater during resting state compared with standing and recovery phases. Compared with ApEn, SampEn seemed to have better discriminating power between non-frail and pre-frail/frail individuals. The quantification of entropy in short length neurocardiovascular signals could provide a clinically useful marker of the multiple physiological dysregulations that underlie physical frailty.

Keywords: approximate entropy; sample entropy; physical frailty; cardiovascular; neurovascular; blood pressure; heart rate; frontal lobe oxygenation; near infrared spectroscopy; NIRS; TILDA

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Citation: Knight, S.P.; Newman, L.; O'Connor, J.D.; Davis, J.; Kenny, R.A.; Romero-Ortuno, R. Associations between Neurocardiovascular Signal Entropy and Physical Frailty. *Entropy* **2021**, *23*, 4. https://dx.doi.org/10.3390/e23010004

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1. Introduction

Frailty can be defined as a biologically driven decrease in reserve and resistance to

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