

# Heterogeneity in human immune aging and vaccine responses

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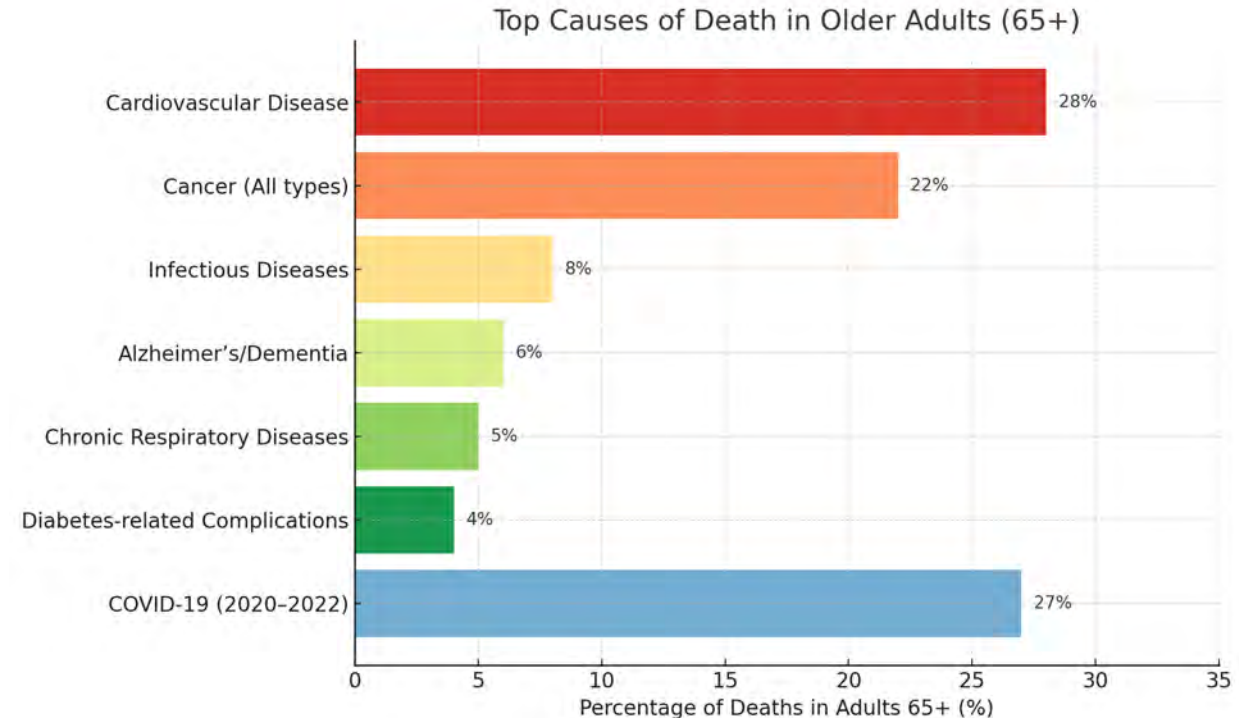
# Disclosures

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# America Is Getting Older: Why It Matters?

- **Today:** 17% of Americans are aged 65+
- **By 2030:** 1/5 Americans will be 65+
- **By 2035:** Older adults are going to outnumber children for the first time in US.
- **Aging diseases will overwhelm our healthcare system**
  - 60% of all cancer cases, 70% of cancer deaths.
  - 75–85% of influenza-related deaths.
  - 10–100× higher fatality rate for COVID-19.



