Climate stressors and their implications for biological aging

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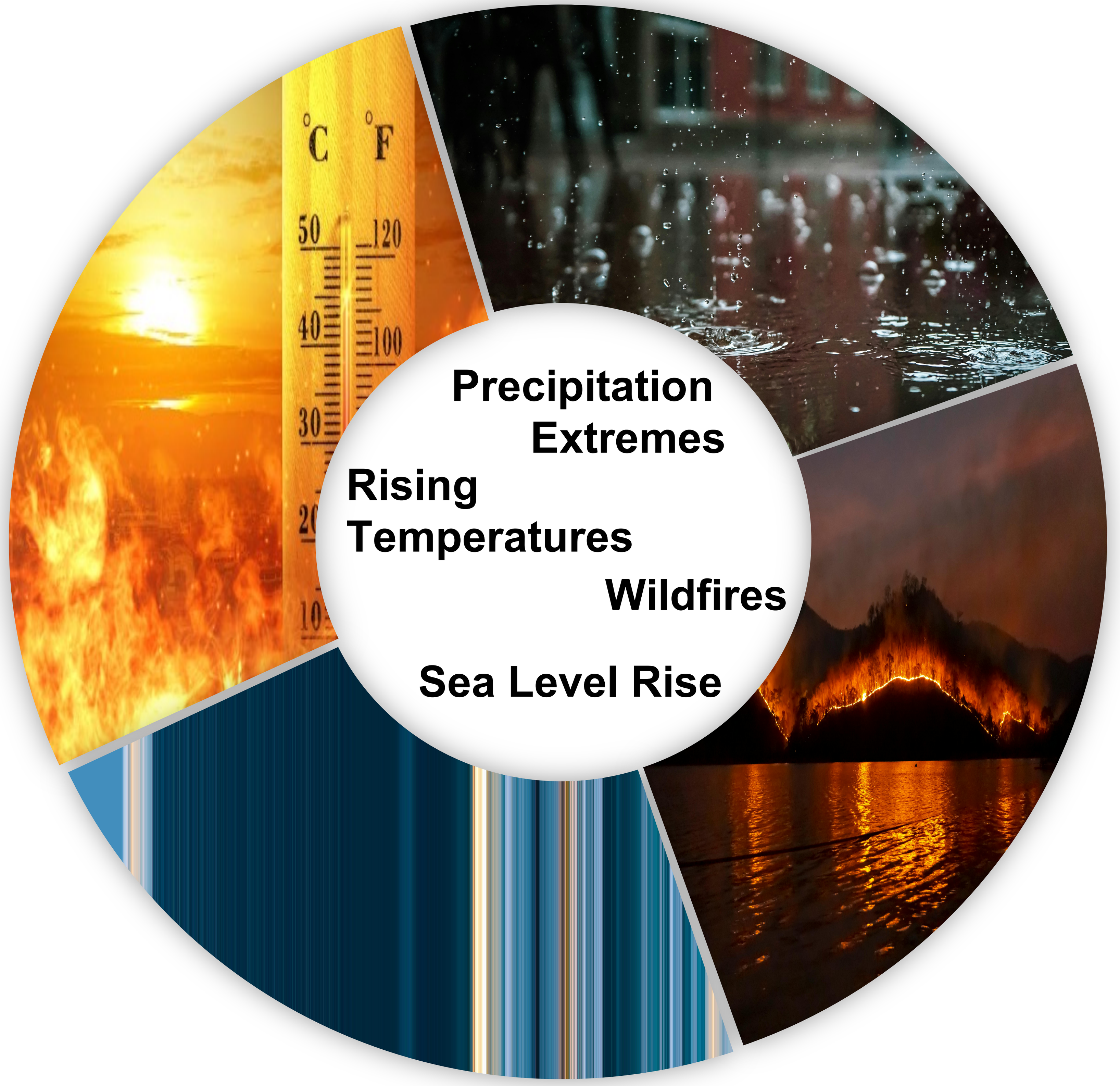
Climate Hazards are Increasingly Known to Adversely Affect Human Health

Climate-related hazards



Biological Aging

- Molecular changes
- Cellular changes
- Decline in system integrity

(1)(2)

Disease (Cardiovascular, respiratory, infectious)

