UNIVERSITY OF BIRMINGHAM

The University of Nottingham

MRC-ARUK Centre for Musculoskeletal Ageing Research

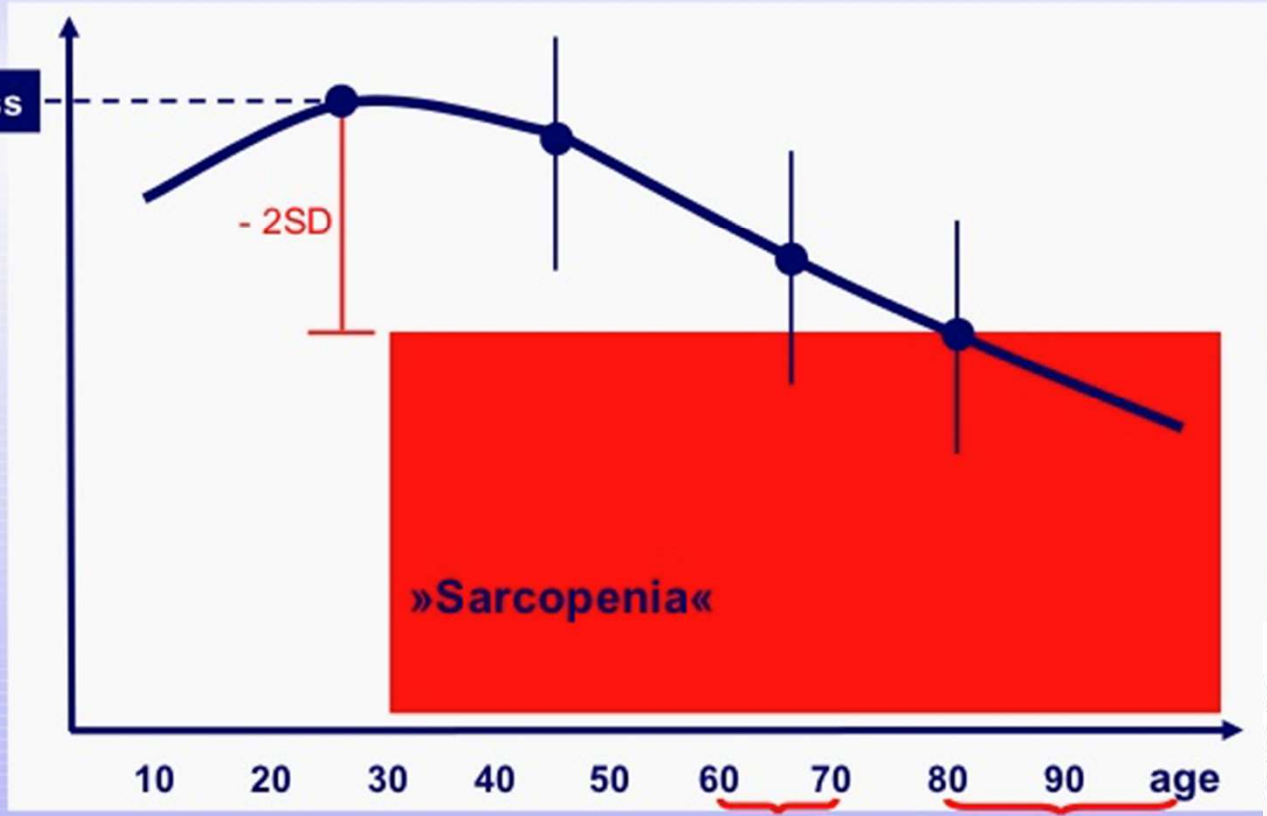
The Price of Inactivity: the imperceptible stressor

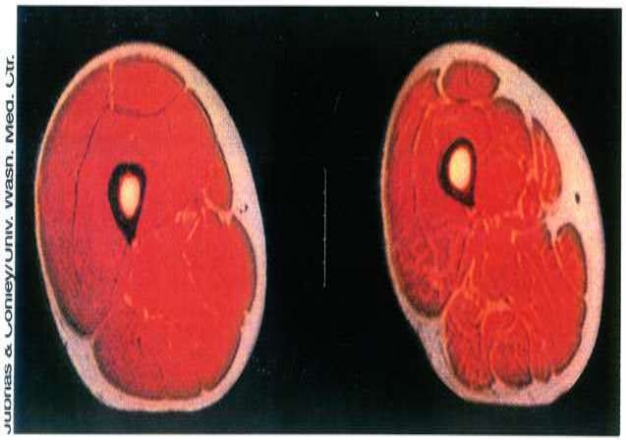
Are we muddying age related changes with inactivity related changes?

Paul Greenhaff, University of Nottingham

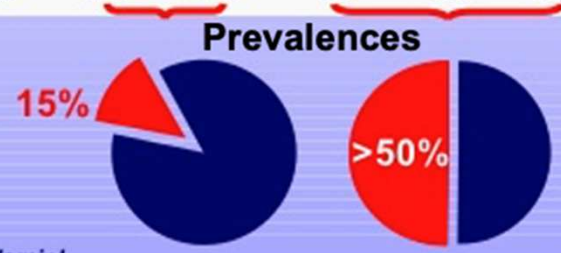
Loss of Muscle Mass with Age

(2-3% per annum from ~40 years)



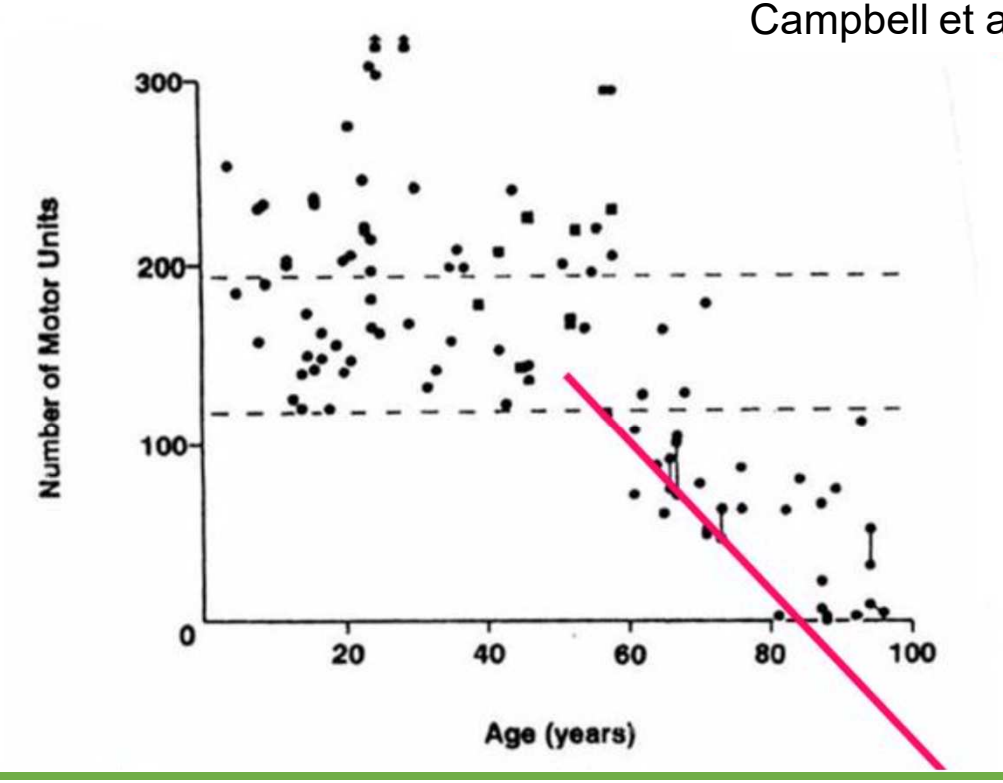


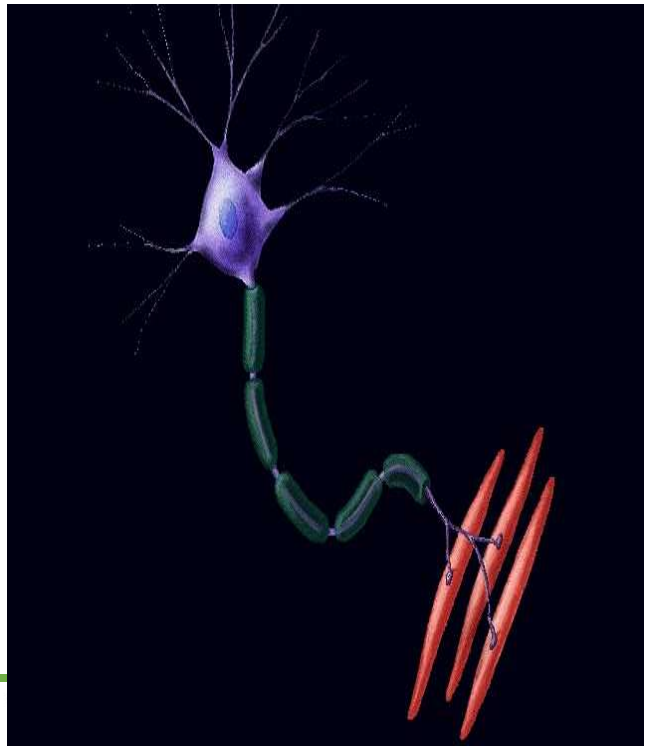
Sarcopenia defined as appendicular skeletal muscle mass being >2 standard deviations below the mean of a young reference group.



