

# Ageing, Epigenetics and Environment

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# Outline for today

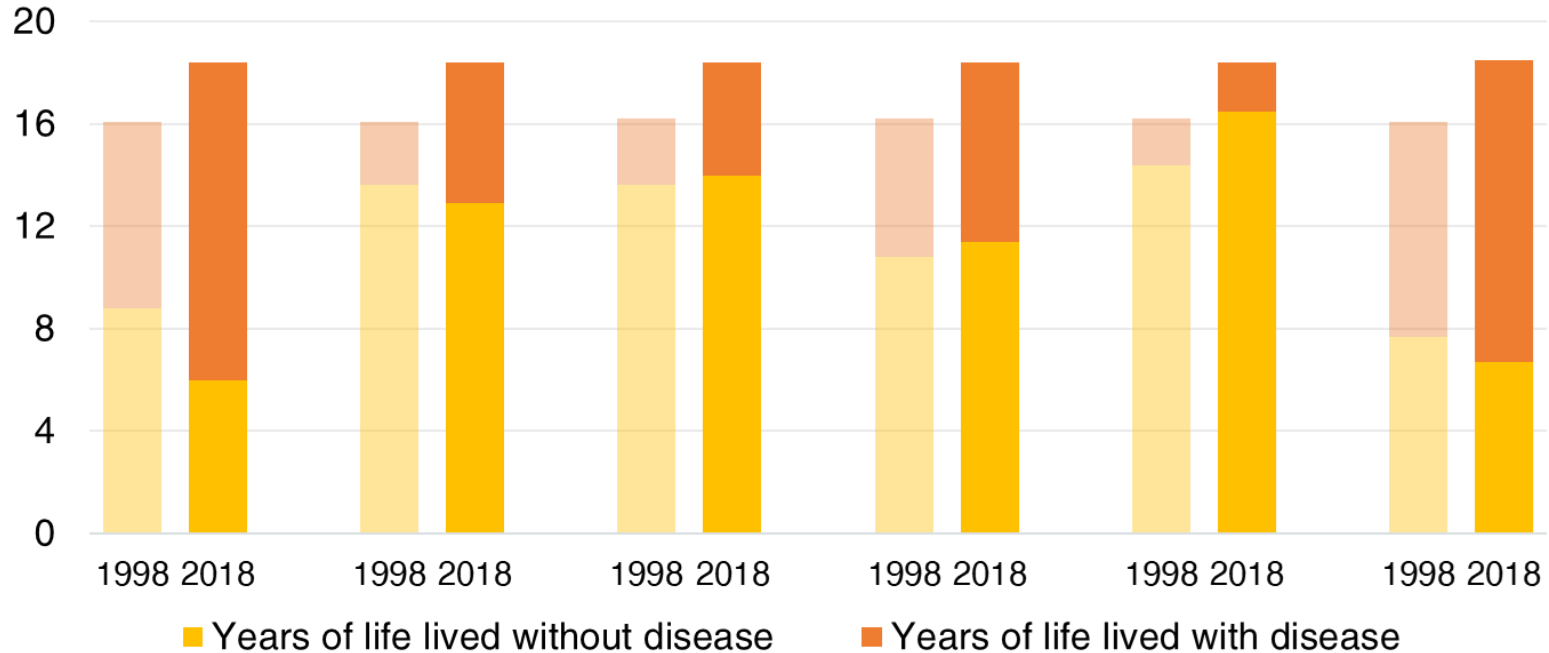
- Healthy ageing
- Biological changes underlying ageing including epigenetics
- The environment, epigenetics, and ageing

# Healthy ageing results from delaying a process of health changes to later ages and increasing healthy years

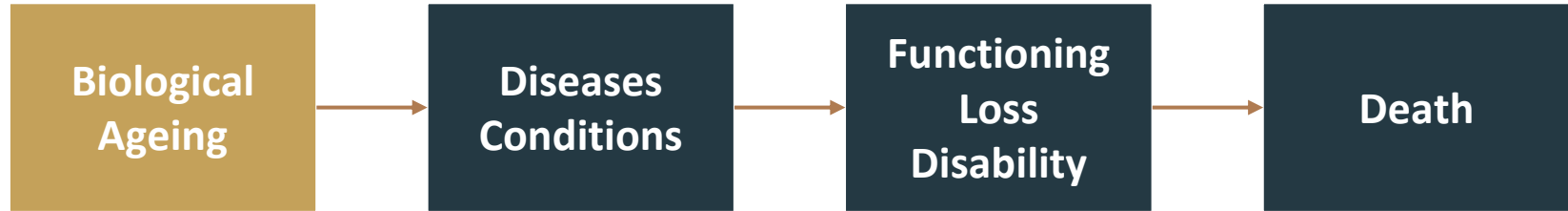


Source: Crimmins EM. Lifespan and healthspan: past, present, and promise. *The Gerontologist*. 2015 Dec 1;55(6):901-11.

**Now we intervene after diagnosis of disease:  
This has had mixed consequences: Increases in life expectancy at age 65  
but increases in life with disease or unhealthy life over time**



**We need to be able to identify adverse ageing earlier in the process - Biological ageing that precedes disease onset**



Source: Crimmins EM. Lifespan and healthspan: past, present, and promise. *The Gerontologist*. 2015 Dec 1;55(6):901-11.

