

Sex and Gender Influences on the Cardiovascular Health of Women

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Mid-Life and Older Women's Health

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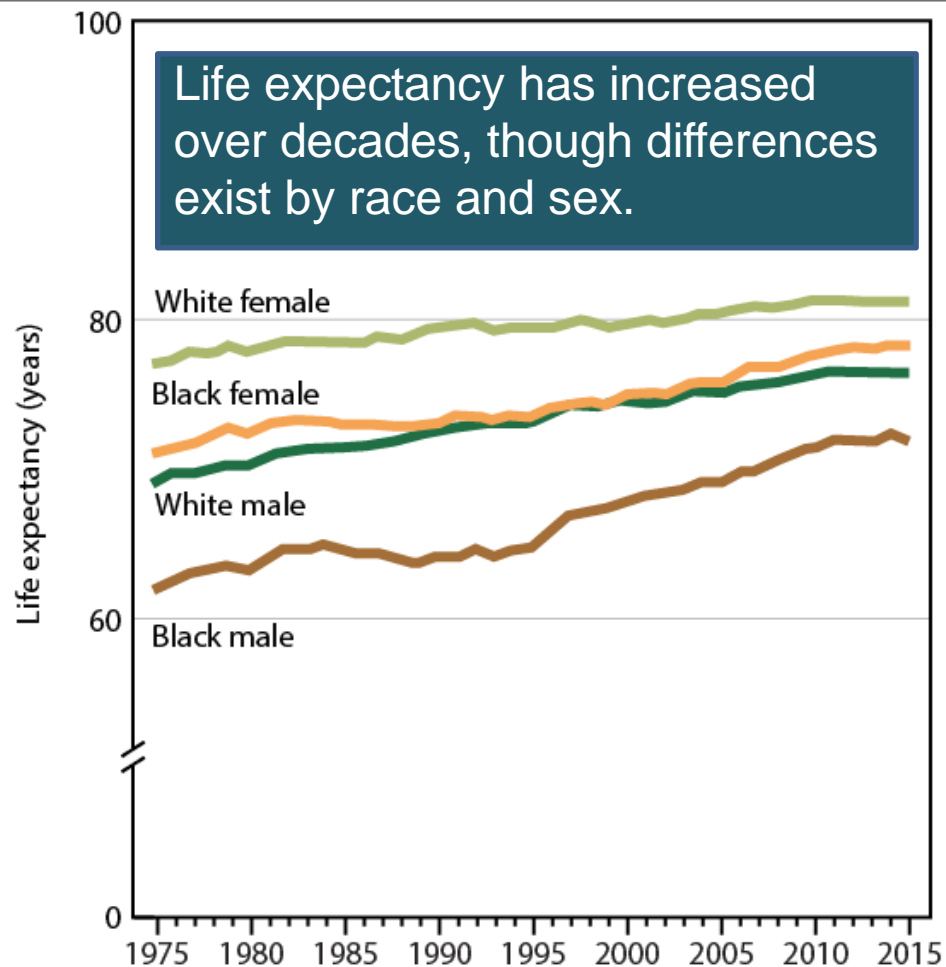


Advancing the Health of Women in Mid-Life and Beyond

- Life-Expectancy and Leading Causes of Morbidity and Mortality
- Sex Differences in Burden of Cardiovascular Disease
- Hypertension as a Key Driver of Cardiovascular Disease in Women
- The Heart-Brain Connection: Shared Risk Factors and Implications
 - Cognitive Impairment and Dementia
- Addressing the Health Challenges of Mid-Life and Older Women a Research Agenda
 - Leveraging a Longstanding Legacy
 - Seizing Opportunities for the Future