Janssen & Ross et al [2005] J Nutr Health Aging / Baumgartner et al [1998] Am J Epidemiol

Campbell et al. J Neurol Neurosurg Psych (1973)





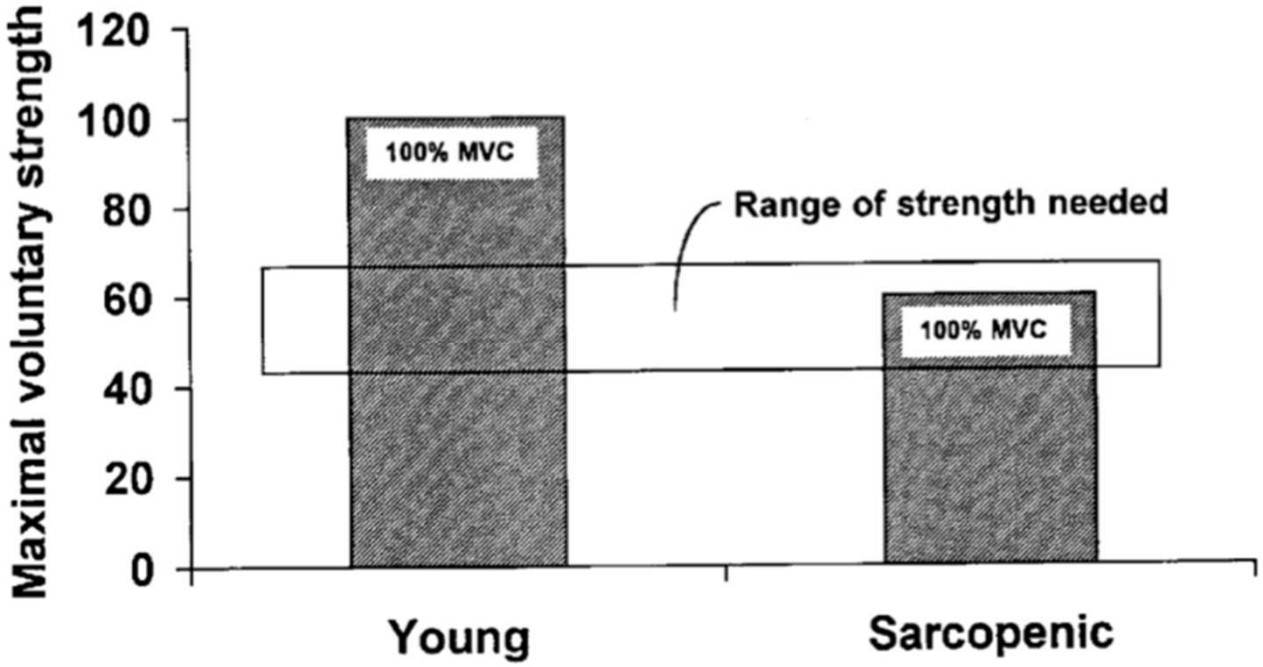
J Physiol 596.9 (2018) pp 1627–1637

Failure to expand the motor unit size to compensate for declining motor unit numbers distinguishes sarcopenic from non-sarcopenic older men

M. Piasecki[1], A. Ireland[1], J. Piasecki[1], D. W. Stashuk[2], A. Swiecicka[3], M. K. Rutter[3,4], D. A. Jones[1] and J. S. McPhee[1]

Loss of strength with ageing

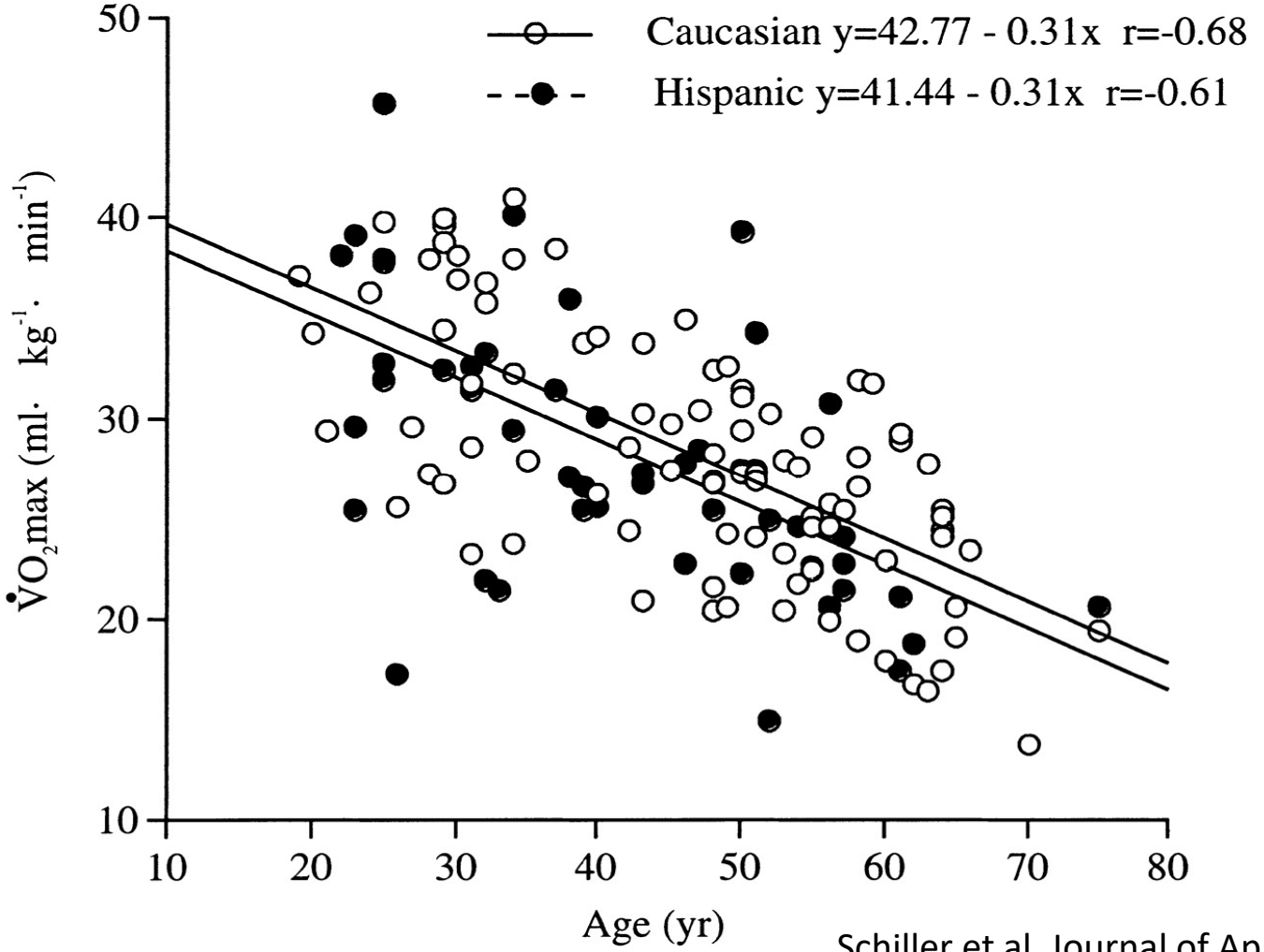
Frontera and Meredith, Exercise rehabilitation of the elderly. In: Rehabilitation of the Aging and Elderly Patient, ed. G Felsenthal, S Garrison & FU Steinberg, 1995, pp 35-45. Baltimore, MD: Williams & Wilkins.

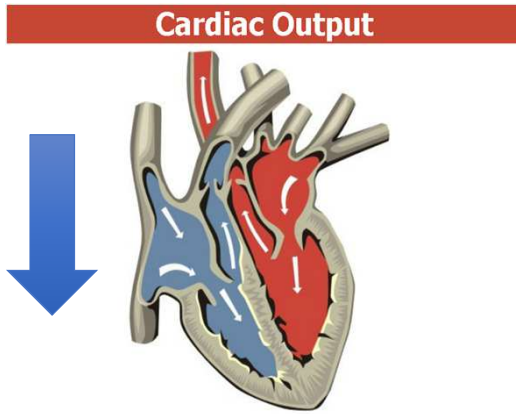


Effect of loss of strength on the ability to perform an action such as rising from a chair, for a young, healthy adult (left) and for a sarcopenic older person of the same body weight (right).

MVC = maximal voluntary contraction. Actions that exceed MVC cannot be performed. Baltimore, MD: Williams & Wilkins.

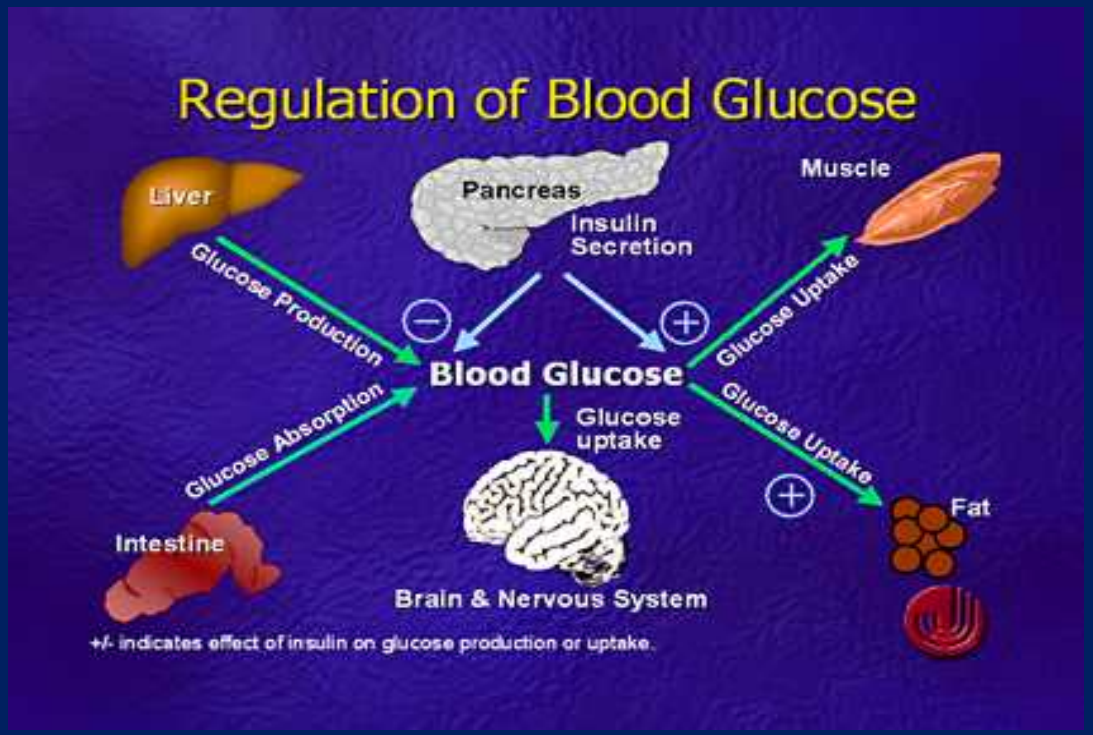
Loss of Cardiorespiratory Capacity and Muscle Quality





