Effect of Exercise on Telomere Length: Connections to Longevity

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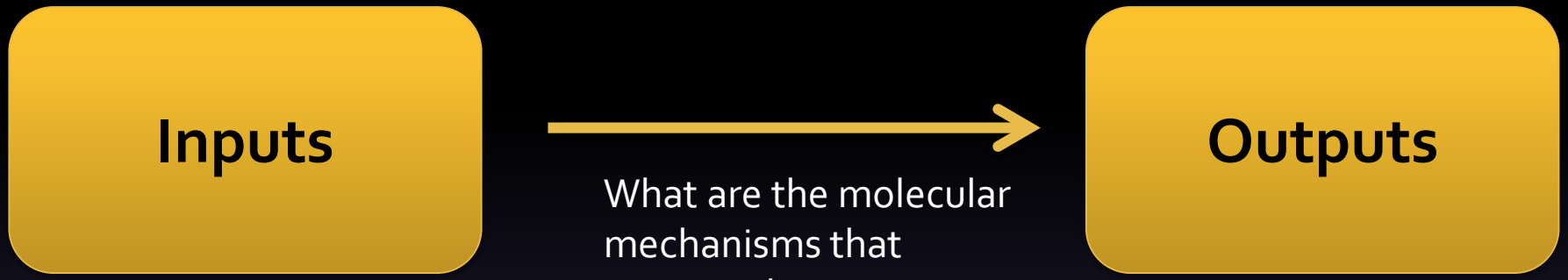
A long and healthy life

- **For as long as is recorded in human history, humans have yearned for a long and healthy life.**
- **A long life is one of the blessings spoken of in the Bible.**
  - **"For by Me your days will be multiplied, and years of life will be added to you**." (Proverbs 9:11)
  - "Honor your father and your mother, **that your days may be long** upon the land which the Lord your God is giving you." (Exodus 20:12)

Factors that seem to matter

- Out of our control
  - Genes – choose your parents wisely!
  - Accidents
  - Natural and man-made disasters
  - Some diseases
  - Environment (some aspects)
- Within our control
  - Diet
  - Physical Activity
  - Mental state
  - Environment (some aspects)
  - Some diseases
  - Sleep
  - Safety

Model



What are the molecular mechanisms that connect the inputs to the outputs?

Contrast between biological age with chronological age

How can one measure one's biological age?

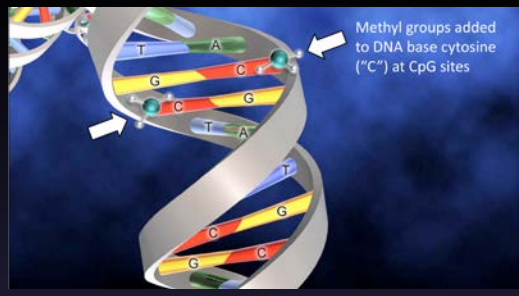
How can one CHANGE one's biological age?

Genes
Diet
Activity
Mental state
Environment
Social Economic Status
Etc.

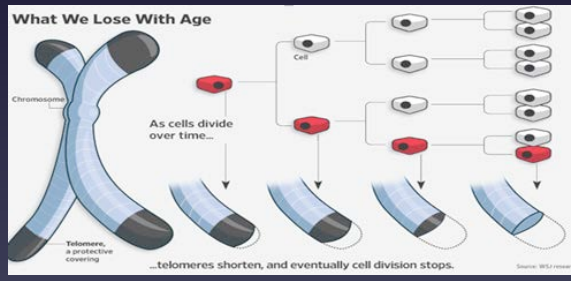
Lifespan
Health and Disease
Performance measurements
Blood chemistries
Etc.

Indicators of biological aging

- Epigenetic patterning
  - Small, methyl molecules can get added to specific cytosine residues
  - Turn off the downstream gene
  - As we age, our pattern of what genes are and are not turned off changes
  - So, looking at our epigenetic pattern gives an estimate of biological age



- Telomere length
  - Telomeres are the "caps" at the ends of our chromosomes
  - They get shorter with each cell division, and with time
  - Therefore, telomere length can also give an estimate of biological age