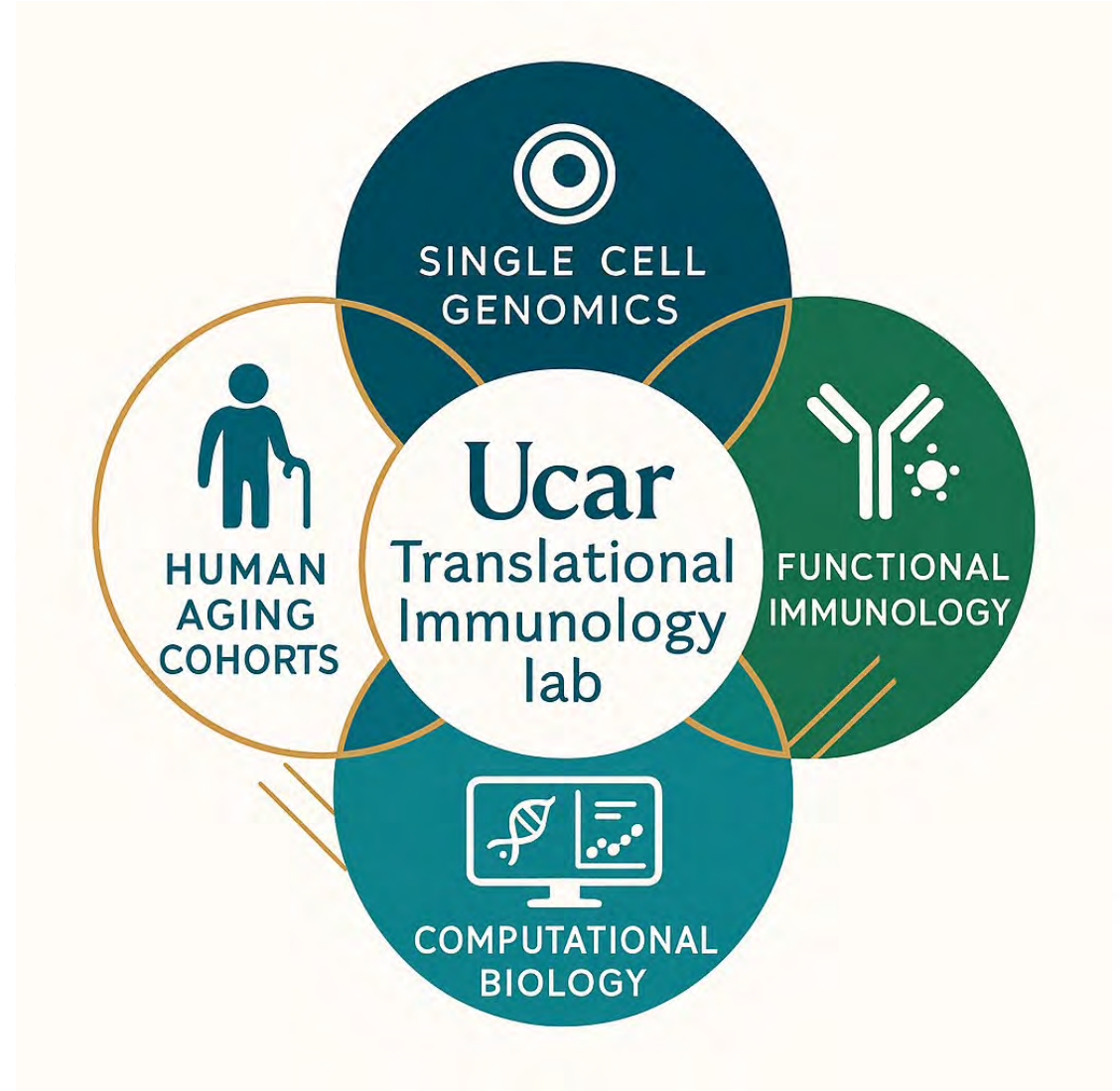
**Immune resilience and identifying biomarkers of immune resilience is a major determinant of functional aging.**