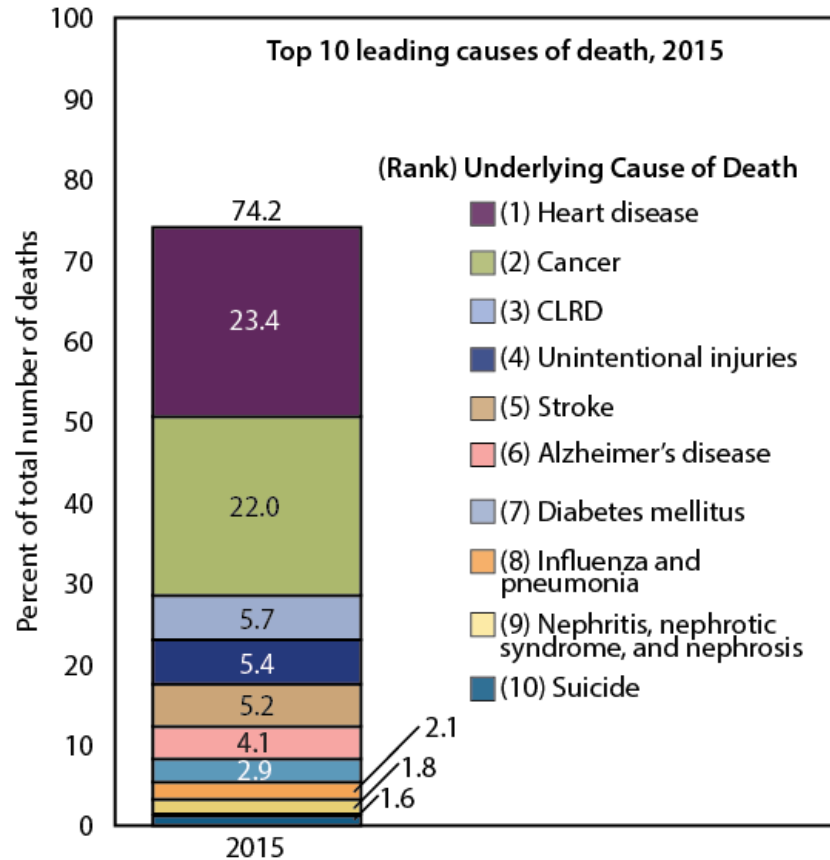
On Average, Women Live Longer Than Men



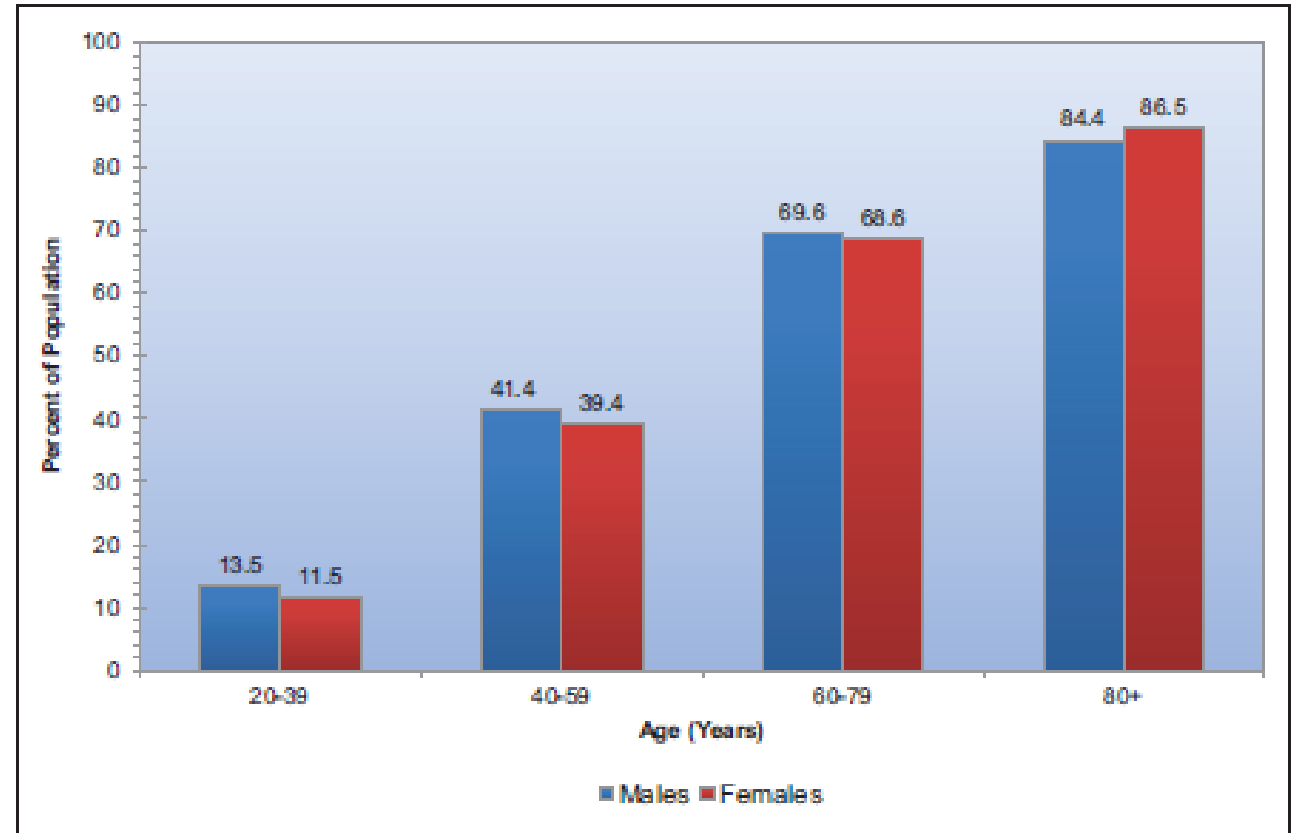
Thus, women represent a large proportion of the older US population and experience health issues of older age including:

- Heart disease as the leading cause of death
- Cardiovascular diseases and specifically those of high prevalence in women
 - Hypertension
 - Heart Failure
 - Stroke
- Cognitive Impairment and Dementia

Heart Disease is the Leading Cause of Death in the United States and Prevalence Increases with Age



1 of every 4 female deaths is due to heart disease.



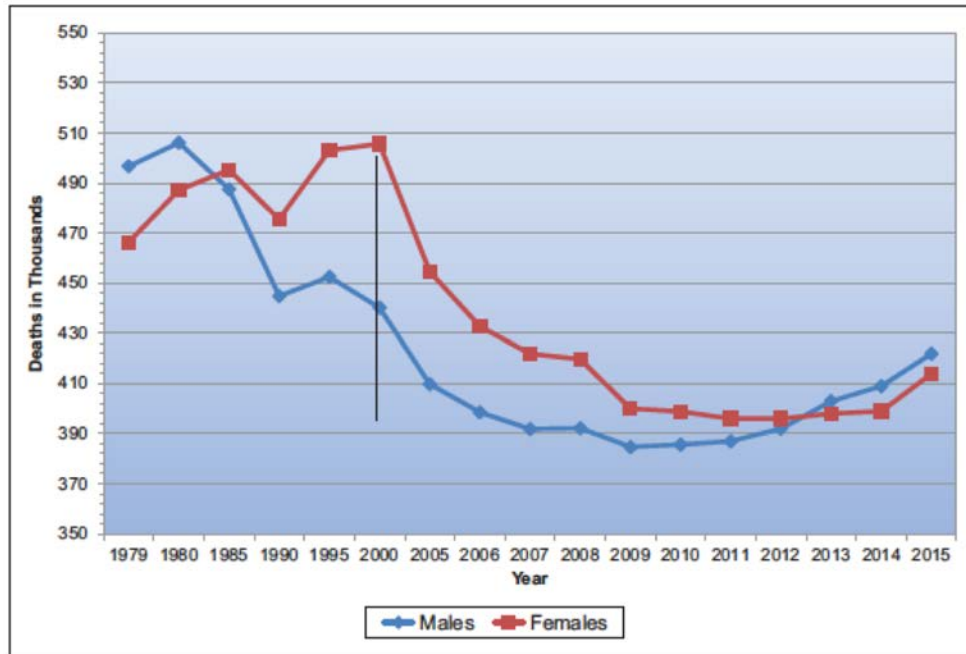
CVD prevalence increases with age. More American women die each year from CVD than all cancers combined.