Injuries

Mental & Neurological Disorders

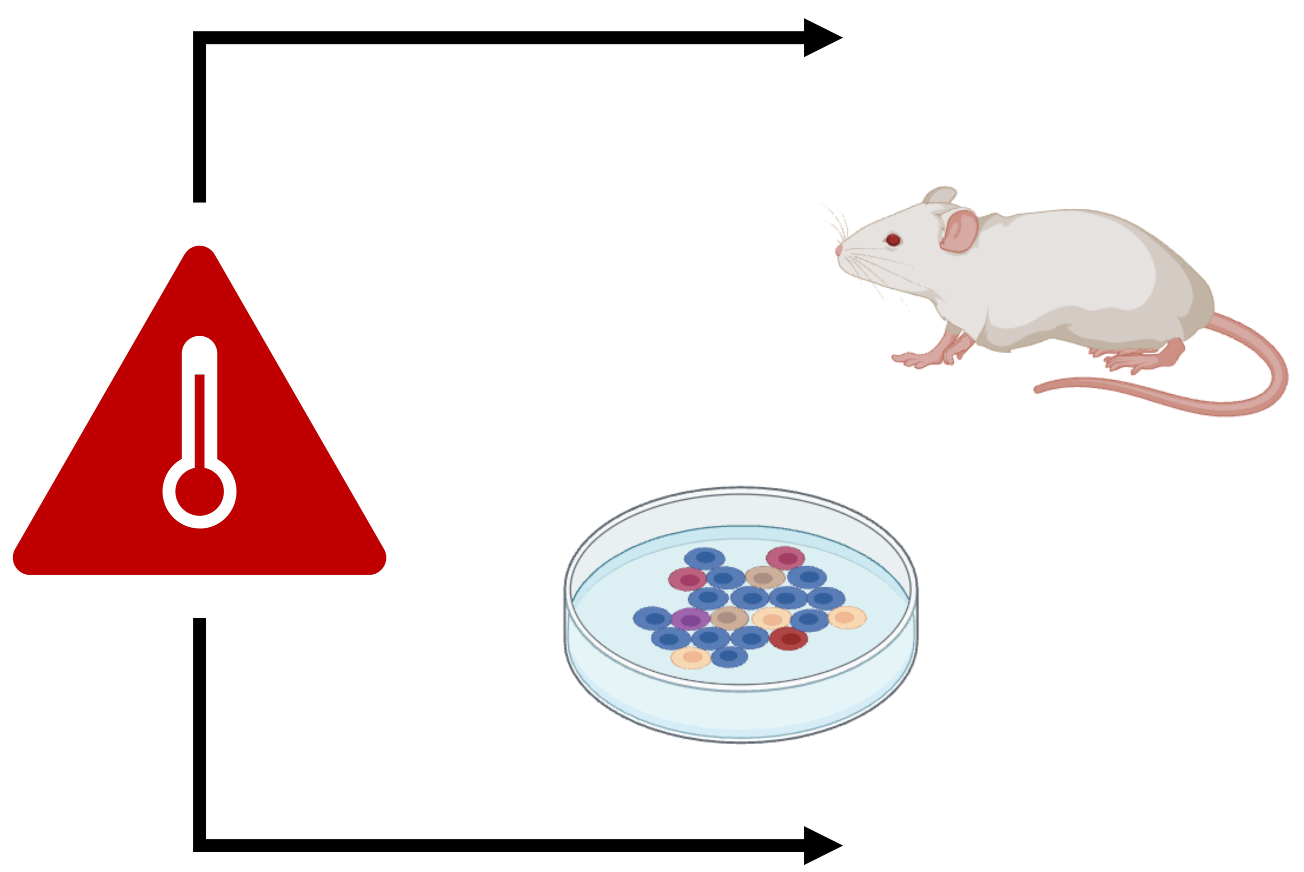
Mortality

Yet, the biological underpinnings are far from clear

(1) Rocque RJ, Beaudoin C, Ndjaboue R, *et al* Health effects of climate change: an overview of systematic reviews *BMJ Open* 2021;**11:**e046333.
(2) Weilnhammer, Veronika, *et al.* Extreme weather events in europe and their health consequences–A systematic review. *Int. J. Hyg. Environ 2021;***233**:13688.

Some Climate Hazard-Biological Links Have Been Well-Characterized

Moderate intensity



Very high intensity

- Induce adaptive epigenetic memory[2]
- Promote the immune system[4]

- Lead to increased DNA damage[1]
- Result in maladaptive epigenetic memory[2]
- Disrupt innate and adaptive immune responses[3]

But do these findings from a model system translate to human health?