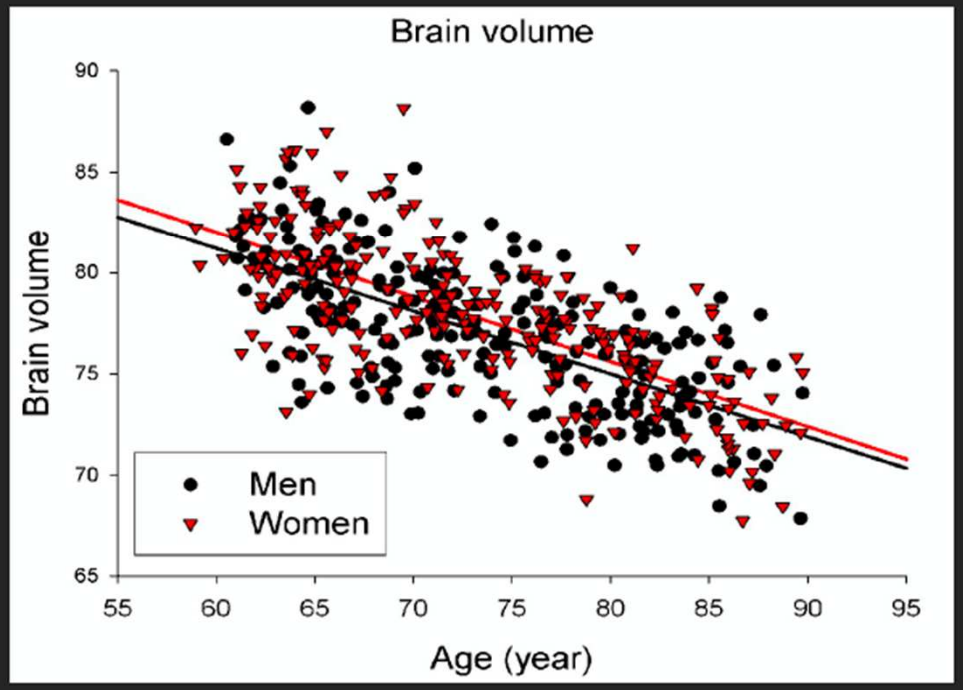
Schiller et al. Journal of Applied Physiology (2001) 91, 1048-1054

Impaired Glucose Tolerance and Ageing

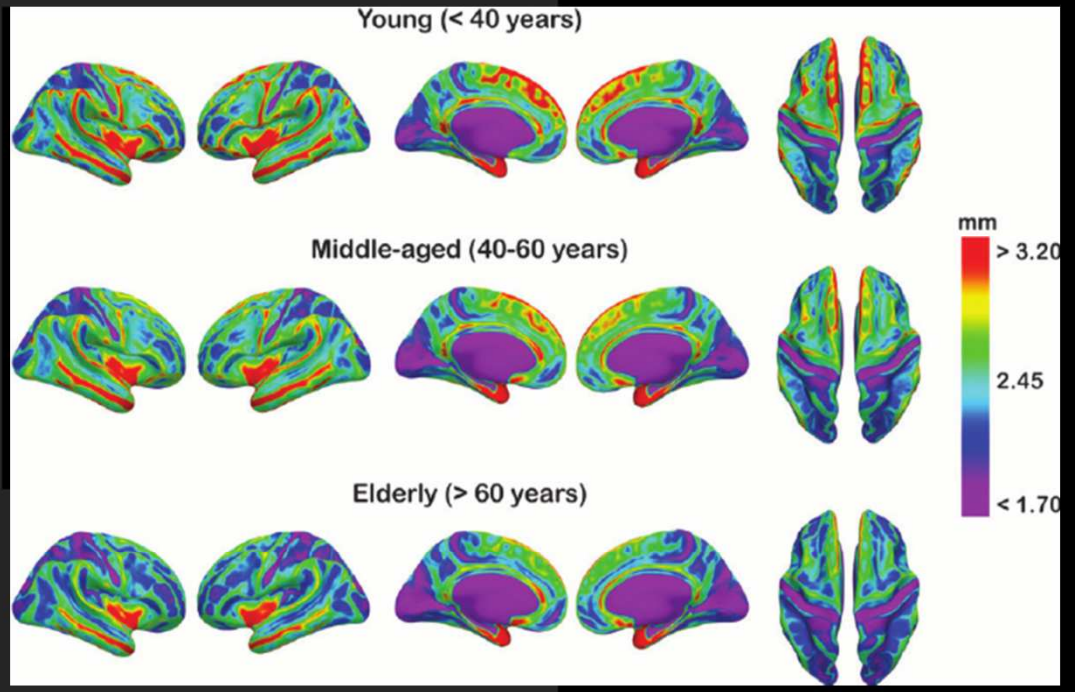


Brain Volume & Cortical Thickness

References values derived from normal aging population



Ikram et al., Neurobiol of Aging 2008



Fjell et al. February 2009 Cerebral Cortex 19(9):2001–12

Physiological Ageing?

HOWEVER…….

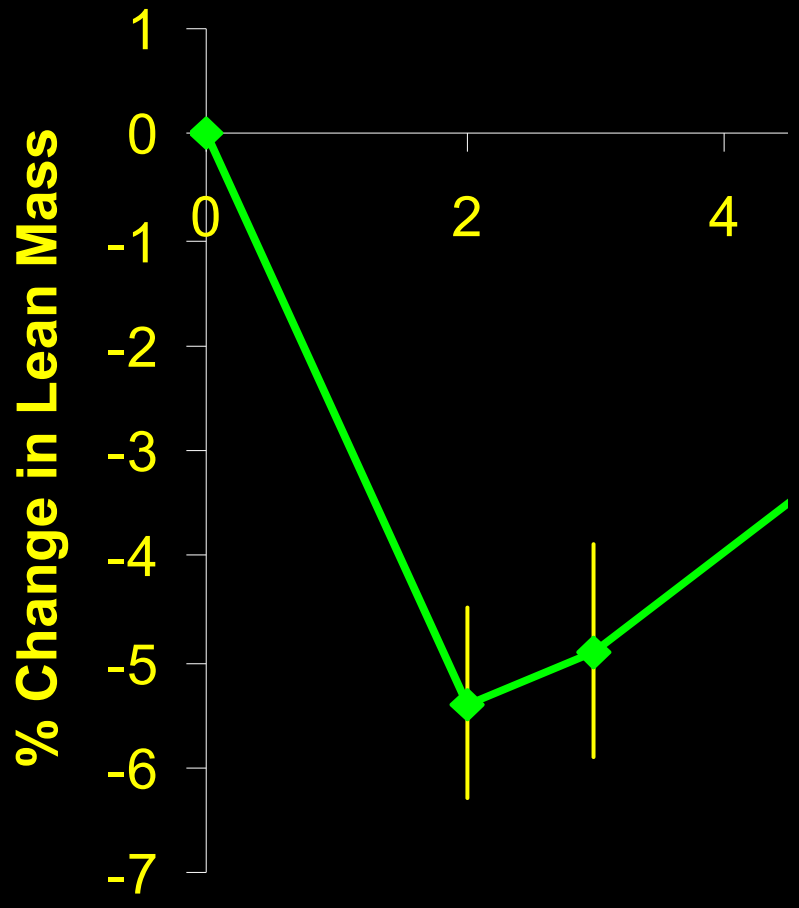
Most of these physiological features of ageing appear to be also major features of inactivity

You can make a young person physiologically age simply by making them inactive.

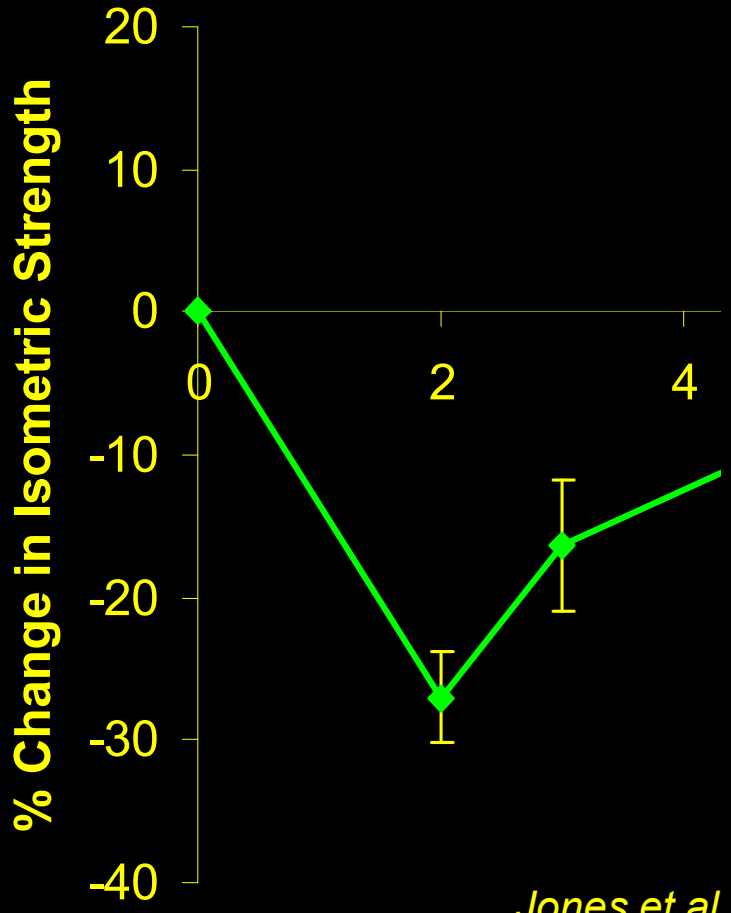
……AND YOU DON'T PERCEIVE IT HAPPENING

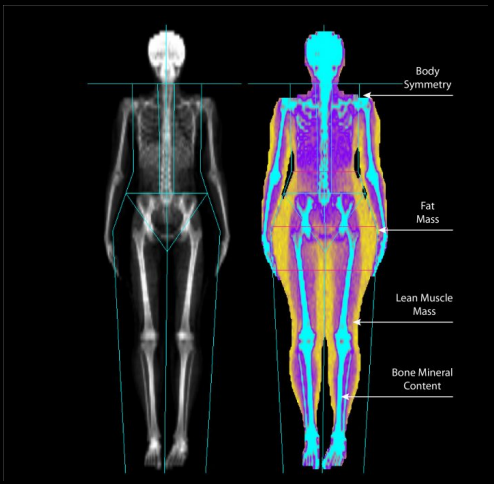
Examples…….