Key Differences Between Men and Women in Cardiovascular Disease

- **Prevalence and Mortality** Absolute numbers of individuals living with and dying from CVD in US higher for women than men.
- **Known Differences** Epidemiology and clinical presentation may differ between men and women.
- **Known Disparities** Clinical outcomes among women have not improved at the same rate as men. Disparities exist in the application of evidence-based therapies.
- **Scientific Importance of Sex as a Biological Variable** Sex-specific pathophysiology influences outcomes.

Differences in Burden of CVD Between Sexes

Beyond the Peak: Narrowing the Sex Gap



CVD Includes:

Coronary Heart Disease

Stroke

Heart Failure

Hypertension

CVD Mortality Trends

Since the mid-80's CVD mortality in women exceeded that of men, until 2013 when the sex gap narrowed.

Cardiovascular Disease Statistics

	Men	Women
Mortality (2015, all ages)	422,355 (51%)	414,191 (50%)
Prevalence (2011-14, age ≥20y), millions	44.3 (37%)	47.8 (36%)
Hospital discharges (2010)	2,571,000	2,220,000

Addressing the Unique Challenges of Acute Myocardial Infarction in Women

State of the Science of AMI in Women

AHA Scientific Statement

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

Laxmi S. Mehta, MD, FAHA, Chair; Theresa M. Beckie, PhD, FAHA, Co-Chair; Holli A. DeVon, PhD, RN, FAHA; Cindy L. Grines, MD; Harlan M. Krumholz, MD, SM, FAHA; Michelle N. Johnson, MD, MPH; Kathryn J. Lindley, MD; Viola Vaccarino, MD, PhD, FAHA; Tracy Y. Wang, MD, MHS, MSc, FAHA; Karol E. Watson, MD, PhD; Nanette K. Wenger, MD, FAHA; on behalf of the American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research

Epidemiology
(Prevalence, Mortality,
Age, Race/Ethnicity)

Pathophysiology
(plaque rupture/
erosion, SCAD,
spasm)

**Influences: AMI
Outcomes in
Women**

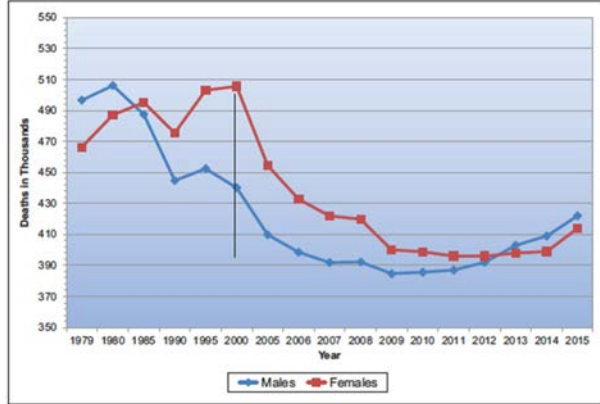
CV Risk Factors
(smoking, HTN, DM,
dyslipidemia, obesity,
psychosocial stress)

Presentation,
Treatment,
Complications

Women present with AMI at an older age with more comorbidities and have more complications of AMI as compared to men.

Differences in Burden of Stroke Between Sexes

Beyond the Peak: Narrowing the Sex Gap



Stroke mortality, prevalence, and hospitalizations in women exceed men.

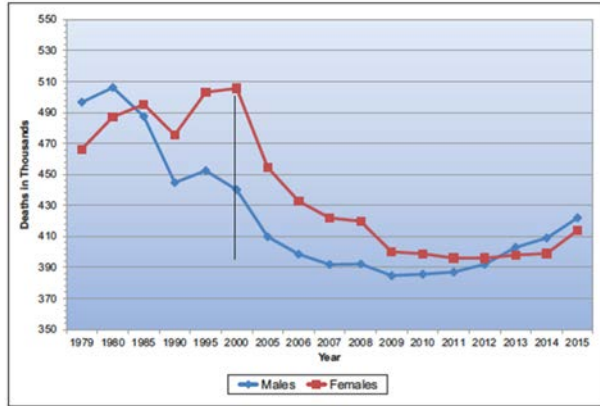
- Each year ~55 000 more females than males have a stroke.
- Females have a higher lifetime risk of stroke than males.
 - 1 in 5 for females compared to 1 in 6 for males 55 to 75 years of age
- In the oldest age groups, age-specific incidence in females \geq males