(1) Habibi, Peymaneh, et al. "Effect of heat stress on DNA damage: a systematic literature review." International journal of biometeorology 66.11 (2022): 2147-2158.
(2) Murray, Kevin O., Thomas L. Clanton, and Michal Horowitz. "Epigenetic responses to heat: From adaptation to maladaptation." Experimental Physiology 107.10 (2022): 1144-1158.
(3) Aggarwal, Anjali, et al. "Heat stress and immune function." Heat stress and animal productivity (2013): 113-136.
(4) Heintzman, Darren R et al. “Subset-specific mitochondrial stress and DNA damage shape T cell responses to fever and inflammation.” Science immunology vol. 9,99 (2024): eadp3475.

Opportunity to Bridge Social and Biological Sciences

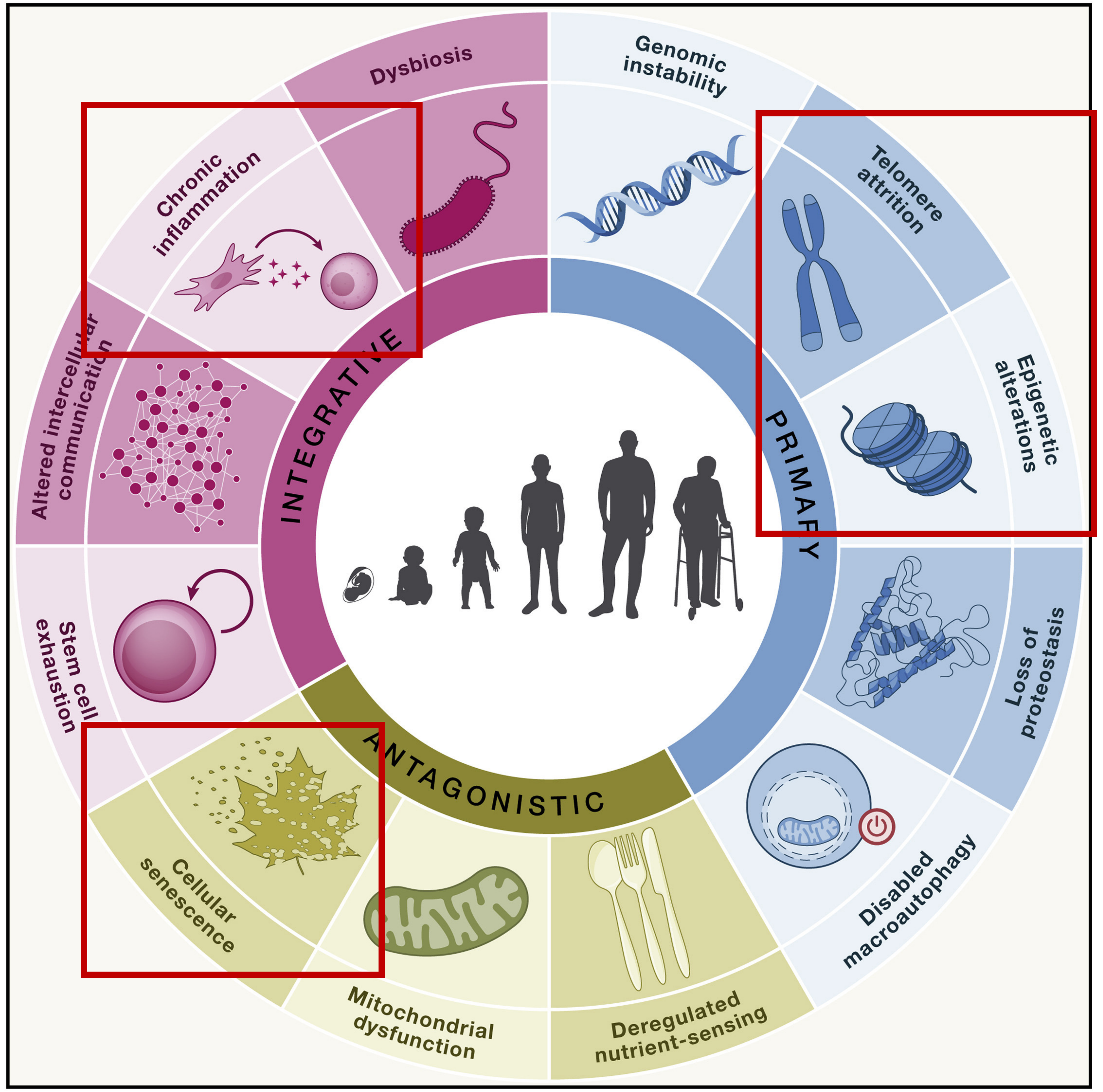
Climate data have increasingly become available at different geographic levels and been linked to population studies