# Biological ageing captured by multisystem changes that are potentially below clinically defined levels of risk

Example - Cathal McCrory with others - found 5 biomarkers could capture this - and predict mortality

- **C reactive protein**
- **Resting heart rate**
- **HDL cholesterol**
- **Waist height ratio**
- **Glycosylated hemoglobin**



Psychoneuroendocrinology

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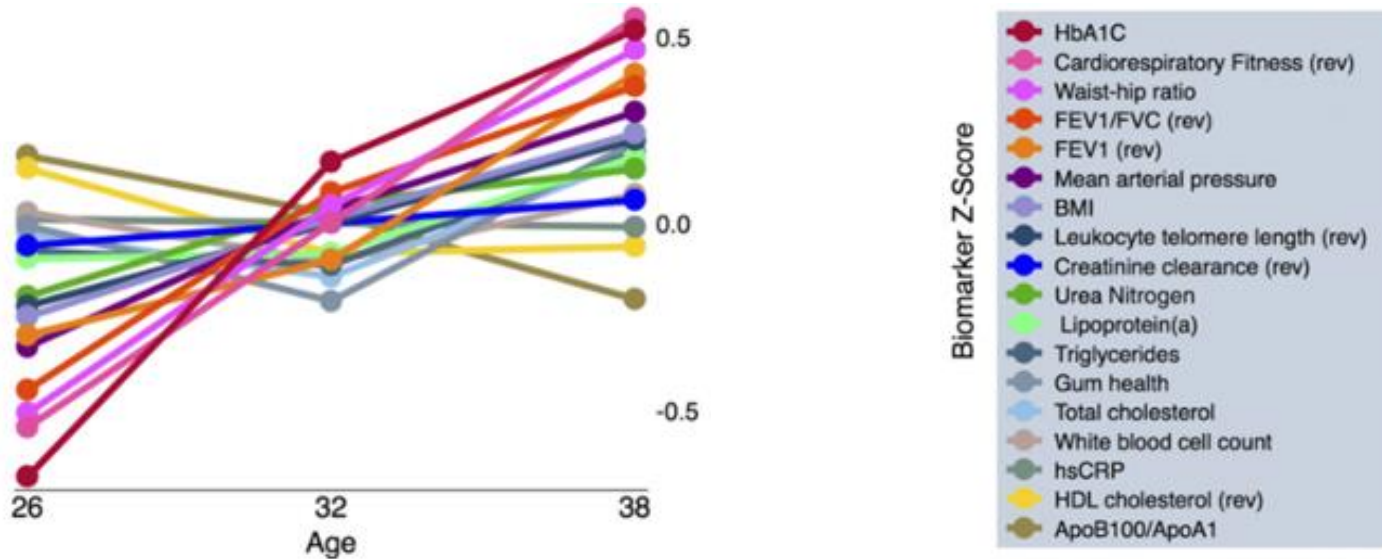


Towards a consensus definition of allostatic load: a multi-cohort, multi-system, multi-biomarker individual participant data (IPD) meta-analysis

Cathal McCrory<sup>a</sup>  , Sinead McLoughlin<sup>a</sup>, Richard Layte<sup>b</sup>, Cliona NiCheallaigh<sup>c</sup>, Aisling M. O'Halloran<sup>a</sup>, Henrique Barros<sup>d</sup>, Lisa F. Berkman<sup>e</sup>, Murielle Bochud<sup>f</sup>, Eileen M. Crimmins<sup>g</sup>, Meagan T. Farrell<sup>e</sup>, Silvia Fraga<sup>d</sup>, Emily Grundy<sup>h</sup>, Michelle Kelly-Irving<sup>i</sup>, Dusan Petrovic<sup>f</sup>, Teresa Seeman<sup>j</sup>, Silvia Stringhini<sup>f k</sup>, Peter Vollenweider<sup>l</sup>, Rose Anne Kenny<sup>a</sup>

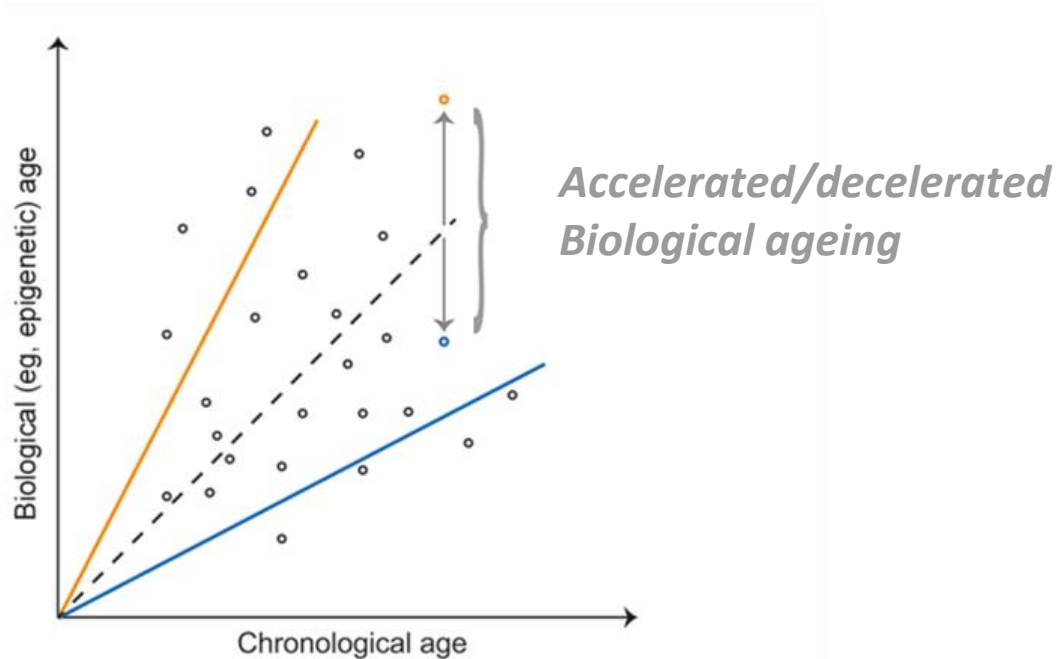
## When does this biological ageing begin?