# Hallmarks of immune system aging

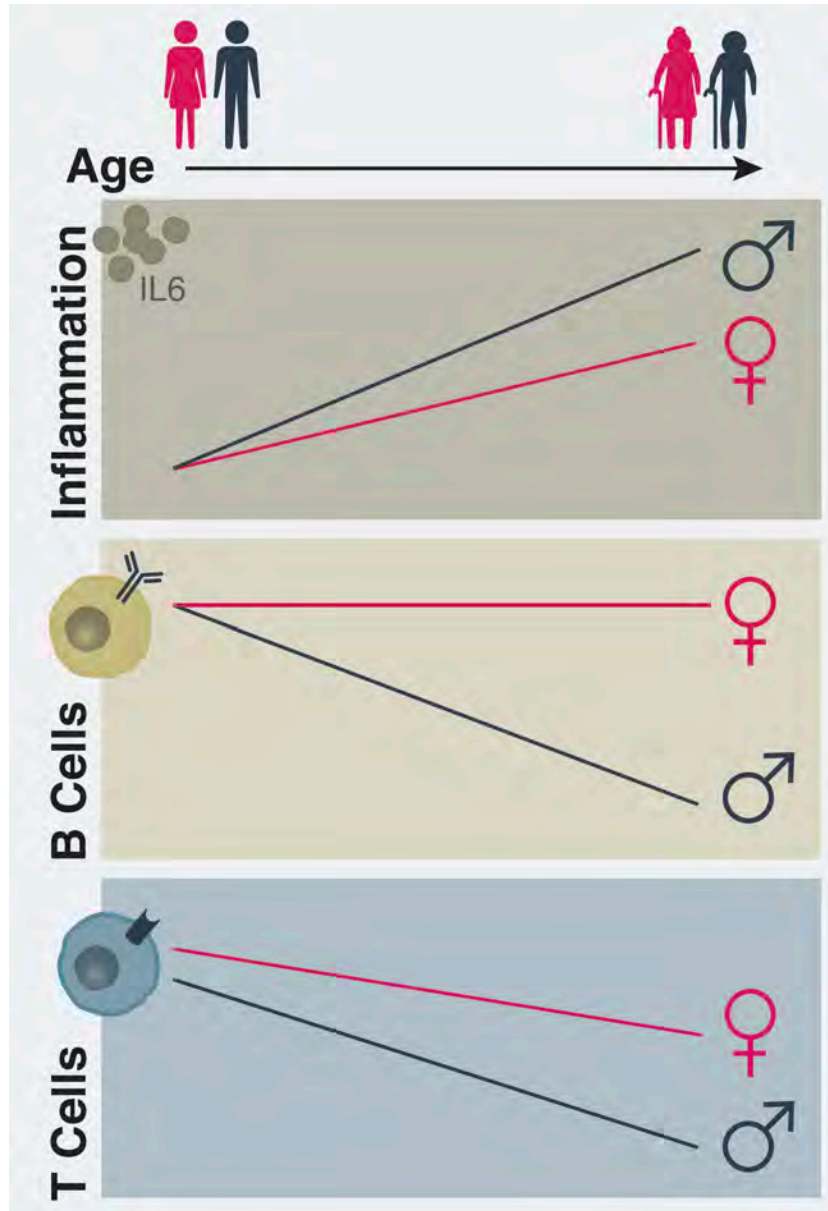
- **Reduced ability to fight against diseases (infections, cancer)**
- **Decreased responses to vaccination and therapy**
- **Shortened health-span and lifespan**

# Immune aging is highly heterogeneous

- Why do some older adults maintain robust immune function?
  - Drivers of this heterogeneity
  - Cellular and molecular biomarkers of immune resilience
- How does this heterogeneity affect immune responses to infections/therapy/vaccination?
- Can we restore immune resilience with interventions?
- **Novel discoveries by combining clinical cohorts with systems immunology and single-cell genomics.**