Biomarker data have been collected for physiological changes and expanded to molecular and cellular levels in large aging studies

Multidisciplinary team provides analytic tools and theoretical models

Hallmarks of Aging
Molecular, cellular, physiological changes associated with aging

(1)



(1) López-Otín, Carlos, et al. "Hallmarks of aging: An expanding universe." Cell 186.2 (2023): 243-278.

How Heat is Associated with Biological Aging?

Ambient Outdoor Heat and Accelerated Epigenetic Aging among Older Adults in the US (Choi & Ailshire, Under Review)

Sample

3,875 adults aged 56+, 2016 Health and Retirement Study DNA Methylation (HRS DNAm) sample

Outcome Measure

Epigenetic Age (or Clocks): Composite indicators of DNA methylation patterns associated with aging across the genome

Outdoor Heat Measure

Heat Index: Air temperature, adjusting relative humidity
Number of Heat Days is defined at Caution+ (80°F+) and Extreme Caution+ (90°F+) levels

*- **Linked** to HRS DNAm sample using their geocoded addresses at the census tract and the date of blood collection (*CBPH HRS CDR)*

Relative Humidity (%)

Heat Index (Apparent Temperature)

Air Temperature °F	40	45	50	55	60	65	70	75	80	85	90	95	100
110	136												
108	130	137											
106	124	130	137										
104	119	124	131	137									
102	114	119	124	130	137								
100	109	114	118	124	129	136							
98	105	109	113	117	123	128	134						
96	101	104	108	112	116	121	126	132					
94	97	100	103	106	110	114	119	124	129	135			
92	94	96	99	101	105	108	112	116	121	126	131		
90	91	93	95	97	100	103	106	109	113	117	122	127	132
88	88	89	91	93	95	98	100	103	106	110	113	117	121
86	85	87	88	89	91	93	95	97	100	102	105	108	112
84	83	84	85	86	88	89	90	92	94	96	98	100	103
82	81	82	83	84	84	85	86	88	89	90	91	93	95
80	80	80	81	81	82	82	83	84	84	85	86	86	87