Belsky et al. used 18 measures but showed changes begin very early from 20s



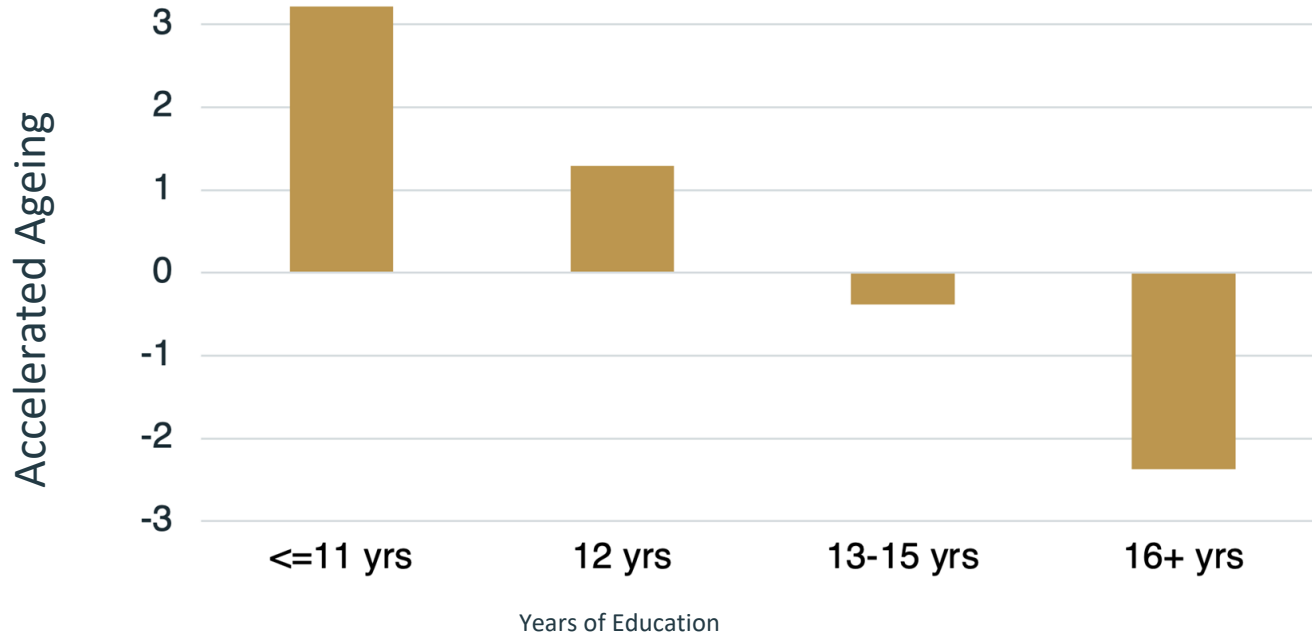
Belsky DW, Caspi A, Houts R, Cohen HJ, Corcoran DL, Danese A, Harrington H, Israel S, Levine ME, Schaefer JD, Sugden K. Quantification of biological aging in young adults. *Proceedings of the National Academy of Sciences*. 2015 Jul 28;112(30):E4104-10.

These markers have been turned into estimates of Biological age and the differences between Biological Age and Chronological Age indicates Accelerated and Delayed Ageing

