

How Does Aging Mechanistically Contribute to Heterogeneity of Treatment Effects?

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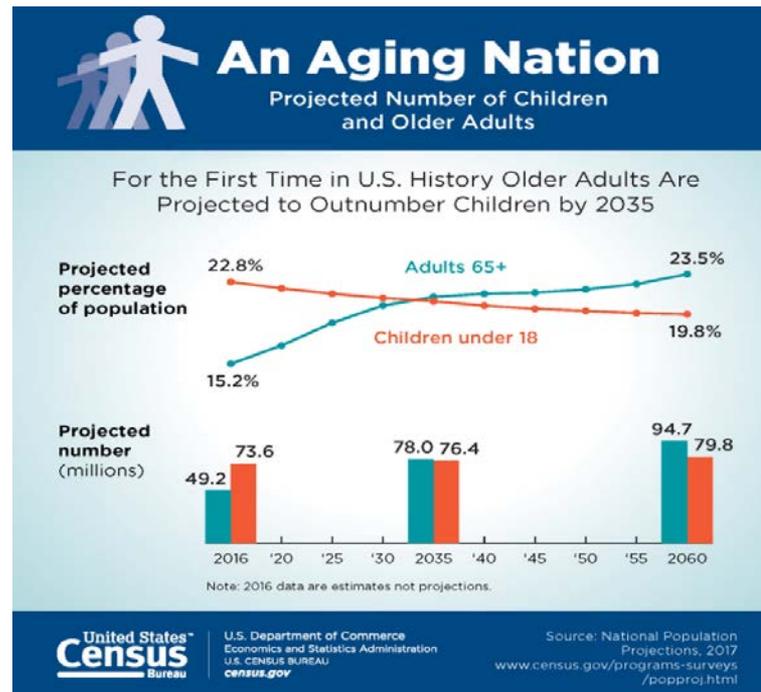
What is Aging?

- Although aging is difficult to concisely define, it can be conceptualized as a multifactorial process characterized by biological, social, and psychological changes
- Aging phenotype: Functional decline, increase in vulnerability, and loss of viability
- Although diseases are among the most noticeable consequences of aging, diseases are not limited to older adults, and aging is not a disease
- A geriatric adult is a person aged 65 years or older

Aging and Heterogeneity

- The geriatric population is heterogeneous
 - No two people age at the exact same rate or manner
 - “There is no ‘typical’ older person” (WHO, Ageing and Health, 2018)
- Rate of aging may be influenced by genetics, lifestyle, diseases as well as environmental and socioeconomic factors
- Aging introduces greater variability in therapeutic responses; hence, it is importance to understand how aging can generate heterogeneity of treatment effects (HTE).

Public Health Significance of Age-related Heterogeneity of Treatment Effects (HTE)



The public health significance of aging-related HTE likely to increase with time

Biological Pathways to HTE in Geriatric Populations

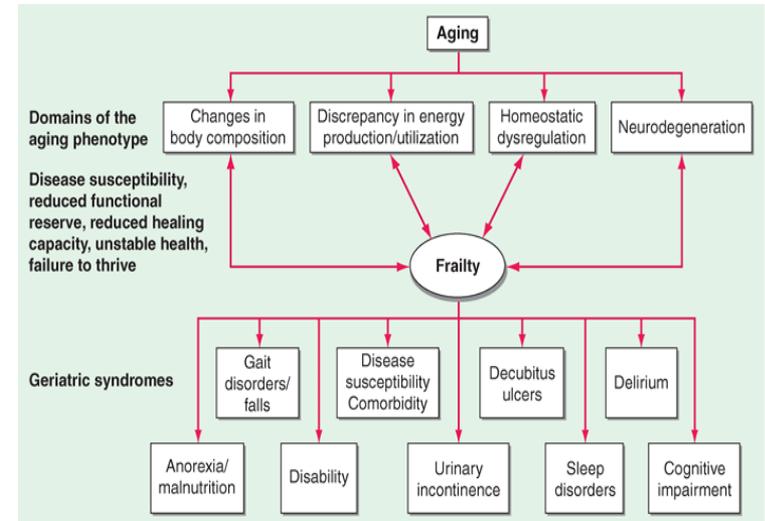
- The biological changes underlying aging include accumulation of cellular damage as well as degradation of repair and maintenance mechanisms
- Aging-related biological changes can affect the pharmacology of therapeutic agents
- Age-related changes in body composition and organs may alter pharmacokinetics
 - Reduction in renal function
 - Increase in percent body mass that is fat
 - Decrease in percent body mass that is water
 - Quantitative changes in serum proteins
 - Hepatic drug clearance may decrease
- Age-related changes in homeostatic response, receptors, and intracellular signaling pathways may alter pharmacodynamics
- May be drug class specific

Psychosocial Dimensions of Aging and HTE

- Psychosocial challenges that accompany aging include changes in social support systems, residence, mental health, and bereavement
- Biological and sociocultural factors influence psychosocial aging
- Psychosocial dimensions of aging can be worsened by decline in physical functions
- Psychosocial aspects of aging contribute to HTE through their effects on the pattern of use of therapeutic agents

Medical Contributors to HTE in Geriatric Populations

- Multimorbidity
- Geriatric syndromes, e.g., Frailty
- Polypharmacy
- Cognitive impairment
- Sensory deficits, e.g., visual and hearing impairments



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com
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Aging and HTE

Examples of Age-Related Changes in Treatment Effects

Drug	Pharmacodynamic effect	Age-related change
Antipsychotics	Sedation, extrapyramidal symptoms	Increased
Benzodiazepines	Sedation, postural sway	Increased
Beta-agonists	Bronchodilatation	Decreased
Beta-blocking agents	Antihypertensive effects	Decreased
Vitamine K antagonists	Anticoagulant effects	Increased
Furosemide	Peak diuretic response	Decreased
Morphine	Analgesic effects, sedation	Increased
Propofol	Anesthetic effect	Increased
Verapamil	Antihypertensive effect	Increased

Jansen and Brouwers, 2012

The biological, psychosocial, and medical dimensions of aging can interact to exaggerate or attenuate treatment responses to generate HTE.

A few of the phenomena that can result from the interaction of biological, psychosocial, and medical dimensions of aging to generate HTE are:

- Increased vulnerability to adverse drug reactions
- Drug-drug or drug-disease interactions
- Unintentional overdose or underdose
- Obstacles to treatment adherence

As the clinical pharmacology of aging evolves, the knowledge gaps in our understanding of determinants of geriatric HTE should improve, as we aim to ultimately individualize therapeutics for older adults.

Geriatric Treatment Effects Recognized in Drug Regulatory Guidances

- Aging is recognized to influence treatment effects in drug regulatory guidances
 - The study of drugs likely to be used in the elderly (1989)
 - Studies in support of special populations (ICH E7)
 - Draft Guidance E7 Studies in Support of Special Populations: Geriatrics Questions & Answers (2009)
 - Reviewer Guidance: Clinical Safety Review
 - The format and content of clinical and statistical section of an application