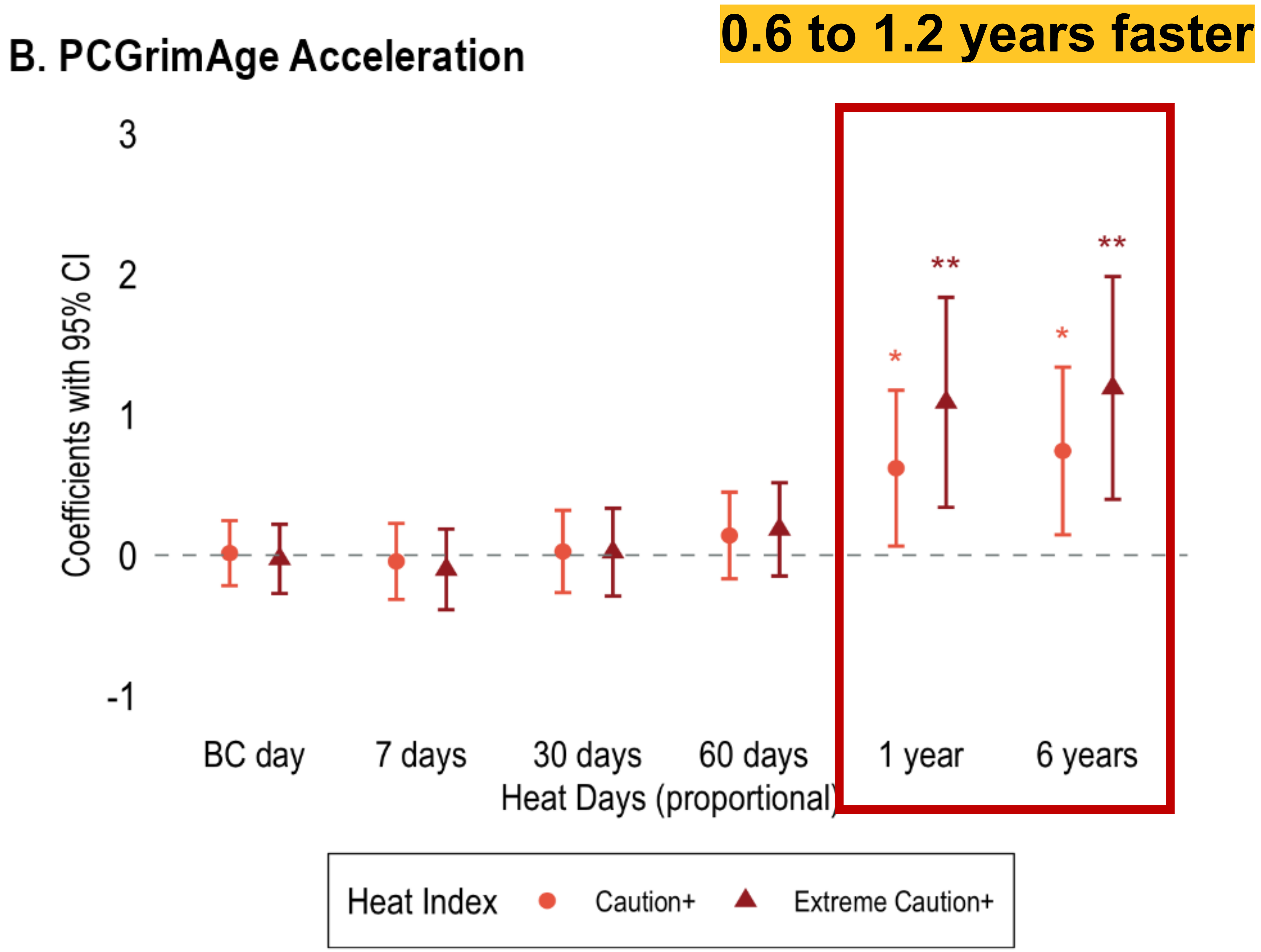
With Prolonged Exposure and/or Physical Activity

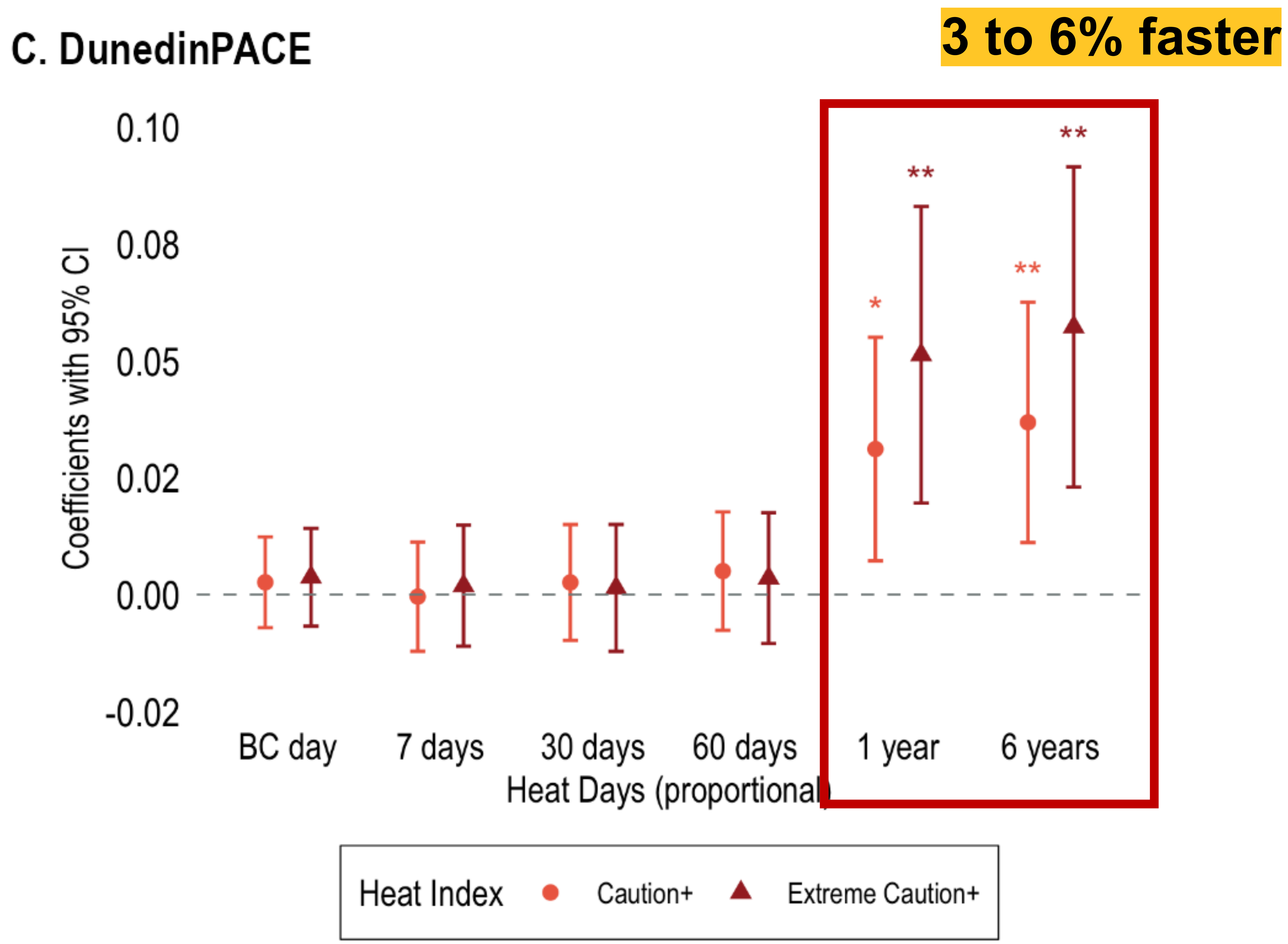
With Prolonged Exposure and/or Physical Activity
Extreme Danger
Heat stroke or sunstroke highly likely
Danger
Sunstroke, muscle cramps, and/or heat exhaustion likely
Extreme Caution
Sunstroke, muscle cramps, and/or heat exhaustion possible
Caution
Fatigue possible