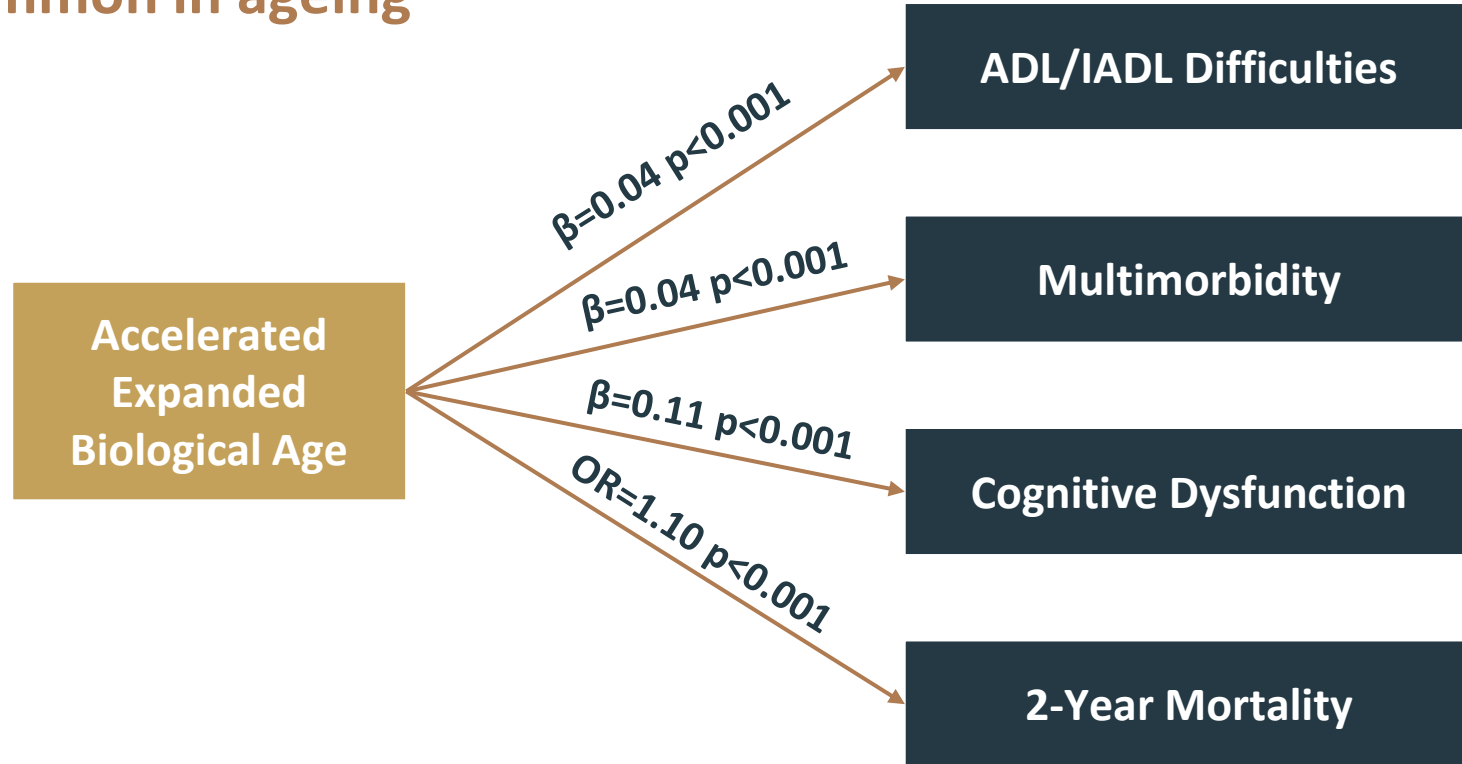




## Example: Lower education is associated with accelerated ageing among older Americans



## Biological ageing is then associated with health outcomes common in ageing

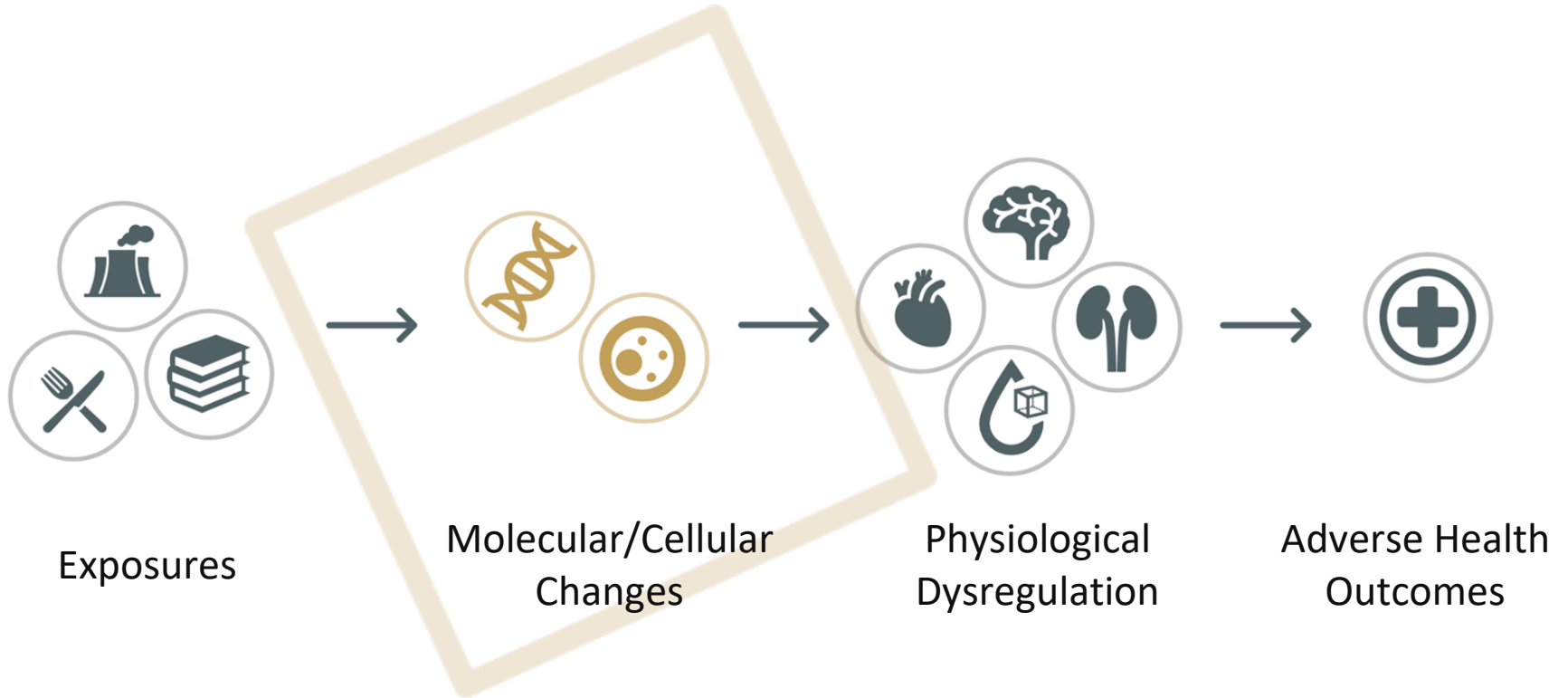


# The new approach to delaying ageing

- Treat more components of biological age and treat at younger ages and lower levels
- Some are treatable now, e.g. metabolic, inflammatory, metabolic
- Some may become more treatable shortly



# Now we have a new level of biology to consider – Geroscience Molecular and Cellular Ageing



# Genetics and Genomics

## Genomics

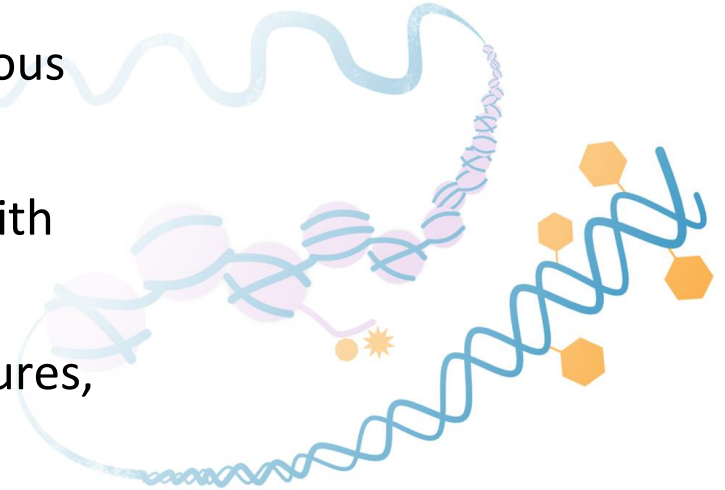
Genes in DNA - Give instructions to cells  
*Do not change*

## Epigenomics

Modifications that can change the instructions to cells  
*Affected by lifetime exposures and experiences*

## Epigenetic measures are now in a number of populations including Northern Ireland (NICOLA), Republic of Ireland (TILDA) and U.S. (HRS)

- Most common are epigenetic clocks that provide estimates of epigenetic age analogous to biological age
- Levels and patterns of change associated with many age-related health outcomes
- Related to adverse life events, social exposures, stress, environmental hazards, etc.