Jonlieffmd.com
Telomererestoration.com

Epigenetic Patterning

DNA methylation age of blood predicts all-cause mortality in later life

Riccardo E Marioni[†], Sonia Shah[†], Allan F McRae[†], Brian H Chen[†], Elena Colicino[†], Sarah E Harris, Jude Gibson, Anjali K Henders, Paul Redmond, Simon R Cox, Alison Pattie, Janie Corley, Lee Murphy, Nicholas G Martin, Grant W Montgomery, Andrew P Feinberg, M Daniele Fallin, Michael L Multhaup, Andrew E Jaffe, Roby Joehanes, Joel Schwartz, Allan C Just, Kathryn L Lunetta, Joanne M Murabito, John M Starr, Steve Horvath[†], Andrea A Baccarelli[†], Daniel Levy[†], Peter M Visscher[†], Naomi R Wray[*†] and Ian J Deary[*†]

http://genomebiology.com/content/pdf/s13059-015-0584-6.pdf

Google Calendar gives count-down remaining life expectancy based on DNA methylation, by Cecile Janssens , Blog Post

How Does the Body Know How Old It Is? Introducing the Epigenetic Clock Hypothesis

Mitteldorf J.

Department of FA... ...ssachusetts Institute of Technology, Cambridge, Mass., USA

...ical clocks that help to regulate circadian cycles, seasonal rhythms, growth, development and sexual maturity. If aging is not a stochastic process of attrition ...reasonable to suspect that the timing of senescence is also influenced by one or more biological clocks. Evolutionary reasoning first articulated by G. ...edundant clocks might influence organismal aging. Some aging clocks that have been proposed include the suprachiasmatic nucleus, the hypothalamus, ...er senescence. Cellular senescence, mediated by telomere attrition, is in a class by itself, having recently been validated as a primary regulator of aging. ...racteristic ways with age, and in particular DNA methylation changes in age-related ways. Herein, I propose a new candidate for an aging clock, ... methylation, particularly in stem cells. If validated, this mechanism would present a challenging but not impossible target for medical

The epigenetic clock is correlated with physical and cognitive fitness in the Lothian Birth Cohort 1936

Riccardo E Marioni[1,2,3], Sonia Shah[1,3,4], Allan F McRae[1,3], Stuart J Ritchie[1,2], Graciela Muniz-Terrera[6], Sarah E Harris[1,2], Jude Gibson[7], Paul Redmond[7], Simon R Cox[1,5], Alison Pattie[5], Janie Corley[5], Adele Taylor[5], Lee Murphy[7], John M Starr[1,8], Steve Horvath[9], Peter M Visscher[1,3,4], Naomi R Wray[4] and Ian J Deary[1,2,*]

[1]Centre for Cognitive Ageing and Cognitive Epidemiology, and [2]Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK, [3]Queensland Brain Institute, and [4]Translational Research Institute, University of Queensland, Brisbane, QLD, Australia, [5]Department of Psychology, University of Edinburgh, Edinburgh, UK, [6]MRC Unit for Lifelong Health and Ageing, London, UK, [7]Wellcome Trust Clinical Research Facility, and [8]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK and [9]Gonda Research Center, David Geffen School of Medicine, Los Angeles, CA, USA

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Abstract

Background: The DNA methylation-based 'epigenetic clock' correlates strongly with chronological age, but it is currently unclear what drives individual differences. We examine cross-section... longitudinal associations between the epigenetic clock and four mortality-linked markers of physical and mental fitness: lung function, walking speed, grip strength a...

http://ije.oxfordjo... .../01/22/ije.dyu277.long

...rkers and ageing: The clock-watcher

...eve Horvath has discovered a strikingly accurate way to measure human ageing through epigenetic ...

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...pectancy based on DNA

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DNA Methylation Predicts Death

02/03/2015

Kristie Nybo, PhD

Researchers link DNA methylation patterns with lifespan, enabling predictions of mortality independent of lifestyle factors such as smoking, diabetes, and cardiovascular disease.

Choices we make in life, such as whether to diet, exercise, or smoke, influence our lifespans for better or for worse. Several cause-and-effect relationships are clear, such as the link between cardiovascular disease and a high fat diet. But even with confirmed connections, the precise molecular mechanisms for how these changes come about aren't clear.

With the exception of mutations, genome sequences remain constant throughout life, yet how those genomes are regulated changes with time and in response to the environment. DNA methylation is one way a cell can significantly alter gene expression in living organisms. Methylation patterns vary across the lifespan, changing with development and age, and studies have also shown that lifestyle choices and environment can alter these patterns. Now, researchers from the University of Edinburgh, collaborating with scientists in Australia and the US, show that methylation patterns can actually predict mortality.

"This new research increases our understanding of longevity and healthy aging. It is exciting as it has identified a novel indicator of aging, which improves the prediction of lifespan over and above the contribution of factors such as smoking, diabetes, and cardiovascular disease," said senior author Ian Deary in a press release.