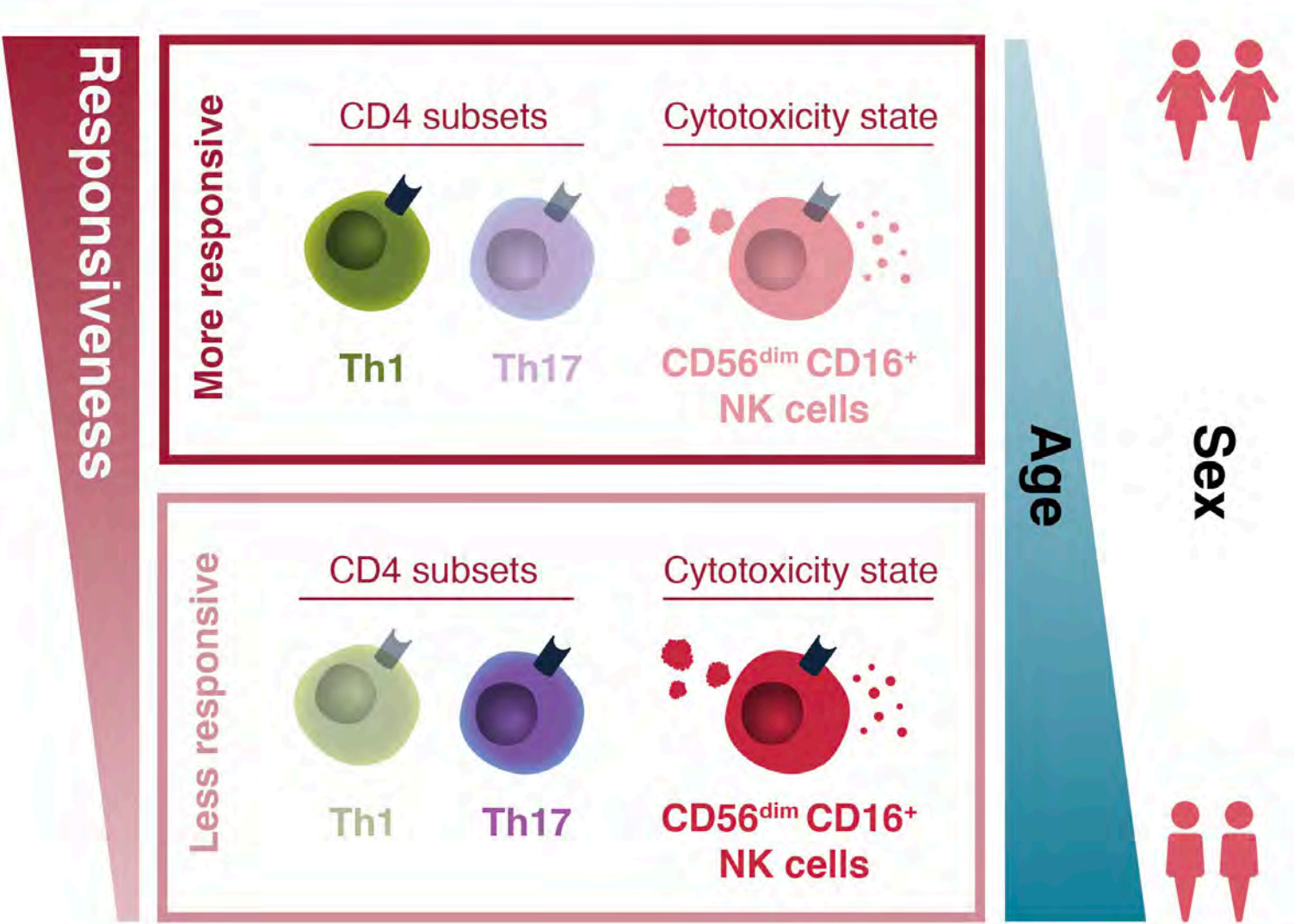


# Biological sex is a factor in immune aging heterogeneity

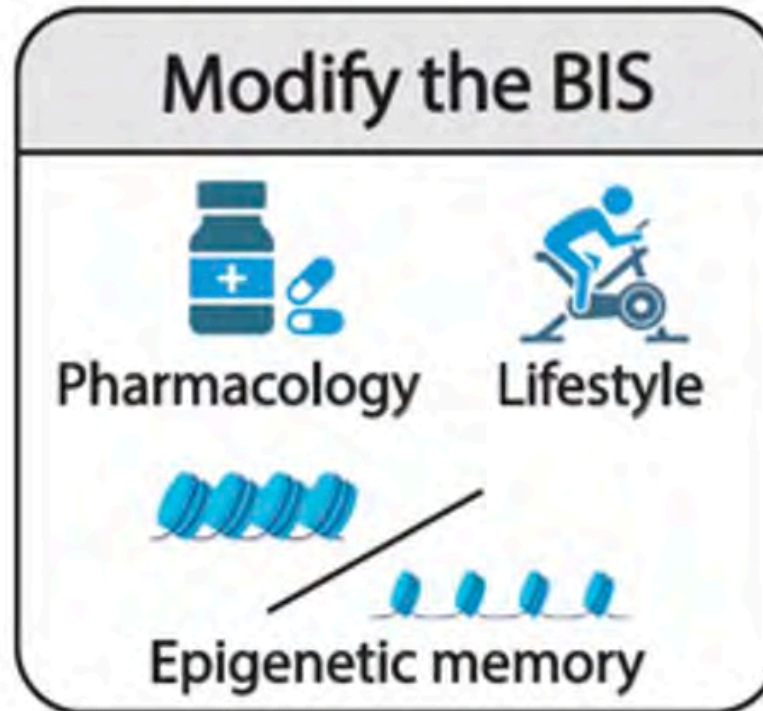
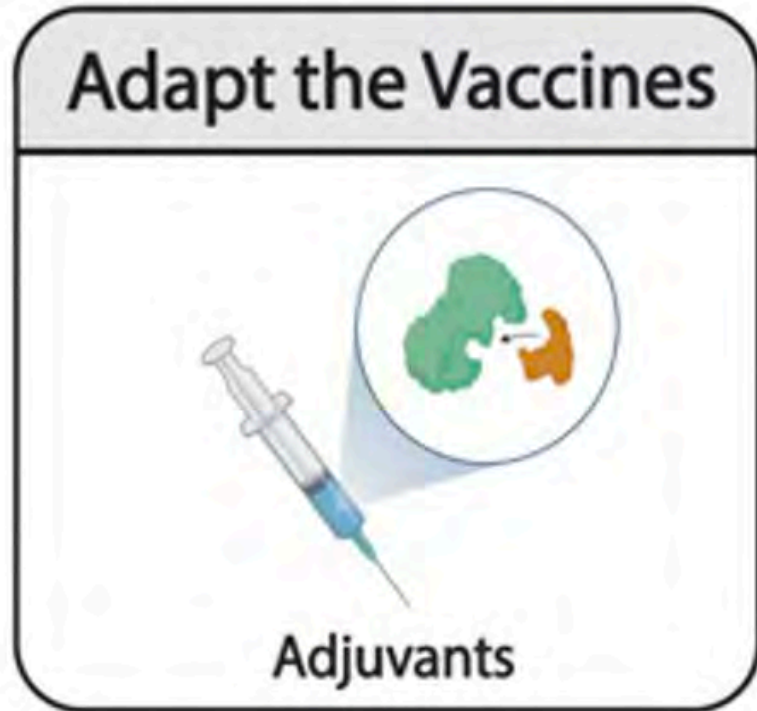