# Epigenetic Clocks have really caught on!

- What we've shown:
  - Sleep problems, social relationships, occupation, ADHD genetic risk, education, traumatic events, adverse childhood experiences, depression, smoking
  - Almost all health outcomes
- Lot of info in a drop of blood
- Epigenetic age may be changeable/treatable!



# Biological Age and Epigenetic Age are changeable

- Calorie restriction over 2 years reduced biological and epigenetic age
- Now being used as endpoints in trials of anti-ageing drugs and supplements, e.g. metformin, vitamins etc.
- Biological and epigenetic age *can be* reduced with good behavior, e.g. weight, smoking, non sedentary behavior
- New drugs are in development with these as endpoints



The  
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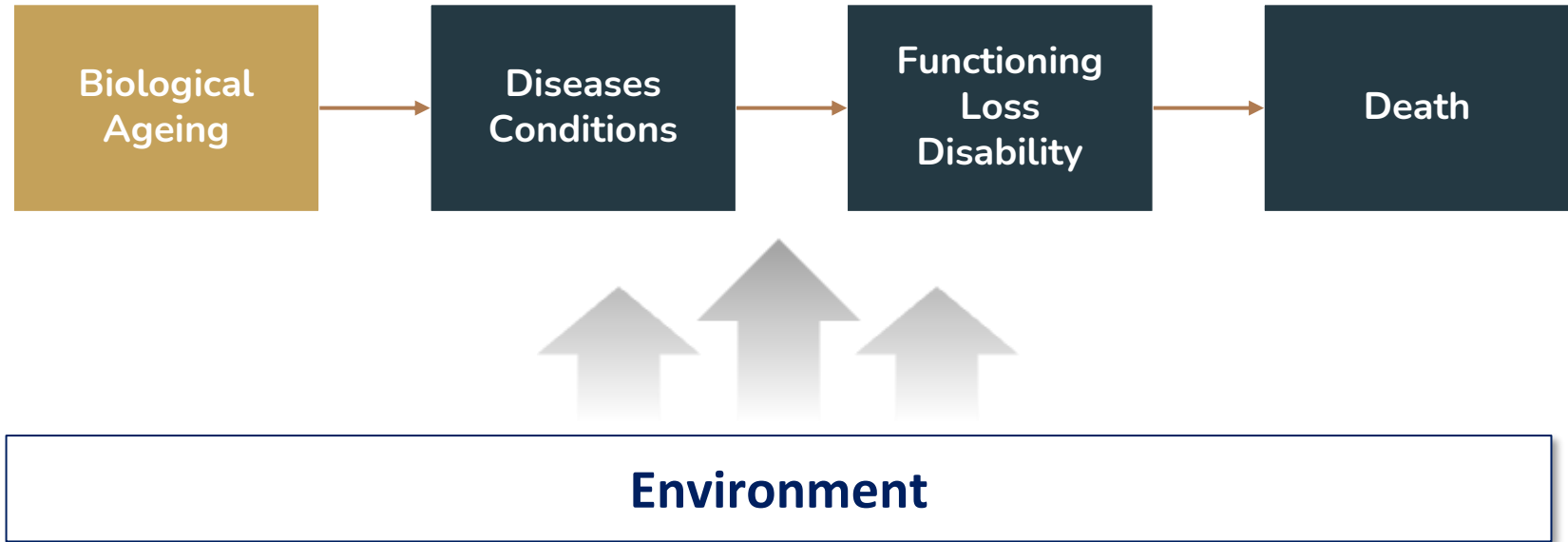
## LIVING TO 120

A SPECIAL REPORT ON HOW TO SLOW AGEING



But do not fall  
for current hype:  
Not ready for primetime

We need to be able to identify adverse ageing earlier in the process – What about environmental risks?