Lean Muscle Mass



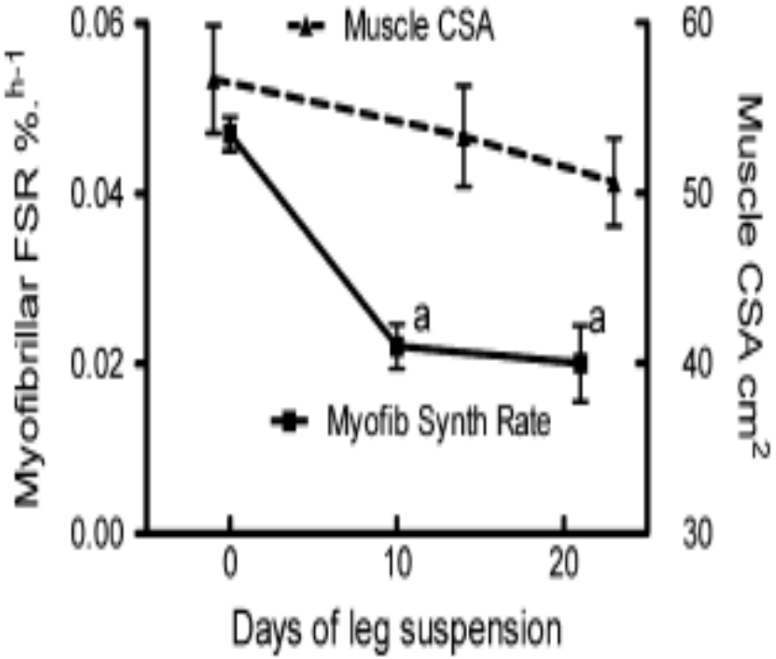
Isometric Strength



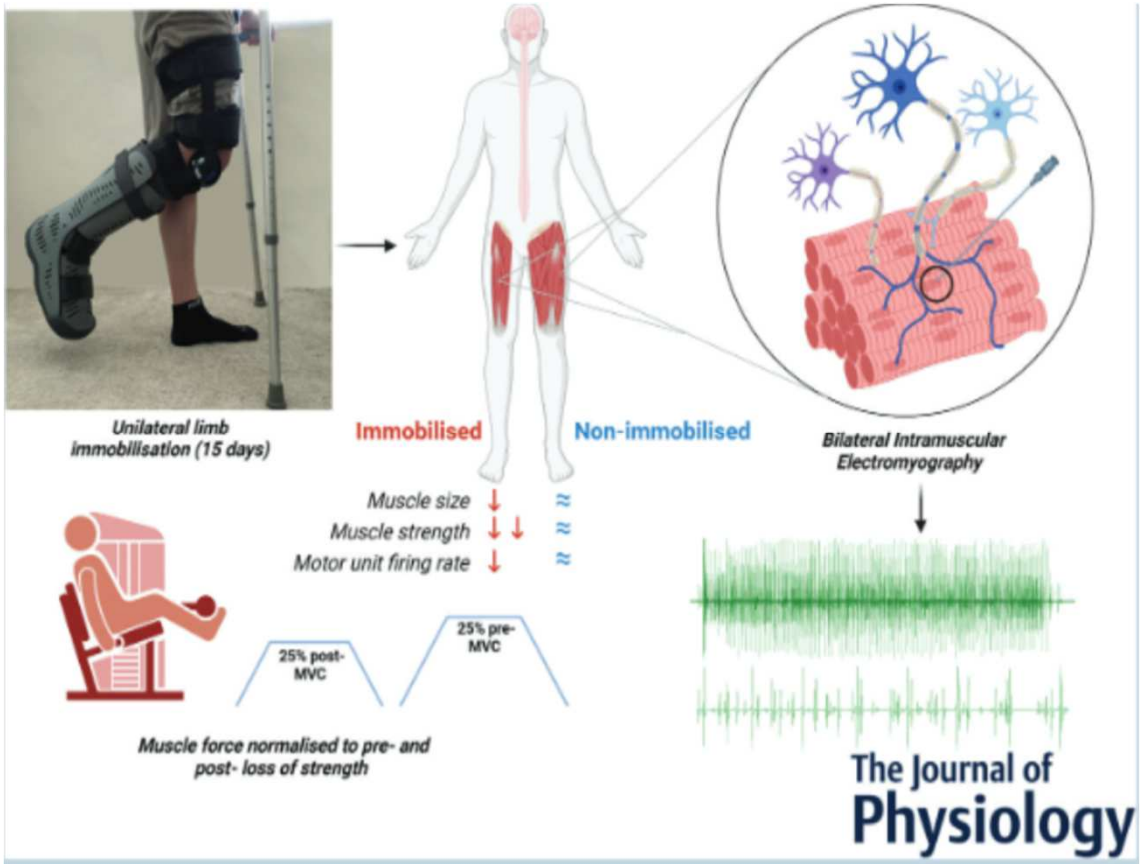


Jones et al. FASEB J, 2004

Limb immobilisation reduces human muscle protein synthesis



de Boer *et al. J Physiol. (2007)* 15;583(Pt 3):1079-91.



J Physiology 2022 Sep 11. doi: 10.1113/JP283425.

Motor unit dysregulation following 15 days of unilateral lower limb immobilisation

Thomas B. Inns[1], Joseph J. Bass[1], Edward J.O. Hardy[1,2], Daniel J. Wilkinson[1], Daniel W. Stashuk[3], Philip J. Atherton[1], Bethan E. Phillips[1] and Mathew Piasecki[1]

[1]Centre Of Metabolism, Ageing & Physiology, MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research and NIHR Nottingham BRC, University of Nottingham, Derby, UK
[2]Department of Surgery and Anaesthetics, Royal Derby Hospital, Derby, UK
[3]Department of Systems Design Engineering, University of Waterloo, Ontario, Canada

Motor unit (MU) potential size was reduced by 11% to 24% with immobilisation, while MU firing rate decreased by 8% to 11% at several contraction levels. All adaptations were observed in the immobilised limb only.

These findings highlight impaired neural input following immobilisation reflected by suppressed MU firing rate which may underpin the disproportionate reductions of strength relative to muscle size.