Telomeres

- In principle, telomeres can either get longer or shorter.
  - An enzyme, telomerase, increases telomere length
  - The act of cell division decreases telomere length
- In most cells, telomere activity is low or absent
- Exceptions:
  - Germ cells
  - Cancer cells

Telomere lengths

- Most often, human studies look at telomere lengths in blood cells
- Sometimes muscle cells are examined
- Usually, researchers will either use TRF (terminal restriction fragment lengths, based on Southern blotting) or qPCR techniques

What shortens telomeres?

- Age – with each division, cellular telomeres get shorter
- Stress – of many types.
  - Oxidative ,environmental and/or lifestyle stress
    - Lead and cadmium
    - Soda consumption
    - Sleep duration
    - Maternal levels of estriol (on the newborn)
    - Obesity
  - Psychological stress
    - Caring for a chronically sick child
    - Major depressive disorder
    - Childhood adversities
  - Environmental stress
    - Educational attainment
    - Socioeconomic issues
    - Real or perceived discrimination issues

What decreases telomere shortening?

- Interestingly, not as much work has been done on the positive aspects
  - Diet
  - Meditation
  - Physical activity

Exercise and telomere length

- Most studies involve cross-sectional studies of people who self-report their activity level
- The most frequently analyzed tissue is blood; some look at muscle
- Very few longitudinal, randomized, interventional studies

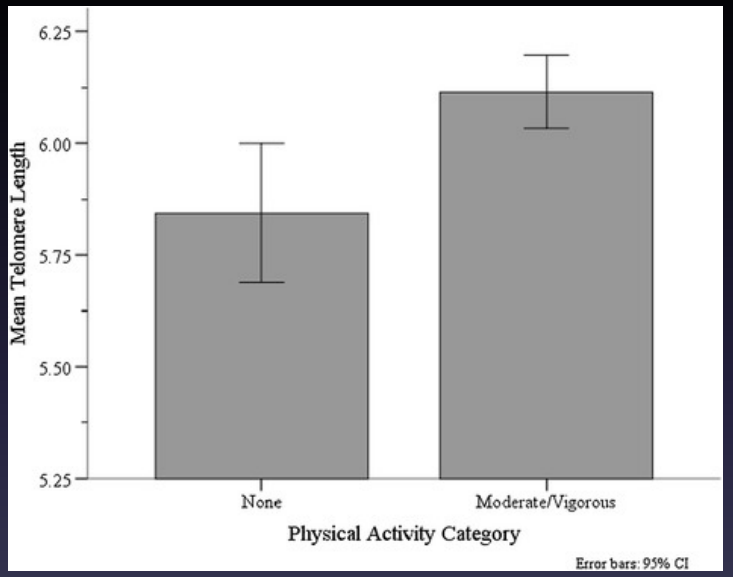
Moderate exercise

- Most studies examining the relationship of moderate exercise to telomere length have found a positive relationship. That is, telomeres are longer in people who exercise.
- Cross-sectional studies:
  - Women, habitual physical exercise was associated with increased telomere length.
    - Kim et al, Habitual physical exercise has beneficial effects on telomere length in postmenopausal women. Menopause 2012, 19:1109;
    - Du et al, Physical activity, sedentary behavior, and leukocyte telomere length in women. Am. J. Epidemiol 2012, 175:414

Moderate exercise

Interventional studies:

- Older adults, sedentary, overweight; over six months, those in an intervention group saw a telomere length increase that was correlated with time spent exercising. Sjogren et al, Br J Sports Med 2014 48:1407.
- Breast cancer survivors who had higher physical activity had longer telomere lengths. Garland et al, Breast Cancer Res. 2014 16:413