Courtesy of the National Weather Service

Source: USC/UCLA CBPH HRS CDR

Chronic Outdoor Heat is Associated with an Increase in Biological Aging Acceleration





Caution+: 80°F+ *Extreme Caution+*: 90°F+; ***p*<.01; * *p*<.05.
Multilevel regression model predicting epigenetic clocks (unstandardized); Model adjusted for cell types, age, sex, race/ethnicity, education, household wealth, smoking status, alcohol use, obesity, physical activity, tract social vulnerability index, urbanicity, and $PM_{2.5}$ and O_3 levels.

How Heat is Associated with Immunity?

Ambient Outdoor Heat and Adaptive Immunity among Older U.S. Adults (Choi, Seshadri, Ailshire, Thyagarajanm, Unpublished Data)

Sample

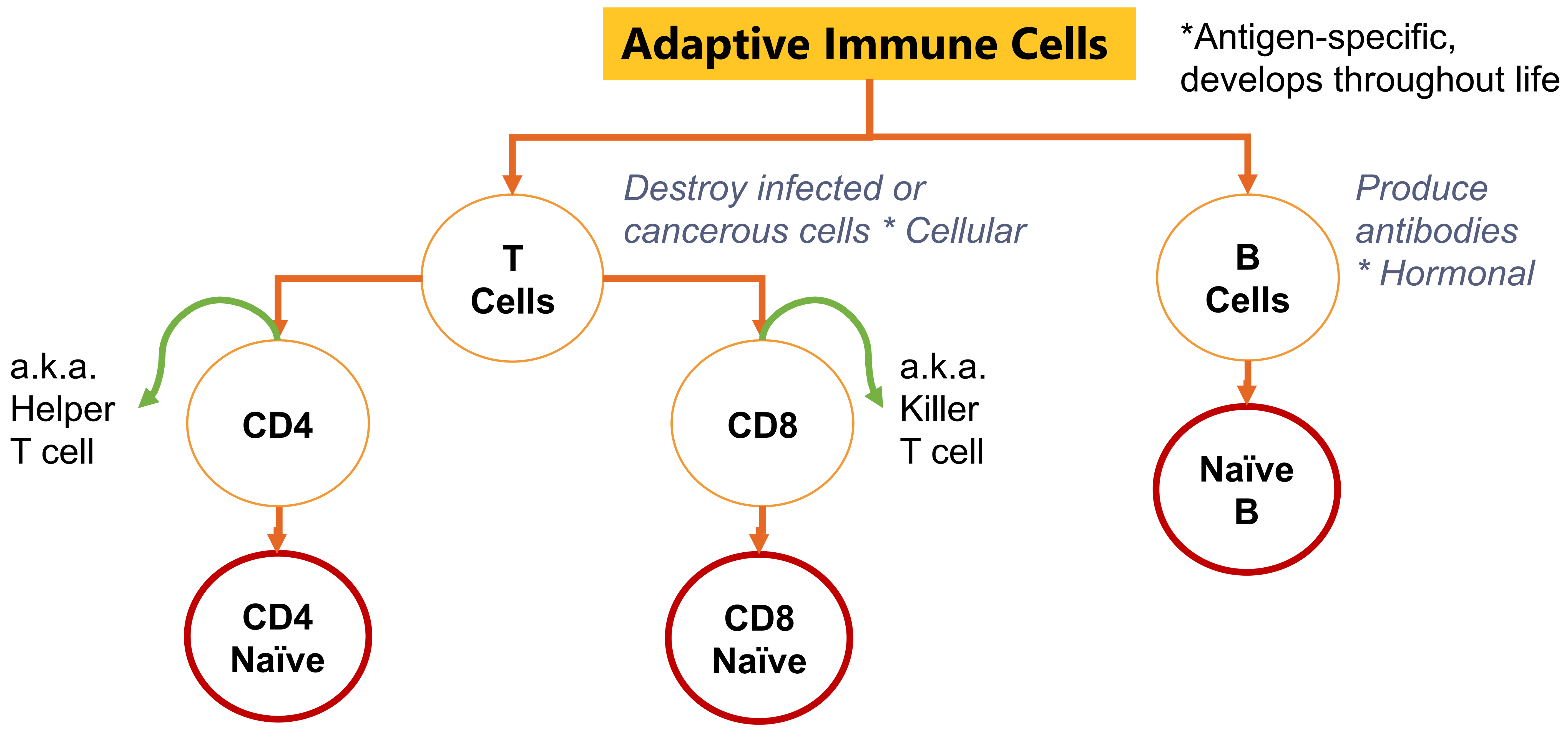
7,302 adults aged 56+, 2016 Health and Retirement Study Venous Blood Study Sample

Outcome Measure

Proportion of **Adaptive Immune Cells**
- CD4 naïve
- CD8 naïve
- Naïve B cells

Outdoor Heat Measure

Mean Heat Index Level



*Simplified

Source: USC/UCLA CBPH HRS CDR

Outdoor Heat is Associated with Immune Responses

****p*<.001; ** *p*<.01; + p <.10; n.s.=not significant

Multilevel regression model predicting proportion of immune cells; Model adjusted for age, gender, race/ethnicity, CMV seropositivity, smoking status, education level, BMI, and comorbidity index

Gaps and Opportunities for Advancing Future Research

- **Longitudinal Biomarker Data**
  - Most existing studies are cross-sectional, limiting understanding of **causality** and tracking **within-person changes** in biological aging to climate stressors over time.

- **Enhance the Specificity of Biomarkers and Link to Other Molecular Factors**
  - Focus on **disease-specific biomarkers**, such as those related to Alzheimer's Disease, cardiovascular, respiratory, could show unique pathways.
  - **Other biomolecular dimensions** – e.g., RNA sequencing data could reveal changes in gene expression related to climate stressors.

Gaps and Opportunities for Advancing Future Research

- **Advanced Modeling Techniques for Total Climate Environments**
  - Climate-related hazard data are increasingly available across time and locations.
  - It is critical to model multiple exposures that occur **simultaneously** and **accumulate over time** in specific locations.

- **Theoretical and Analytic Innovation for Population Heterogeneity**
  - Vulnerability to climate stressors is likely shaped by a **combination of** demographic, socioeconomic, and non-climate environmental factors.
  - How can we **conceptualize** and **model this complexity** in climate-outcome relationships?

Nam, Choi, & Ailshire "Unveiling Population Heterogeneity in Health Risks Posed by Environmental Hazards Using Regression-Guided Neural Network." *arXiv preprint arXiv:2409.13205* (2024).

Thank you

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