**UNRAVELING THE INFLUENCE  
OF ENVIRONMENTS ON  
AGEING AND EPIGENETICS**



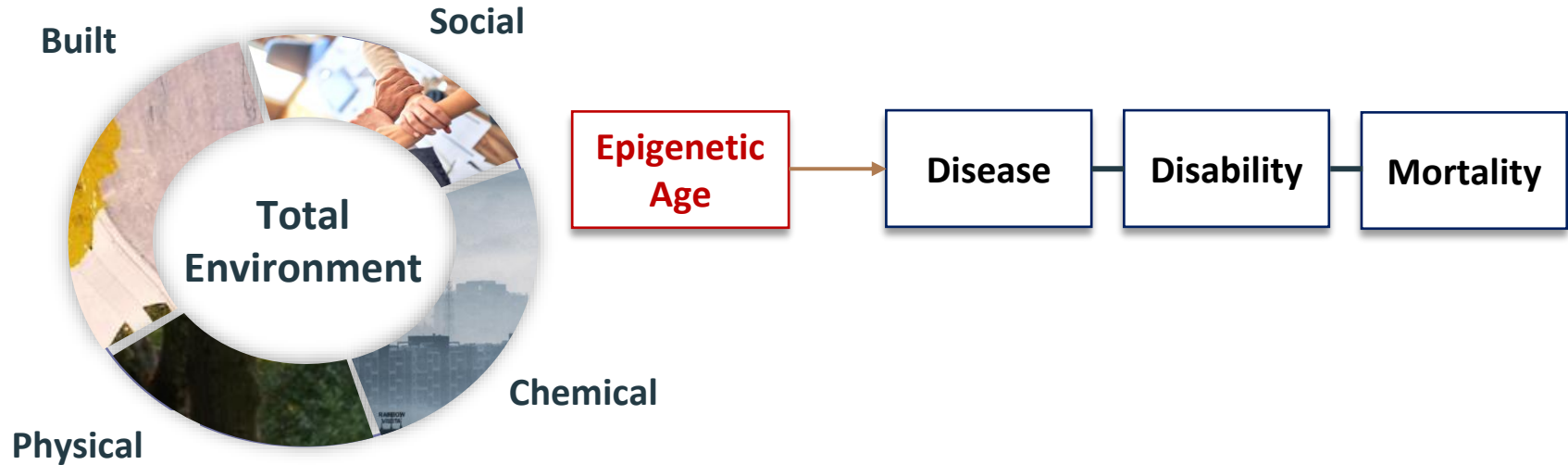
# Importance of Environment in Ageing

- Addressing environment rather than people in policies and programs
  - Place-based interventions are effective health policy
  - Environmental changes can impact *many* individuals and *many* outcomes
- Shifting perspectives on the key drivers of individual and population health
  - Lives are experienced in a broader context
  - Environments can determine how health evolves over the lifecourse

# Environment and Ageing-Related Outcomes

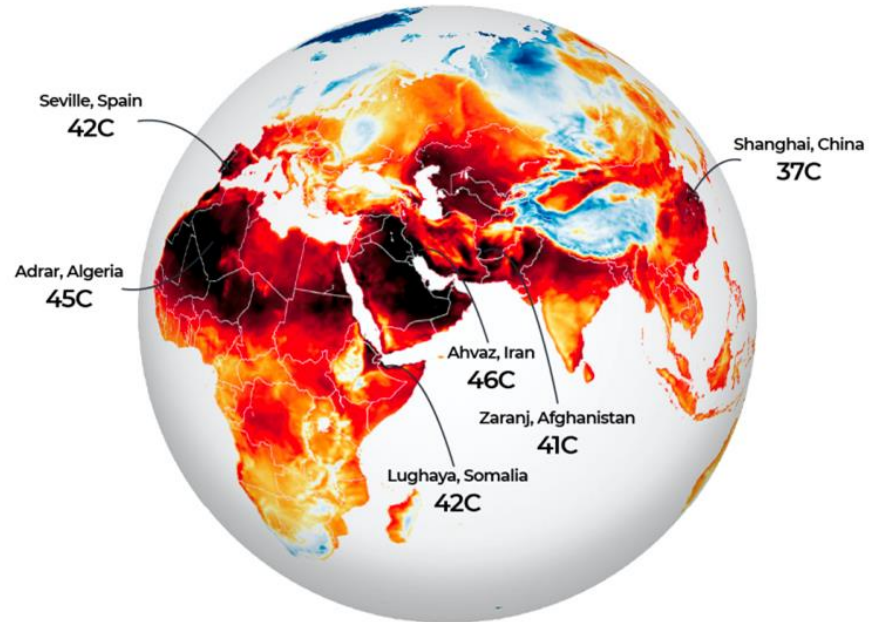
Upstream

Downstream



# Increasing frequency, intensity, and duration of extreme heat around the world

- The global mean for 2023 is the third highest on record
- Extreme heat has struck Europe, North Africa, and Middle East and Asia, causing many heat-related deaths



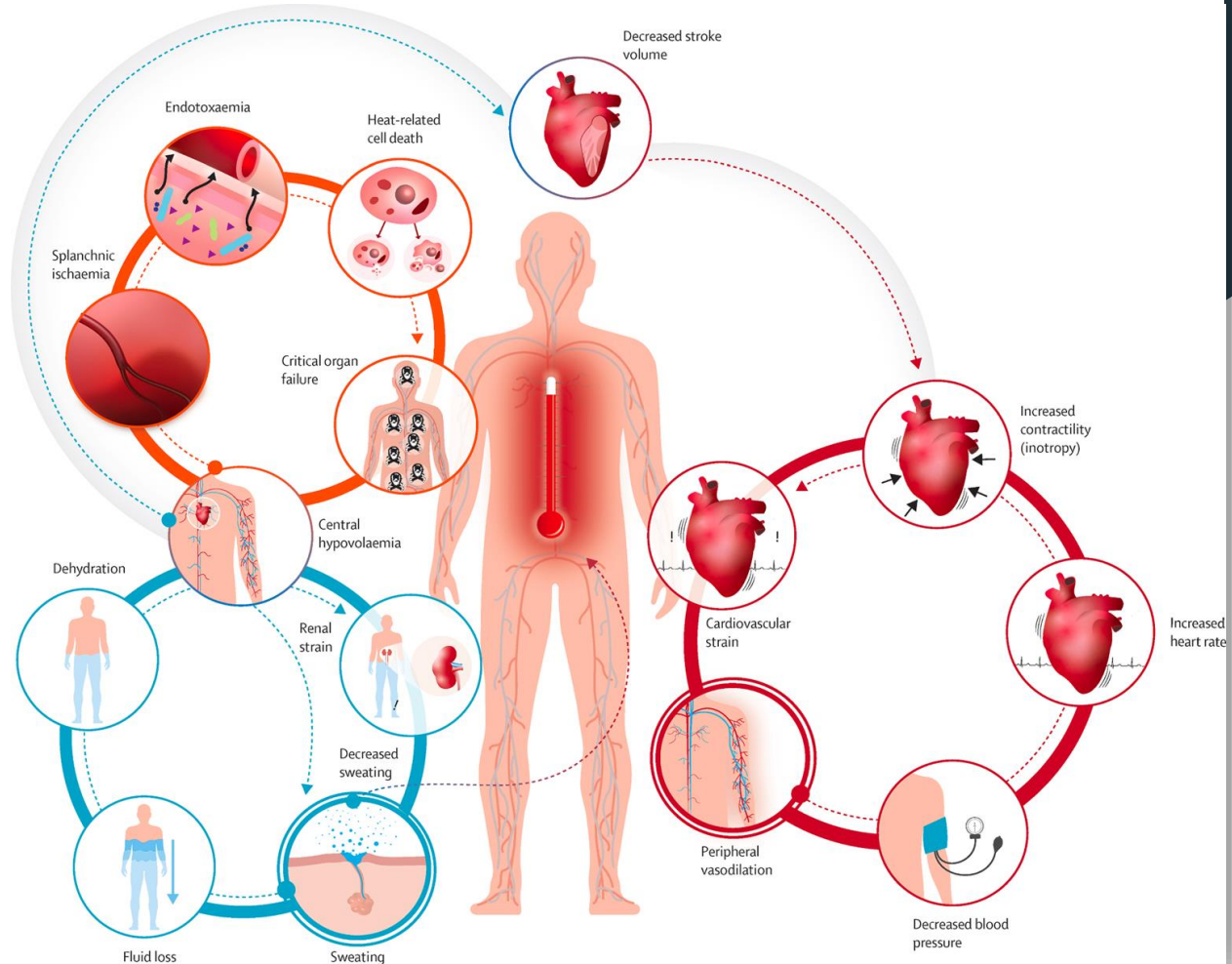
Source: <https://www.aljazeera.com/news/2023/8/8/july-2023-hottest-month-on-record-as-heatwaves-scorch-earth>