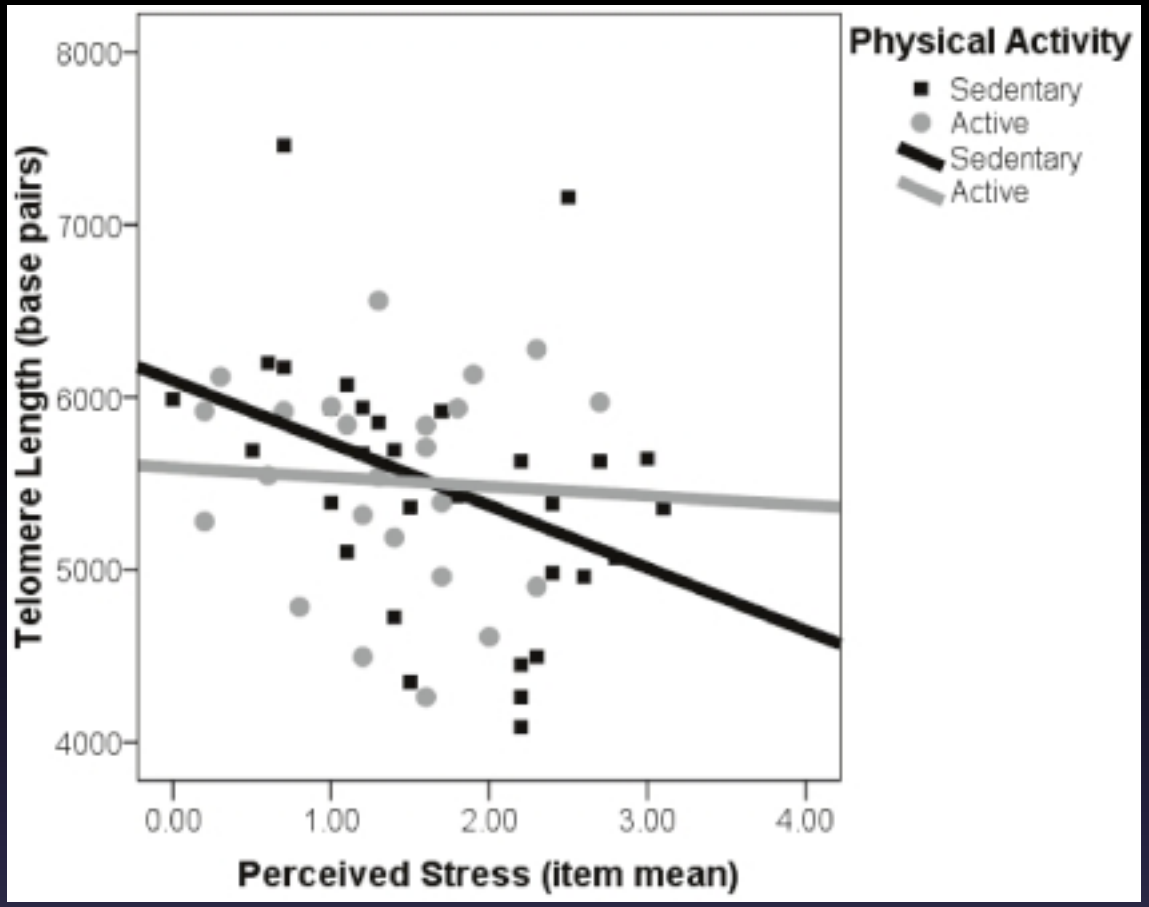
Strenuous exercise

- Studies with marathoners and ultra-marathoners, as well as with more mixed groups
- These results are more mixed, with some showing benefit and some showing harm
  - Denham et al, Longer leukocyte telomeres are associated with ultra-endurance exercise independent of cardiovascular risk factors, PLoS One 2013 8:e69377
  - Osthus et al, Telomere length and long-term endurance exercise: does exercise training affect biological age? A pilot study. PLoS One 2012, 7:e52769
- There may be an inverse U-shaped curve
  - Ludlow et al, Med Sci Sports Exerc. 2008, 40:1764
  - Savela et al, Physical activity in midlife and telomere length measured in old age, Exp. Gerontol 2013 48:81

Can exercise buffer the adverse effects of stress?

- Postmenopausal women; telomere lengths and Perceived Stress Scale, reporting minutes of vigorous activity for three successive days
- Among non-exercisers, a one unit increase in the Perceived Stress Scale was related to a 15-fold increase in the odds of having short telomeres
- Among exercisers, perceived stress appeared to be unrelated to telomere length