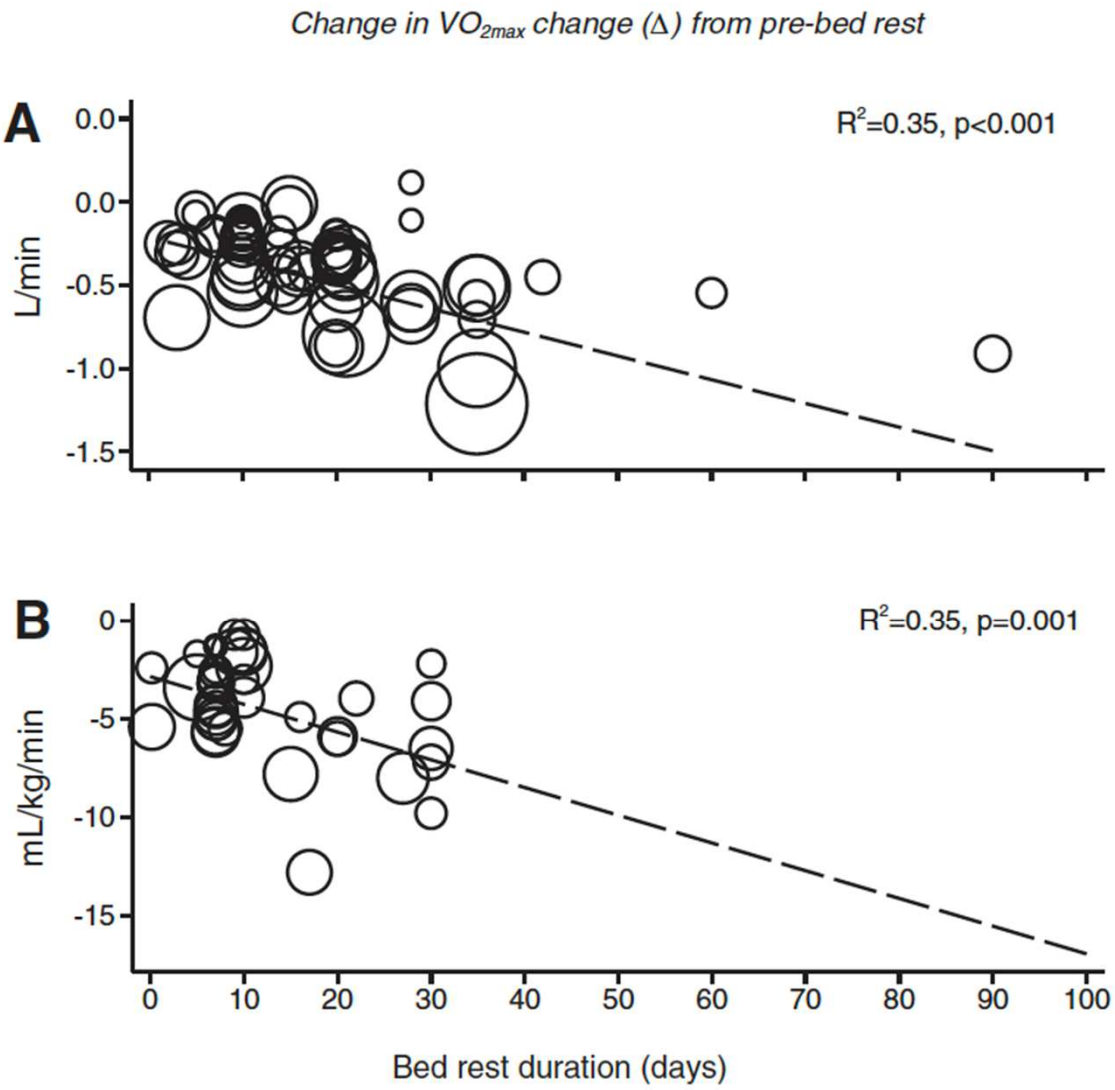


Fig. 2. Change in the absolute (l/min; *A*) or relative (ml·kg^{-1}·min^{-1}; *B*) $\dot{V}O_{2max}$ during bed rest. The area of each circle is inversely proportional to the variance of the estimate.

J Appl Physiol 123: 790–799, 2017.
First published July 13, 2017; doi:10.1152/japplphysiol.00415.2017.

RESEARCH ARTICLE

Effects of strict prolonged bed rest on cardiorespiratory fitness: systematic review and meta-analysis

Mathias Ried-Larsen,[1,2] Hugo M. Aarts,[2] and Michael J. Joyner[2]

[1]*Centre for Physical Activity Research, Rigshospitalet, Copenhagen, Denmark; and* [2]*Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota*

Eighty studies published since 1949 involving a total of 949 participants (mainly young men) of median age (interquartile range) 24.5 (22.4 –34.0) yr.

The duration of bed rest ranged from 1 to 90 days.

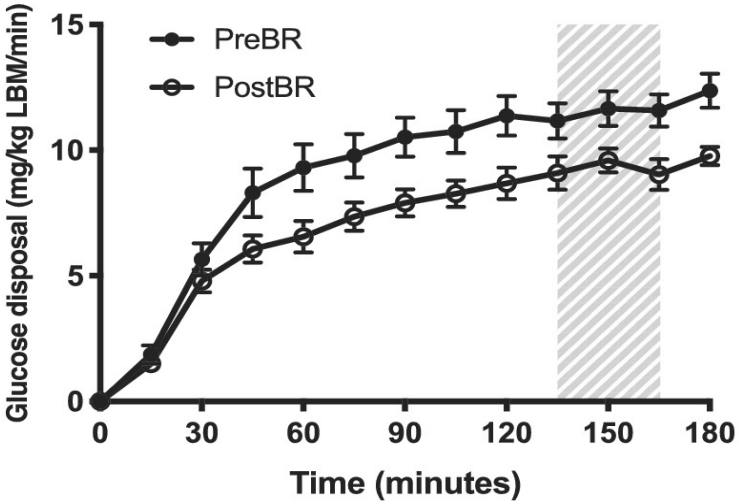
Maximal oxygen uptake declined linearly across bed rest duration.

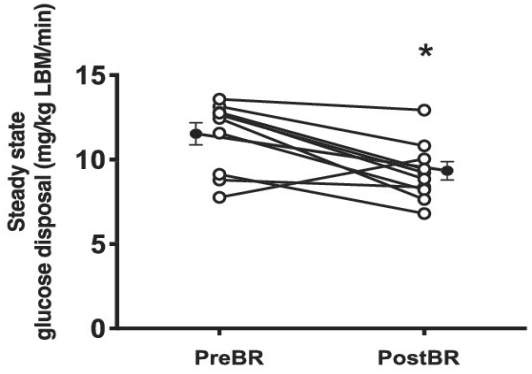
Acute bed rest

Chronic bed rest

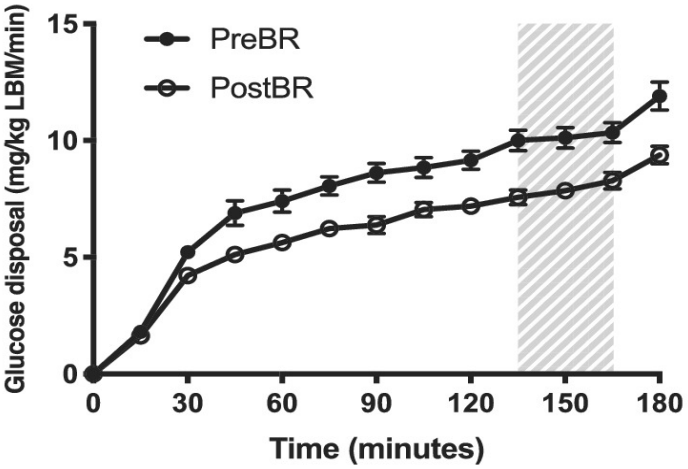
Shur et al. JCS&M 13, 2022

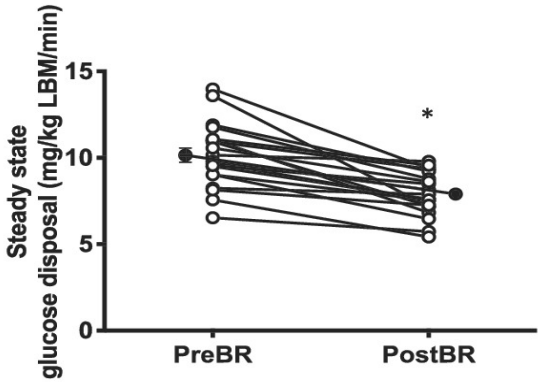
(A)





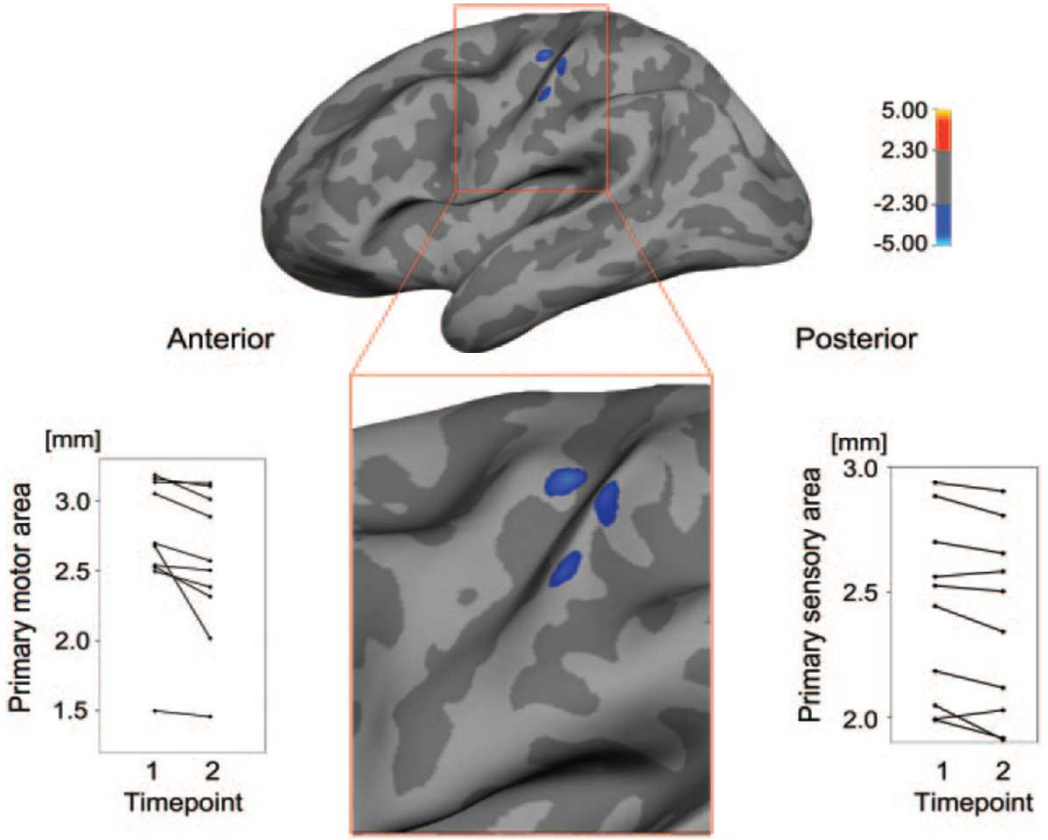
(B)