Source: NASA Earth Observatory image by Joshua Stevens | July 13, 2022



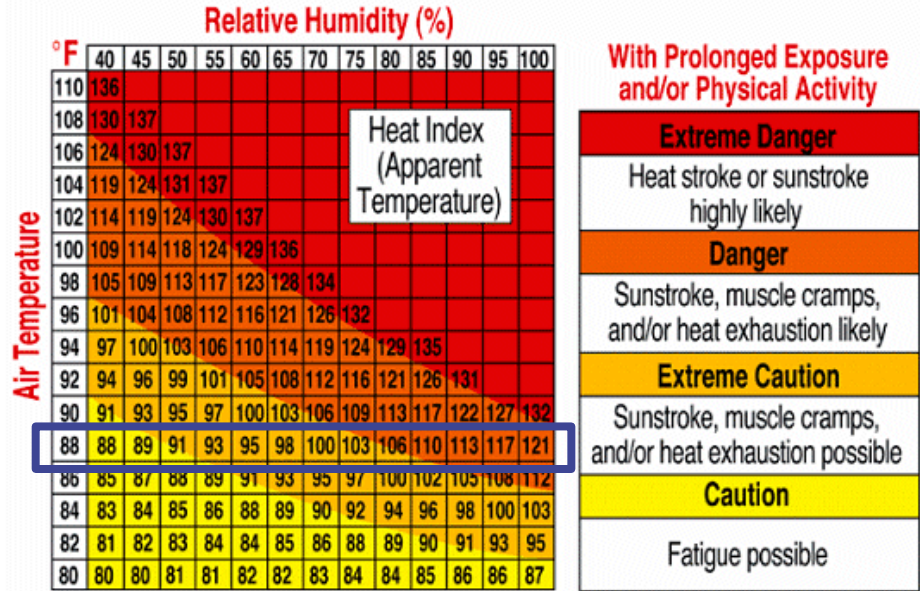
# Heat exposures may accelerate biological ageing



Source: Ebi et al. (2021). Hot weather and heat extremes: health risks. *The Lancet*, 398(10301), 698-708.

# How do we measure extreme heat exposure?

- The Heat Index is a measure of how hot it “feels” to humans (air temperature + relative humidity)
- Higher levels of moisture make it harder for bodies to cool down
- At 88F (31 C), one is in “**Caution**” at 40% humidity, but shifts to “**Extreme Caution**” at 70% humidity and “**Danger**” at 90% humidity.



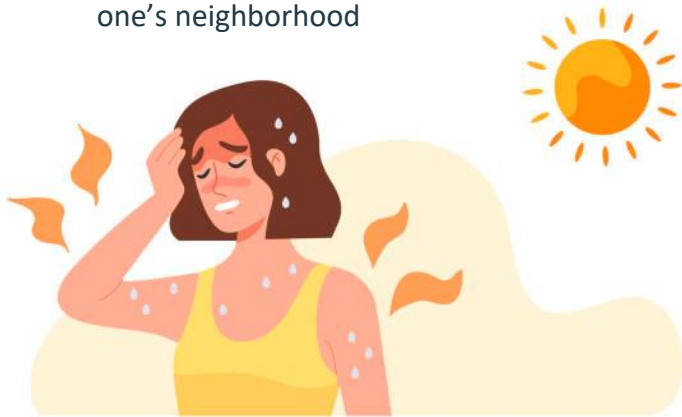
Source: Courtesy of the National Weather Service , All Rights Reserved.