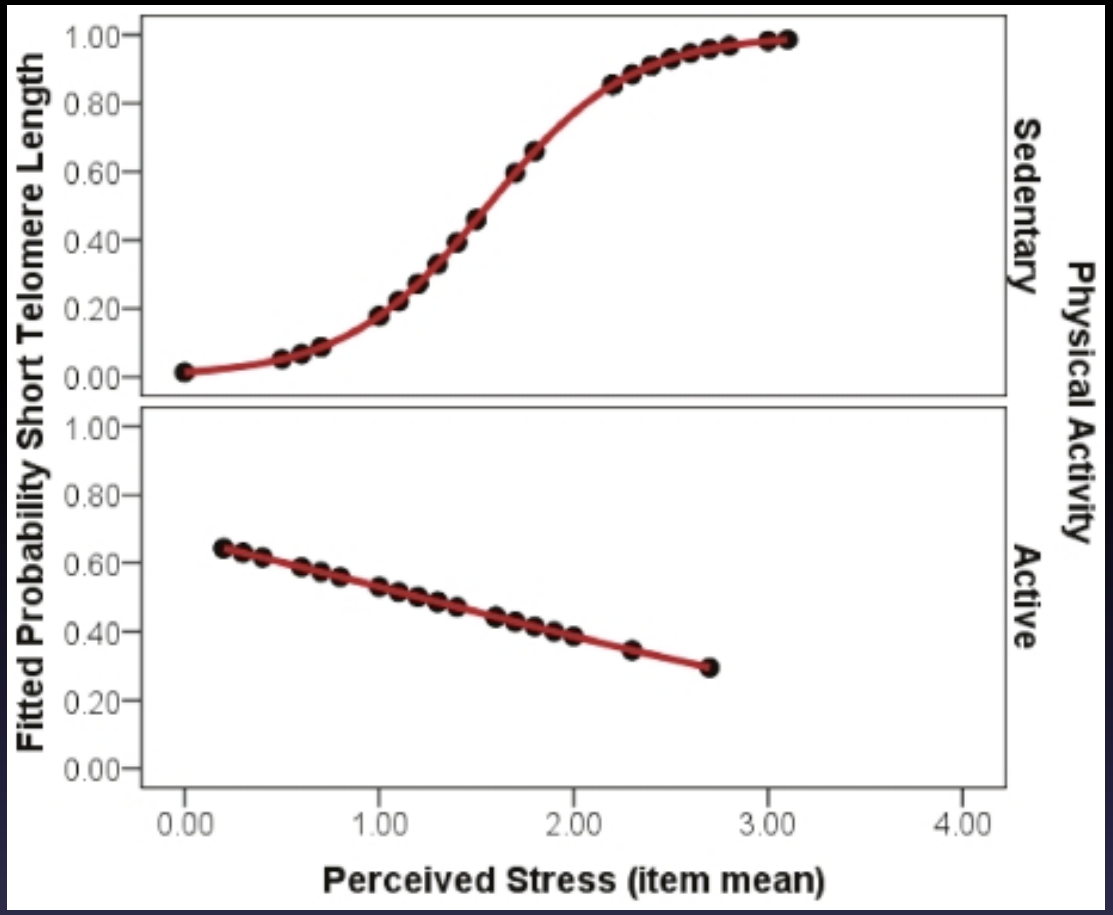
Puterman et al, PlOS 2010 5:e10837



Relationship between perceived stress and telomere length as a function of physical activity.

Note. Physical activity categories are based on whether the participant met CDC recommended levels of exercise per week. Perceived stress ratings are based on the Perceived Stress Scale. The relationship between perceived stress and telomere length was significant in sedentary participants only.

Puterman et al, PlOS 2010 5:e10837



Fitted Probability of short telomeres as a function of perceived stress for sedentary and active individuals.

Note. Physical activity categories are based on whether the participant met CDC recommended levels of exercise per week. Perceived stress ratings are based on the Perceived Stress Scale. The interaction effect was significant ($p<.05$), indicating that the relationship between perceived stress and telomere length was significant in inactive participants only. The Y axis probability presents the probability of categorization into short telomere length (bottom tertile) as a function of perceived stress in inactive (top of figure) versus active (bottom of figure) participants. Probability scores were calculated from the fitted regression equations, assuming mean BMI and education level.

Puterman et al, PlOS 2010 5:e10837

Possible Mechanisms

- Decreased overall damage would decrease the number of cell divisions necessary to replace lost cells
- Some aspects may also turn on a bit more telomerase activity