CVD Statistics - Stroke

	Men	Women
Mortality (2015, all ages)	58,288 (42%)	82,035 (58%)
Prevalence (2014, age \geq 20y), millions	3.1 (2%)	4.1 (3%)
Hospital discharges (2014)	434,000	454,000

Differences in Burden of Heart Failure Between Sexes

Beyond the Peak: Narrowing the Sex Gap



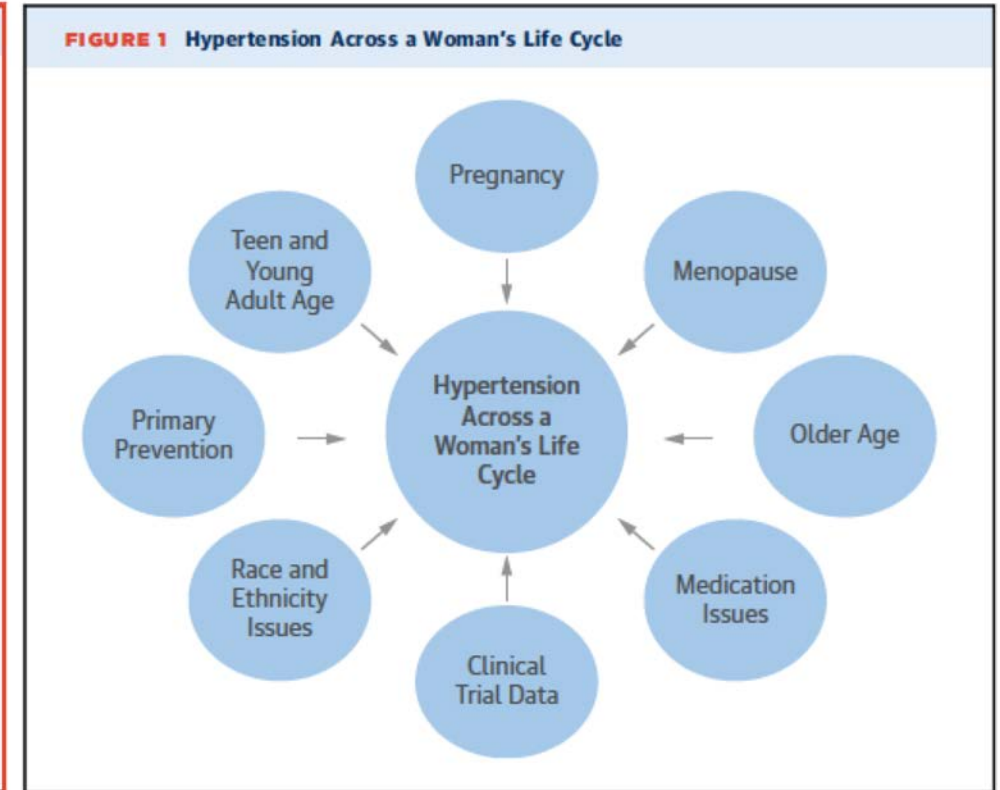
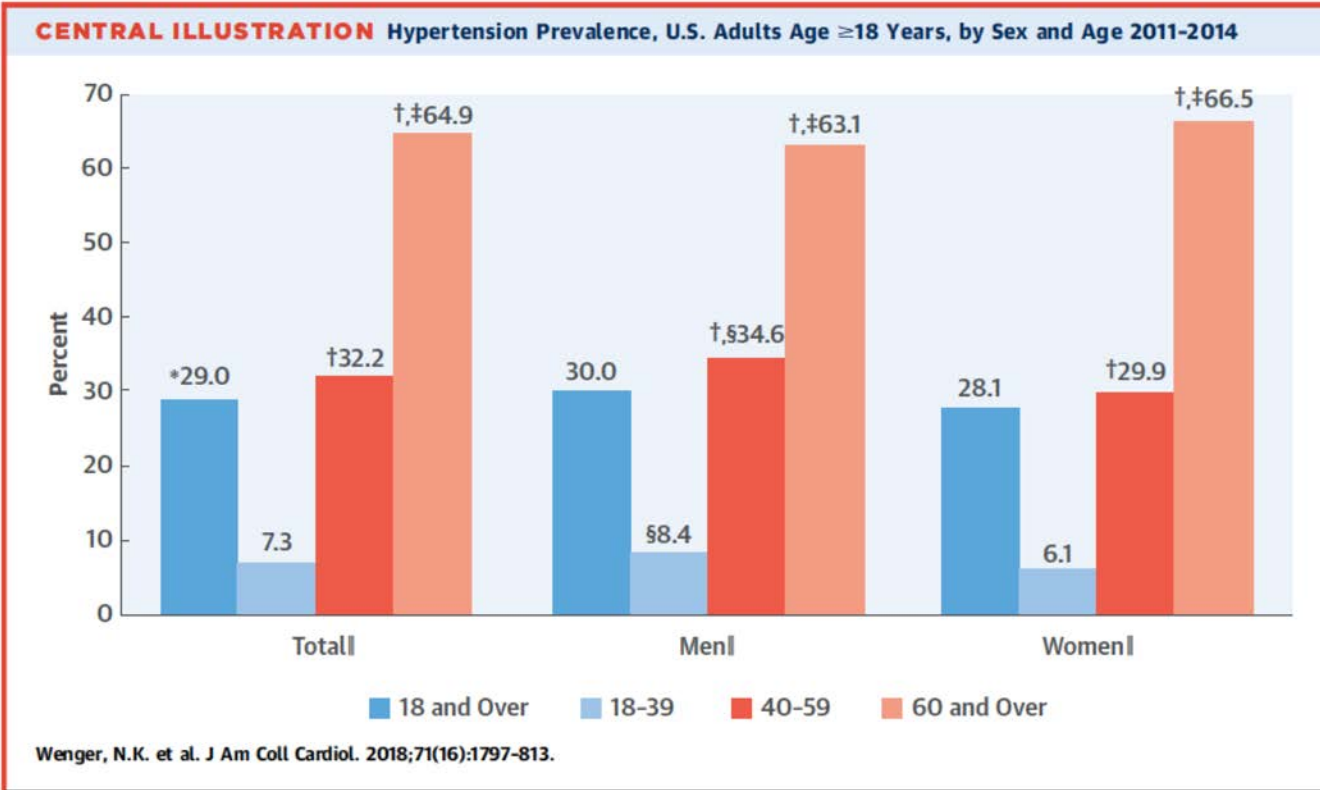
Heart failure mortality and hospitalizations in women exceed men.