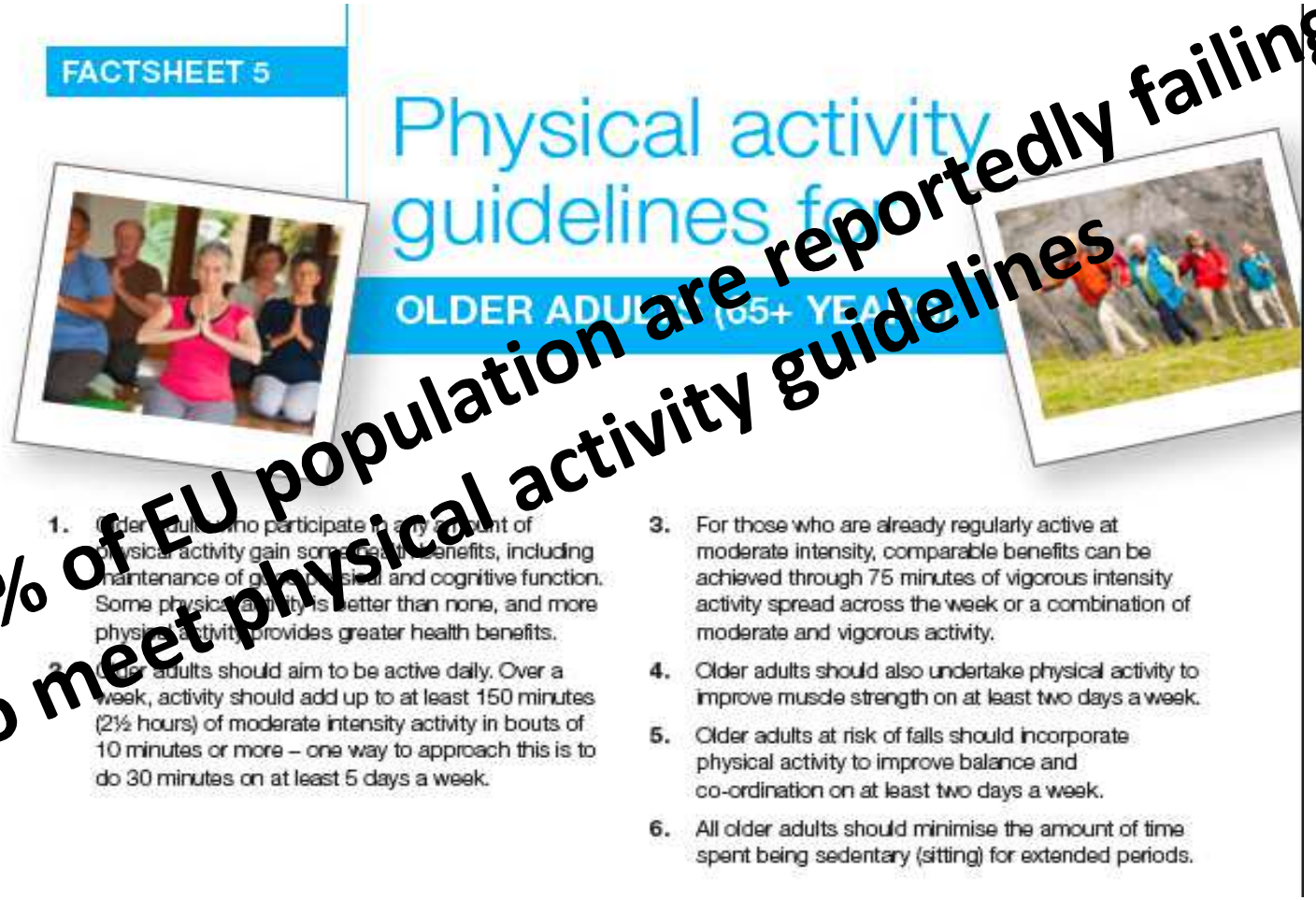


Langer et al. Neurology. 2012 Jan 17;78(3):182-8.

Effects of limb immobilisation on brain plasticity: declines in cortical thickness by deprivation of motor and sensory input



Question: Is age related physiological decline as much a function of inactivity as ageing phenomena per se?



50% of EU population are reportedly failing to meet physical activity guidelines

NRC Research Press

REVIEW

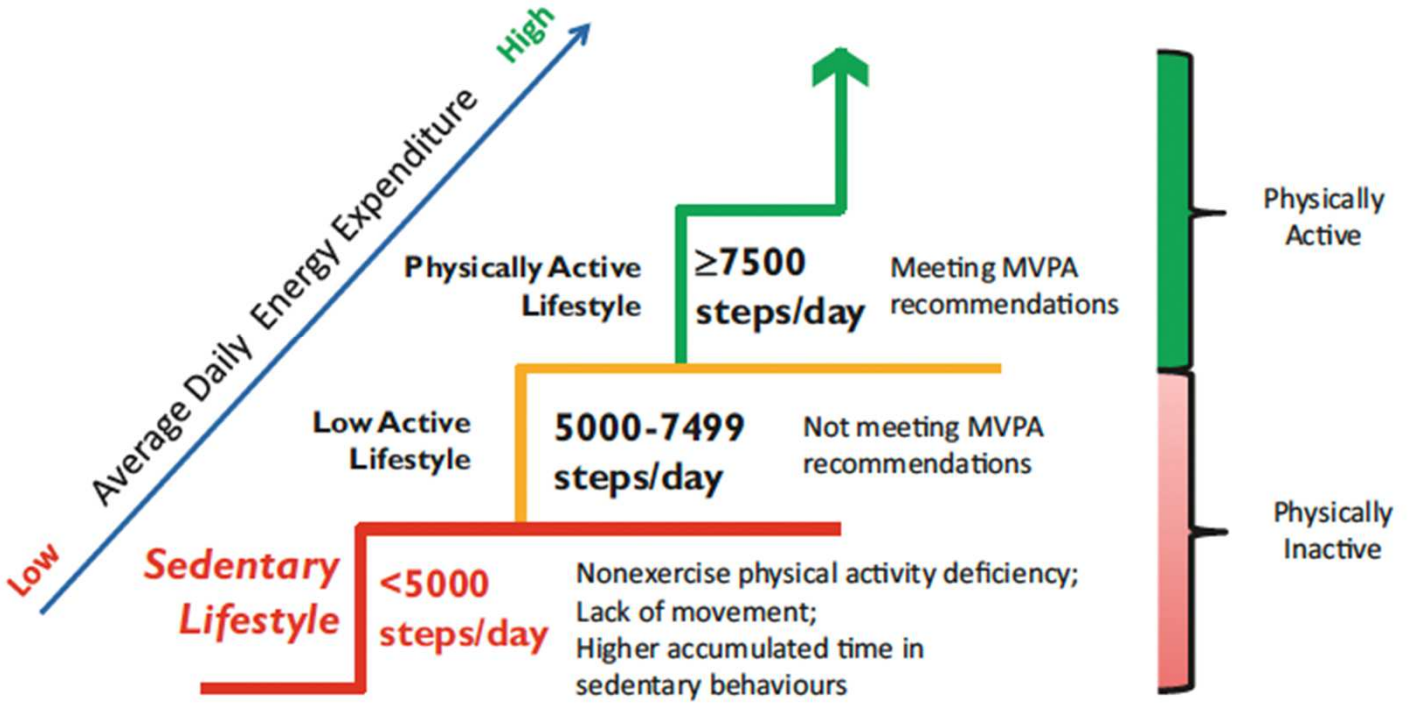
A step-defined sedentary lifestyle index: <5000 steps/day

Catrine Tudor-Locke, Cora L. Craig, John P. Thyfault, and John C. Spence

Appl. Physiol. Nutr. Metab. 38: 100–114 (2013)

dx.doi.org/10.1139/apnm-2012-0235

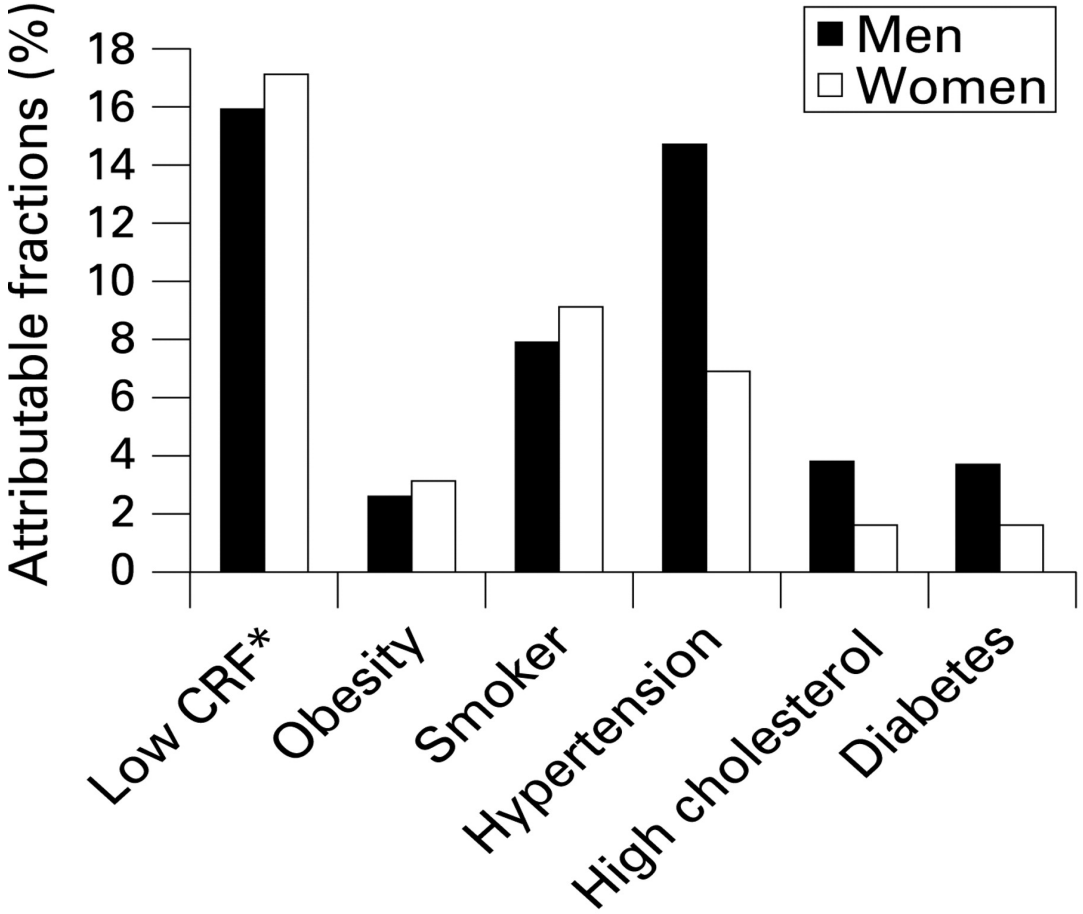
Fig. 1. Step-defined sedentary lifestyle index for adults. MVPA, moderate-to-vigorous physical activity.