Possible mechanisms

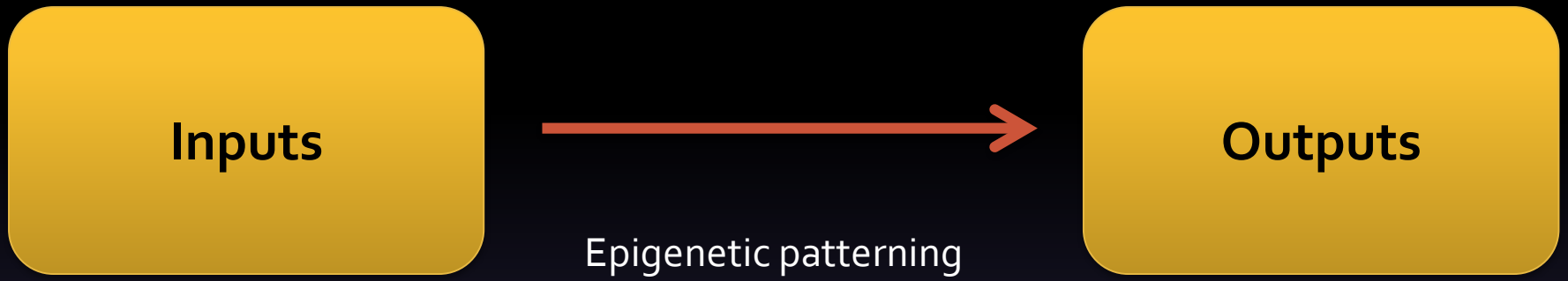
- Changes in gene expression (stress response, growth/proliferation, and/or telomerase pathways)
  - Researchers noted changed expression of mRNA and miRNAs involved in telomerase activity when participants ran on a treadmill for 30 minutes at 80% of peak oxygen uptake – Chilton et al, PLosOne, 2014, 9:e92088
- Changing balance between oxidative stress and antioxidants
- Autonomic, neuroendocrine, cognitive pathways

Conclusions

- "Telomere length decreases with age in sedentary individuals, longer telomeres are observed in individuals who are moderately active, and extreme long-duration endurance training for an extended portion of one's lifetime may result in telomere shortening."

Ludlow et al, Do Telomeres Adapt to Physiological Stress? Exploring the Effect of Exercise on Telomere Length and Telomere-Related Proteins. Biomed Res Int. 2013, 2013:601368

Model



Genes
Diet
Activity
Mental state
Environment
Social Economic Status
Etc.

Epigenetic patterning
Telomere length
Differential gene expression
Cellular and tissue damage
DNA damage
Other mechanisms

Lifespan
Health and Disease
Performance measurements
Blood chemistries
Etc.

References and Resources

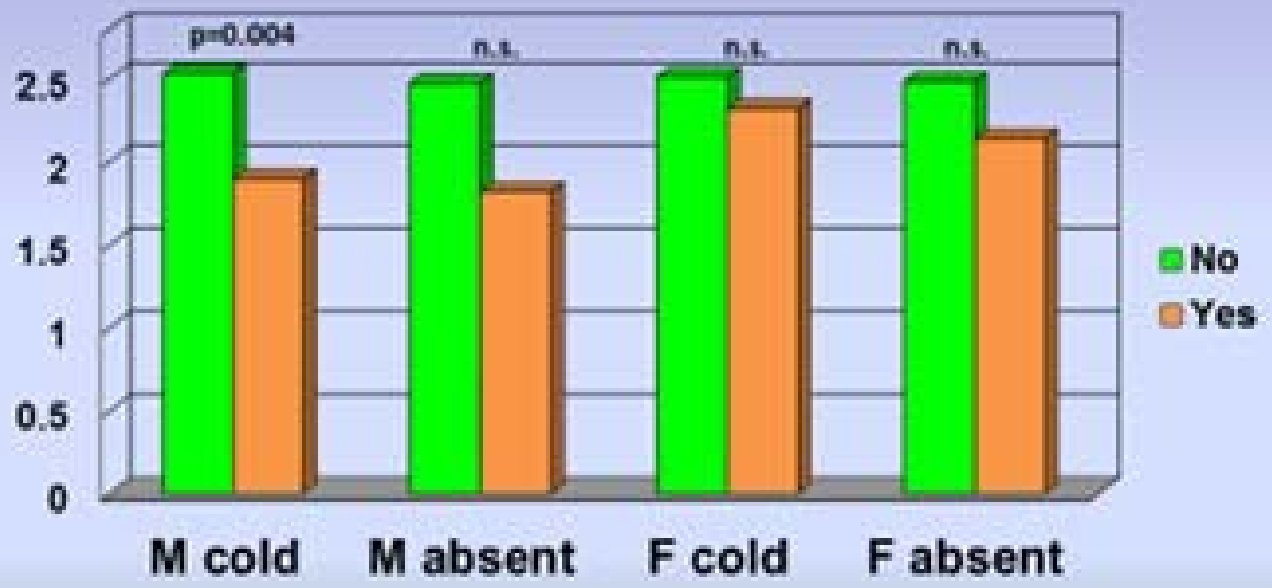
- AR Starkweather, et al, An integrative review of factors associated with telomere length and implications for biobehavioral research. Nurs Res. 2014, 63;36.
- E Puterman et al, The Power of Exercise: Buffering the Effect of Chronic Stress on Telomere Length. PLoS One 2010: 5(5): e10837
- AT Ludlow et al, Do telomeres adapt to physiological stress? Exploring the effect of exercise on telomere length and telomere-related proteins. Biomed. Res. Int. 2013, 2013:601368.