- Accelerated immune aging phenotype in men
  - Stronger activation of innate immunity
  - Stronger inactivation of adaptive immunity
  - Earlier start of changes (~5 year)
- Male and female blood immune cells diverge after 65
  - Older women have more active adaptive immunity
  - Older men have more active innate immunity
- **Biological sex is an important factor and should be considered**
- **Underrepresentation of diverse racial/ethnic populations limits generalizability.**

# Emerging biomarkers of vaccine responsiveness in older adults



# Clinical implications of identifying biomarkers associated with vaccine responses



**BIS: Baseline Immune State**

Nehar-Belaid\*, Sokolowski\*, Ravi\*, ..., Ucar, Seminars in Immunology, 2023. PMID: 37717525.

Yanicke & Ucar, Sex differences in immune system aging and responsiveness to vaccination, Public Policy & Aging Report, 2023.

# Toward Precision Immunology for older Adults

- Aging trajectories vary widely.
  - Personalized strategies and biomarkers of immune resilience are needed
  - A better understanding of drivers of heterogeneity
- Systems immunology enables novel discoveries and actionable pathways.
  - Advances in single cell genomics and computational methods combined with well-characterized clinical cohorts enable novel discovery
- Opportunity to intervene before frailty.
  - Genomic biomarkers should be linked to functional outcomes (vaccine/therapy response)
  - Biomarkers should be informative about intervention pathways.

# Knowledge Gaps

- Why do some older adults maintain immune resilience despite chronological aging?
- How innate and adaptive immune coordination changes across aging trajectories.
- Lack of validated biomarkers predicting vaccine responsiveness across populations.
- Underrepresentation of diverse racial and ethnic groups in aging immunology cohorts.
- Sex-specific mechanisms remain poorly understood and incorporated into clinical trial design.
- Mechanistic links between baseline immune state and long-term protection remain unclear.

# Research opportunities

- Longitudinal multi-omic profiling across lifespan to define immune aging trajectories.
- Development of predictive biomarkers to guide precision vaccination strategies.
- Integration of sex, ancestry, and social determinants into immune aging studies.
- Mechanistic studies linking inflammation, metabolism, and immune resilience.
- Clinical trials testing immune rejuvenation strategies and vaccine personalization.

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## ALL OF OUR RESEARCH VOLUNTEERS!



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<http://ucarlab.com/>

<https://github.com/UcarLab>

JAX cores: Genome Technologies, Single Cell Biology Lab, Flow Cytometry, RPD