Although few alternative values have been considered, the continued use of <5000 steps/day as a step-defined sedentary lifestyle index for adults is appropriate for researchers and practitioners and for communicating with the general public.

What's the significance of being inactive?

Blair Br J Sports Med 2009, 43: 1: 1-2



Attributable fractions (%) for all cause deaths in 40,842 (3333 deaths) men and 12,943 (491 deaths) women in the Aerobics Center Longitudinal Study.

The attributable fractions are adjusted for age and each other item in the figure.

*** = cardiorespiratory fitness determined by a maximal exercise test on a treadmill.**

Evidence from Public Health Epidemiology –

Meta-analysis | Published: 14 August 2012

Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis

E. G. Wilmot, C. L. Edwardson, F. A. Achana, M. J. Davies, T. Gorely, L. J. Gray, K. Khunti, T. Yates ✉ & S. J. H. Biddle

Diabetologia **55**, 2895–2905 (2012) | Cite this article

Sedentary time is associated with an increased risk of diabetes, cardiovascular disease and cardiovascular and all-cause mortality; the strength of the association is most consistent for diabetes.

Amount of time spent in sedentary behaviors and cause-specific mortality in US adults

Charles E Matthews ✉, Stephanie M George, Steven C Moore, Heather R Bowles, Aaron Blair, Yikyung Park, Richard P Troiano, Albert Hollenbeck, Arthur Schatzkin

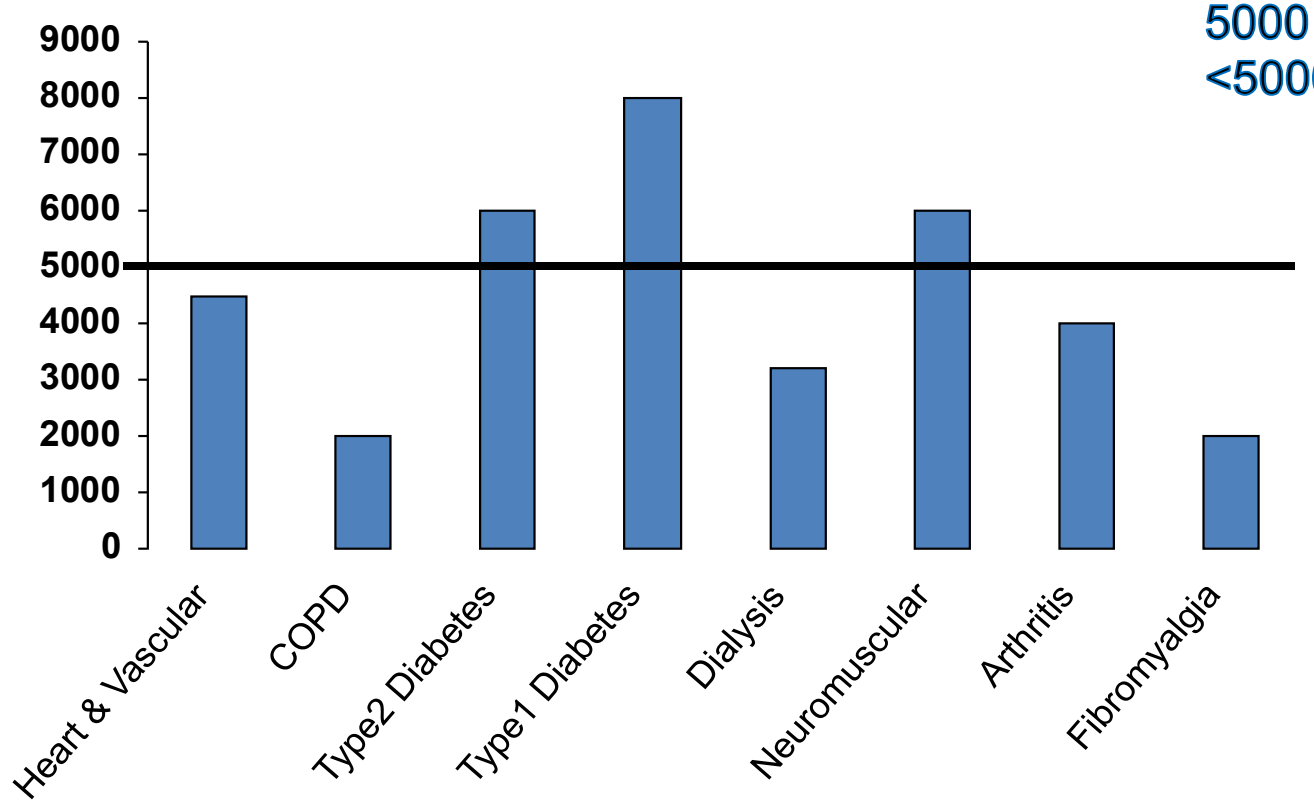
The American Journal of Clinical Nutrition, Volume 95, Issue 2, February 2012, Pages 437–445, https://doi.org/10.3945/ajcn.111.019620

Examined 240,819 adults (aged 50 –71 y) who did not report any cancer, cardiovascular disease, or respiratory disease at baseline. Mortality was ascertained over 8.5 y. Time spent in sedentary behaviours was positively associated with mortality

Inactivity in chronic disease

Physical activity (daily step count) chronic disease

7000-13000	Physically Active
5000 - 7499	Limited activity
<5000	Sedentary



Tudor-Locke *et al.* Preventative Medicine 2009

How far to walk to benefit?

THE LANCET
Public Health

ARTICLES | VOLUME 7, ISSUE 3, E219-E228, MARCH 01, 2022

Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts

Amanda E Paluch, PhD • Shivangi Bajpai, MS • Prof David R Bassett, PhD • Prof Mercedes R Carnethon, PhD • Prof Ulf Ekelund, PhD • Prof Kelly R Evenson, PhD • et al. Show all authors

Open Access • Published: March, 2022 • DOI: https://doi.org/10.1016/S2468-2667(21)00302-9 •

Fifteen studies involving 47,471 adults, among whom there were 3013 deaths (10.1 per 1000 participant-years) over a median follow-up of 7.1 years ([IQR 4.3–9.9]; total sum of follow-up across studies was 297,837 person-years).

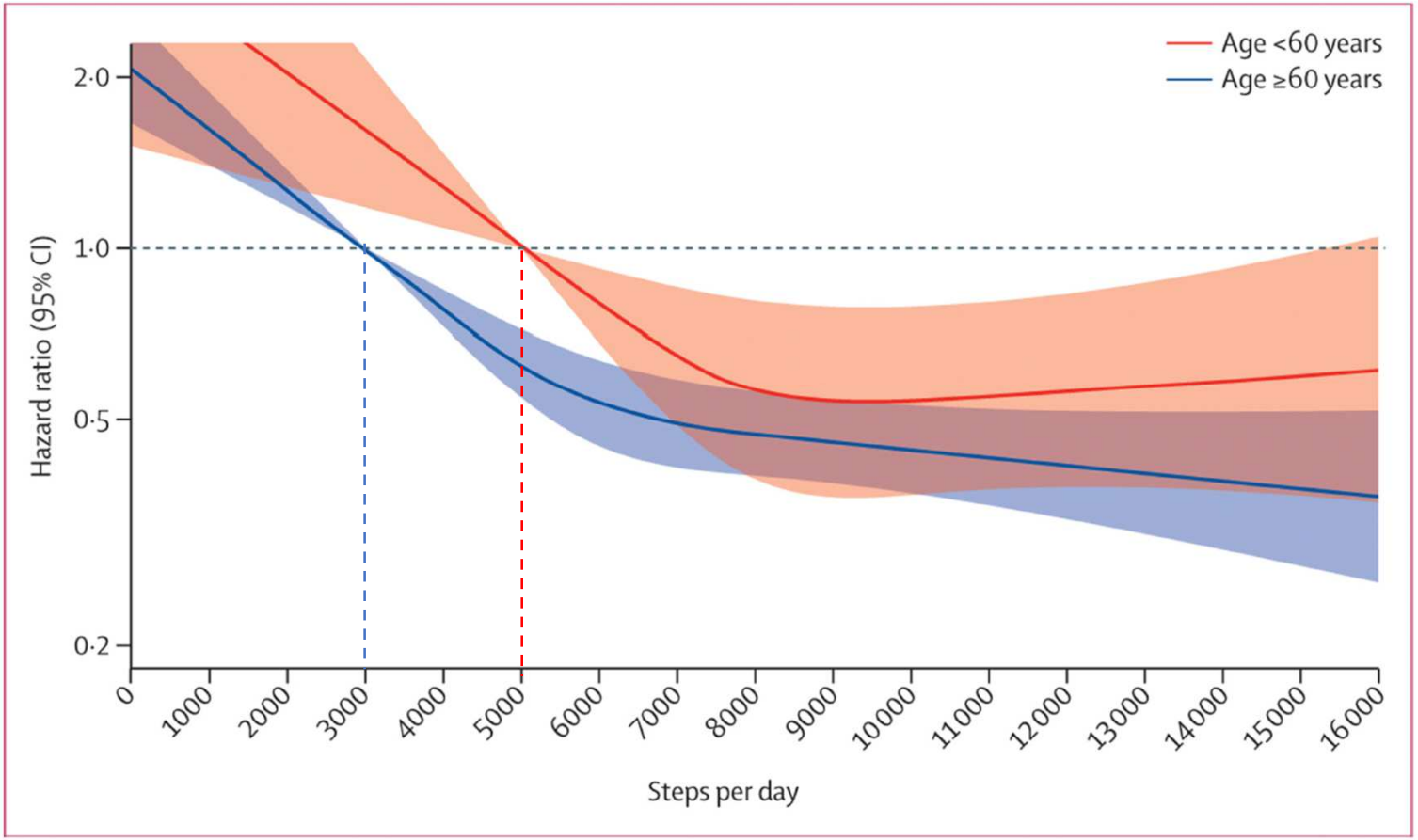


Figure 3: Dose-response association between steps per day and all-cause mortality, by age group
Thick lines indicate hazard ratio estimates, with shaded areas showing 95% CIs. Reference set at the median of the medians in the lowest quartile group (age ≥60 years = 3000 steps per day and <60 years = 5000 steps per day). Model is adjusted for age, accelerometer wear time, race and ethnicity (if applicable), sex (if applicable), education or income, body-mass index, and study-specific variables for lifestyle, chronic conditions or risk factors, and general health status. $p_{interaction}$=0.012 by age group. 14 studies included in spline analysis, excluded Baltimore Longitudinal Study of Aging.[19] The y-axis is on a log scale.