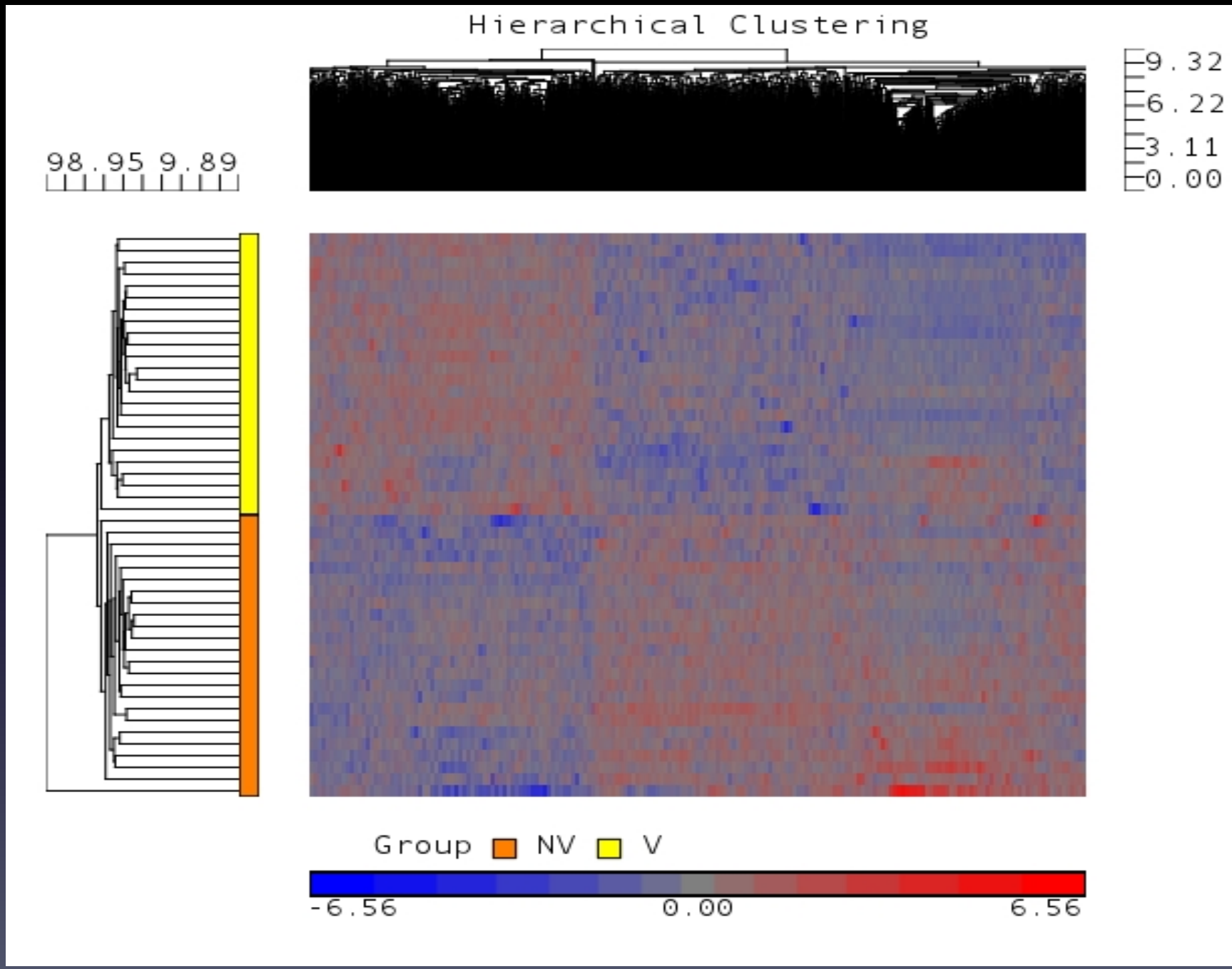
References and Resources

- Ludlow and Roth, Physical activity and telomere biology: exploring the link with aging-related disease prevention. J Aging Res 2011, 2011:790378
- Google or PubMed Blackburn, E and Ludlow, AT

Questions?