# Study of heat and epigenetic ageing in U.S. older adults

## Extreme Heat

Number of Heat Days at Caution, Extreme Caution, Dangerous Level in one's neighborhood



### Contextual Data Resource

gridMet data repository of high spatial resolution (~4-km) surface meteorological variables



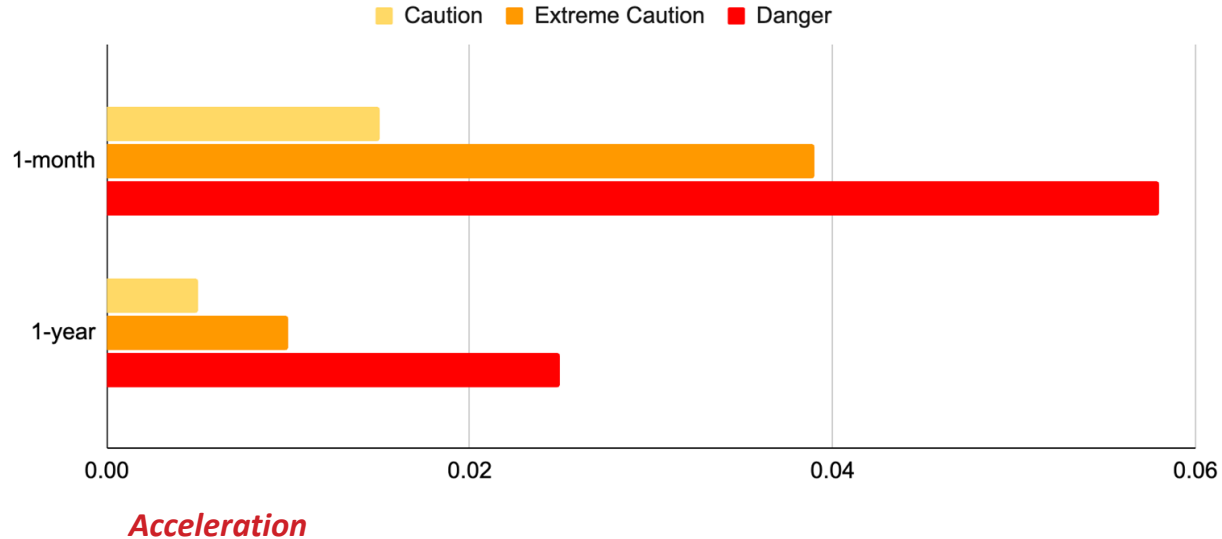
## Epigenetic Clocks

Adults aged 50 and older (N~3,500)

### Health and Retirement Study



# Heat exposure and accelerated epigenetic Ageing



- Every additional heat day is associated with increased accelerated epigenetic aging.
- Greater intense, recent heat exposure matters more.

# Heat disproportionately affects vulnerable individuals



61,000 Europeans may have died in last summer's heat waves, exper

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CLIMATE IN CRISIS

## 61,000 Europeans may have died in last summer's heat waves, experts say

As human-caused climate change drives temperatures higher, heat waves are becoming more frequent and severe.

- Most victims *are older adults, women, and those who live alone*

# Study of neighbourhood social environment and epigenetic ageing in U.S. older adults

## Social Environment

Signs of disorder and neglect.  
Perceptions of neighbourliness.



## Epigenetic Clocks

Health and Retirement  
Study



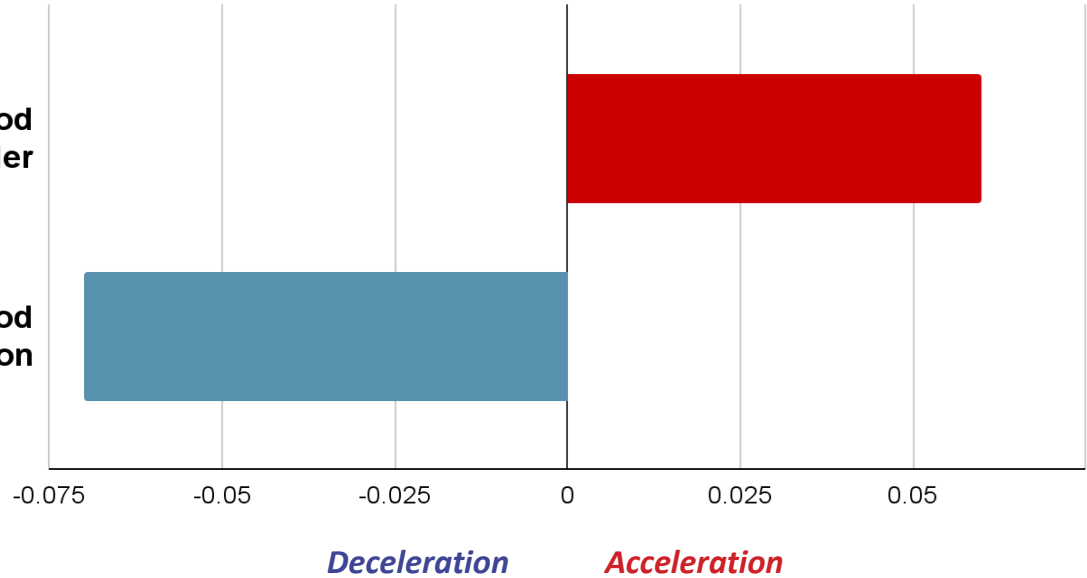
# Neighborhood Social Environment and Epigenetic Aging



**Neighborhood Disorder**



**Neighborhood Cohesion**



# Emerging evidence strongly suggests important environment-epigenetic connection



- More green space  
~Slower epigenetic ageing  
(Kim et al. 2023; Xu et al. 2021)

- Air pollution  
~ Faster epigenetic ageing  
(Ward-Caviness et al., 2016)

- Neighborhood deprivation  
~ Faster epigenetic ageing  
(Smith et al. 2017; Lei et al. 2022)

Lead, mercury,  
magnanes, and copper  
~ Faster epigenetic  
ageing (Lodge et al. 2022)

# Ageing, Epigenetics, and Environment: Concluding Thoughts

- Efforts to reduce epigenetic aging (e.g., through drugs, diets) may be thwarted by growing environmental threats
- We need to think about how our environments may be aging us
- Improving environmental conditions as important as drug discovery and individual-level solutions
- Improving aging across populations will take a cells to society approach



Thank you!