How far to walk to benefit?

Age and step count relationship with all-cause mortality

Progressively decreasing risk of mortality among **adults aged 60 years and older with increasing number of steps per day until 6000–8000 steps per day** and among **adults younger than 60 years until 8000–10 000 steps per day**.

Conclusion

Taking more steps per day was associated with a progressively lower risk of all-cause mortality, up to a level that varied by age.

How fast to walk to benefit?

1705 men aged 70 or more participating in CHAMP (Concord Health and Ageing in Men Project) followed for a mean of 59.3 months.

The mean walking speed was 0.88 (range 0.15-1.60) m/s.

Survival analysis showed that **older men who walked faster than 0.82 m/s (about 2 miles per hour) were 1.23 times less likely to die** (95% confidence interval 1.10 to 1.37) **than those who walked slower.**

When **a walking speed of 1.36 m/s (about 3 miles per hour) or greater was achieved risk of death was almost eliminated.**

Stanaway et al. BMJ 2011;343:d7679

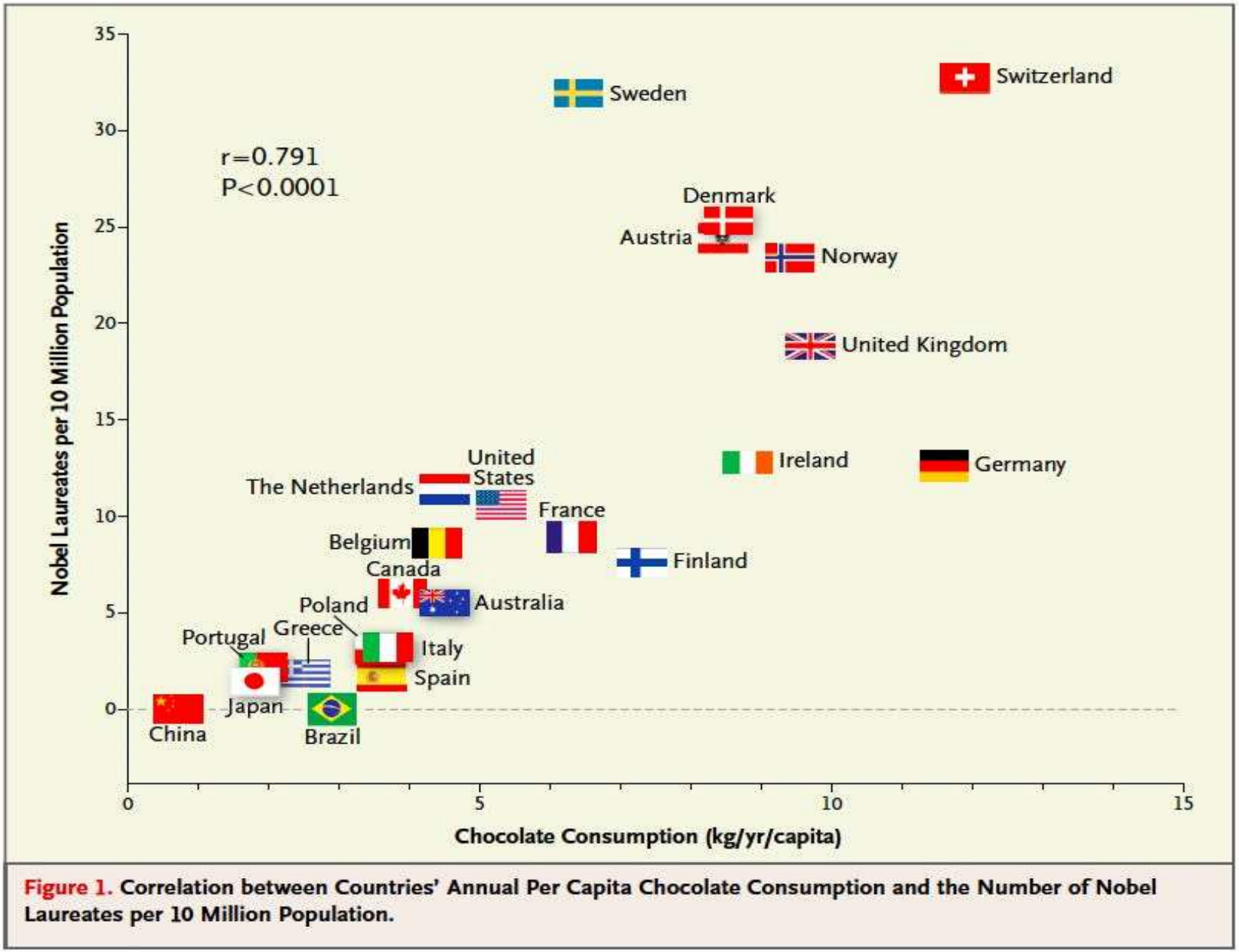
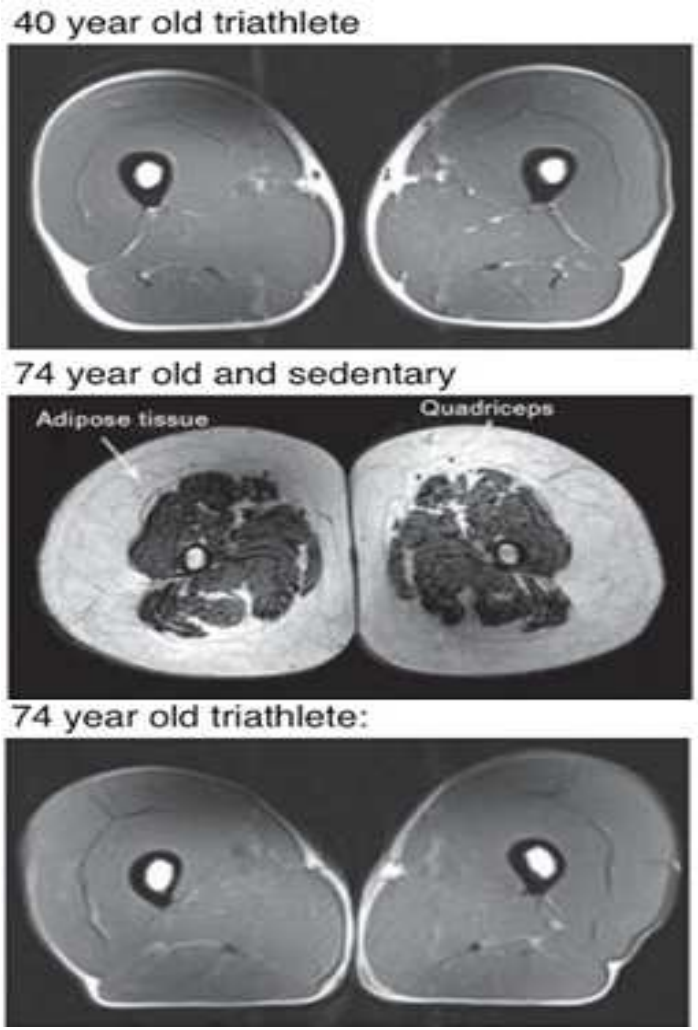


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Epidemiology will bring evidence of association, but cannot provide any evidence of mechanisms responsible for any association reported.

Do not assume cause and effect relationships exists.

Wroblewski, A., et. al. Chronic Exercise Preserves Lean Muscle Mass in Masters Athletes. The Physician and Sports medicine. 39, 2011.



Physical inactivity is likely to be the primary driver of poor health span and chronic disease progression.

Epidemiological evidence of associations between inactivity and chronic disease and mortality is strong.

However, we urgently need to understand the mechanistic basis of these associations to arrive at robust health guidelines. This will require longitudinal human volunteer intervention studies in different cohorts of people employing state of the art biomedical analytical approaches.

University of Nottingham
UK | CHINA | MALAYSIA

CHAIN Study
University of Nottingham

*Concurrent multi-organ responses to **CH**ronic physical **A**ctivity and **IN**activity intervention, to increase research discovery in human health and wellbeing.*

Participants Required for a Research Study

How Physical Activity Affects Our Bodies

Who?

- Overweight (BMI 25-29.9kg/m²) & aged between 55-65 years
- Not involved in exercise training and walk fewer than 5000 steps per day
- Spend more than 8 hours a day sitting

What? → Over a 6 month period participants will be asked to:

→ Increase their physical activity

→ Attend 3 supervised cycling sessions per week

→ Have body function, diet & activity levels measured before, during & after the 6 month period

Where?

University of Nottingham Medical School at Queen's Medical Centre

Participants Required for a Research Study

How Inactivity Affects Our Bodies

Who?

- Overweight (BMI 25-29.9kg/m²) & aged between 55-65 years
- Not exercise training but walking 8000 – 10000 steps per day
- Fewer than 6 hours of sitting down a day

What? → Participants will be asked to reduce physical activity to match the UK average for adults, for 6 months

→ Have fewer than 4500 steps per day

→ Have sitting time of 7 hours or more per day

→ Have body function, diet and activity levels, measured during & after the 6 month period

→ Attend 3 months of supervised exercise sessions post-study to restore fitness levels

Where?

University of Nottingham Medical School at Queen's Medical Centre