Figure 1. Telomere length according to parenting style and parental presence during childhood.




Hierarchical Clustering
9.32
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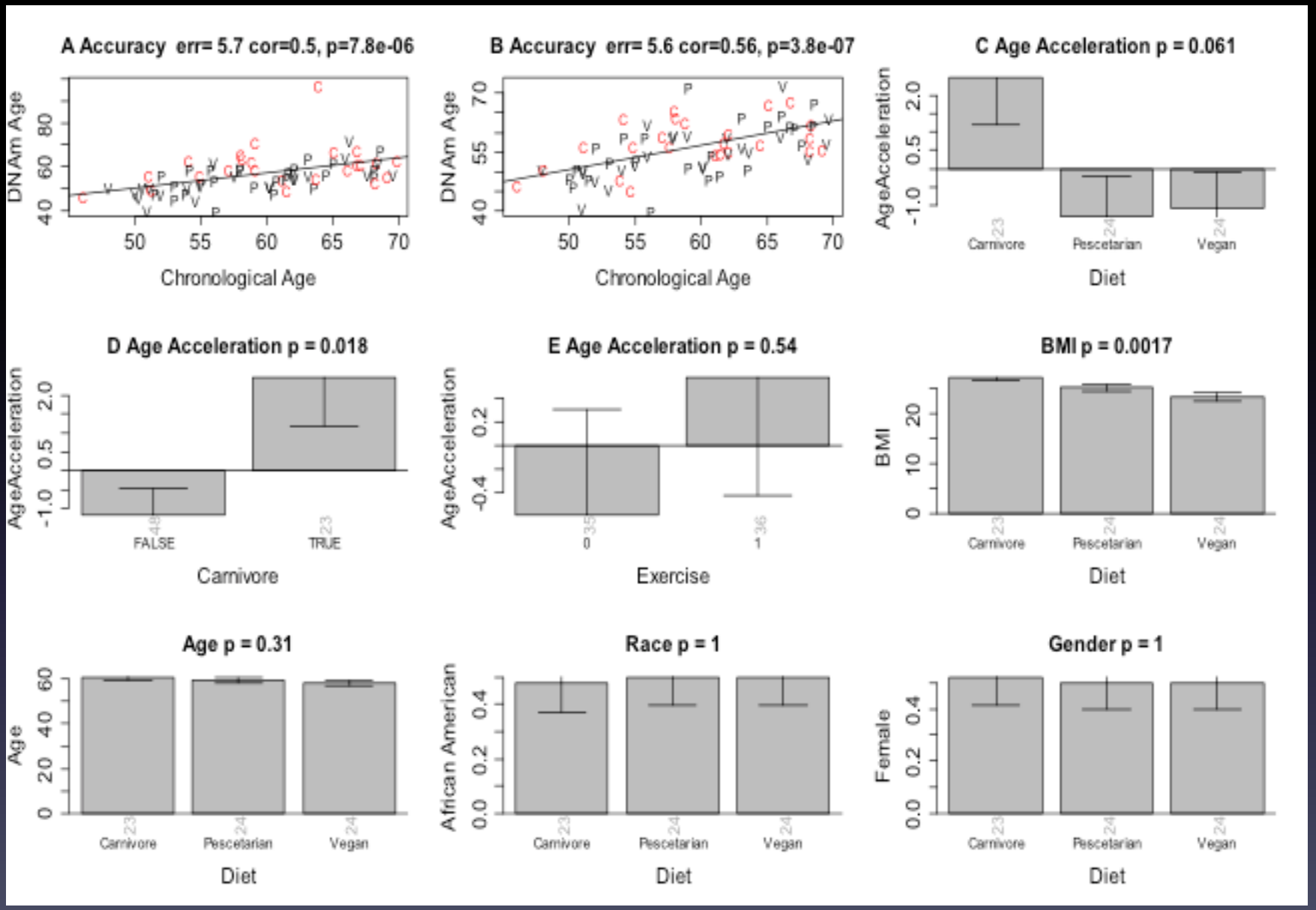
A Accuracy err= 5.7 cor=0.5, p=7.8e-06
DNAm Age
Chronological Age
B Accuracy err= 5.6 cor=0.56, p=3.8e-07
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C Age Acceleration p = 0.061
AgeAcceleration
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D Age Acceleration p = 0.018
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TRUE
Carnivore
E Age Acceleration p = 0.54
AgeAcceleration
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Exercise
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Diet
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Carnivore
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Vegan
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