- HF disproportionately affects older adults
 - 80% of cases occur in individuals ≥ 65 years.
- U.S. population ≥ 65 years will double by 2050, with women outnumbering men.
- 40-70% incident HF occurs as HFpEF, which is more common in women.

CVD Statistics – Heart Failure

	Men	Women
Mortality (2015, all ages)	33,667 (45%)	41,584 (55%)
Prevalence (2011-14, age ≥ 20 y), millions	2.9 (2%)	3.6 (3%)
Hospital discharges (2014, all ages)	462,000	438,000

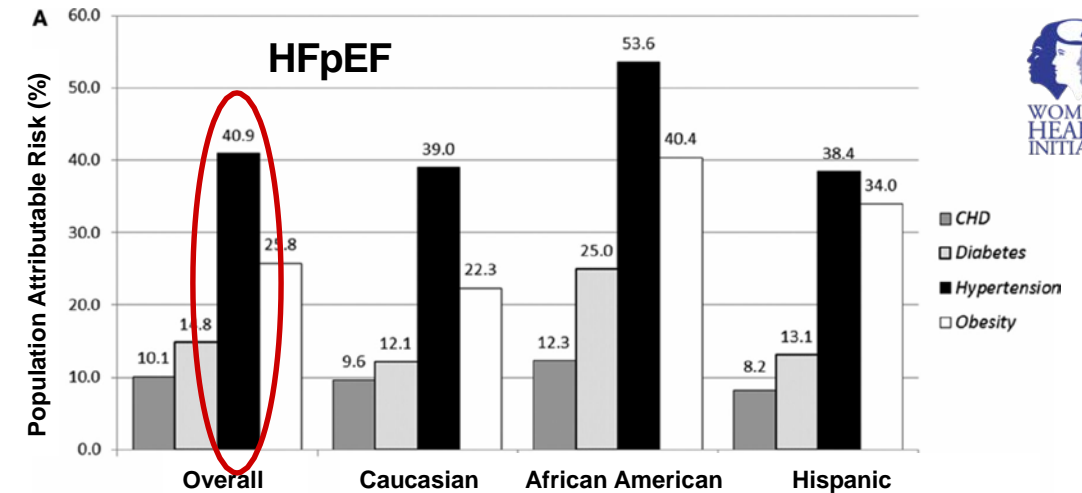
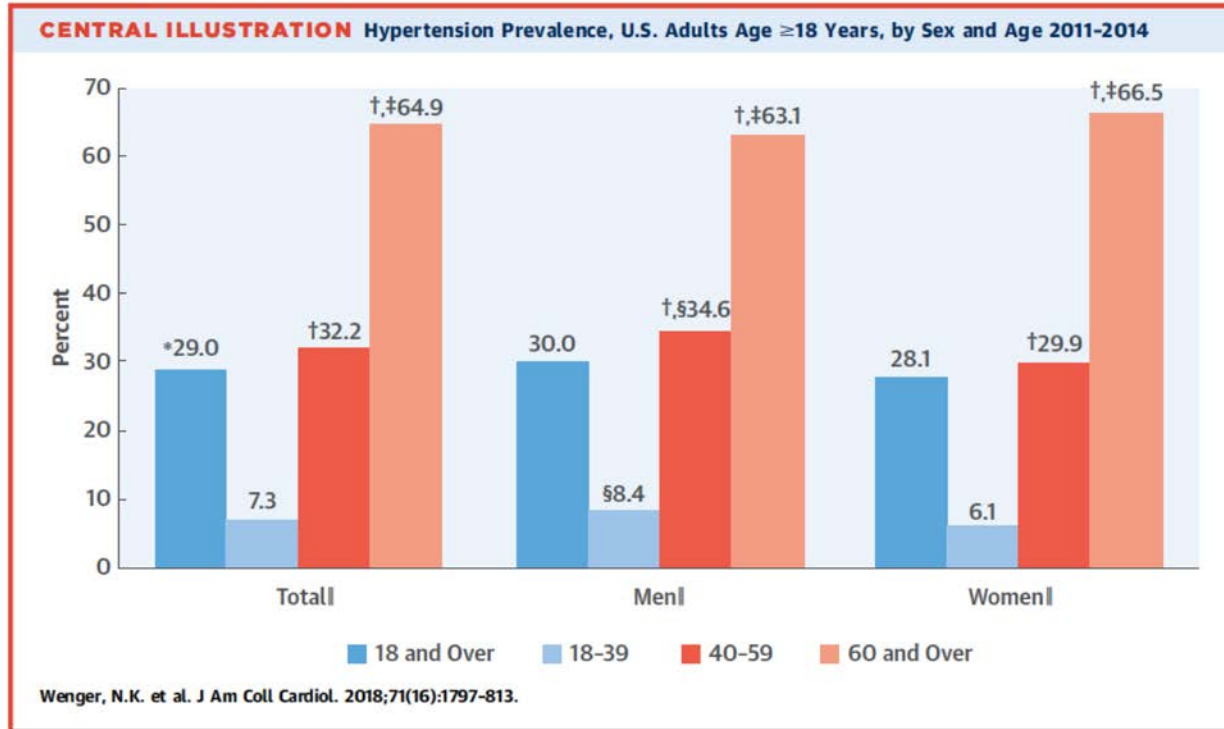
Hypertension Across the Life Course: Increasing Prevalence with Age and Multiple Contributors



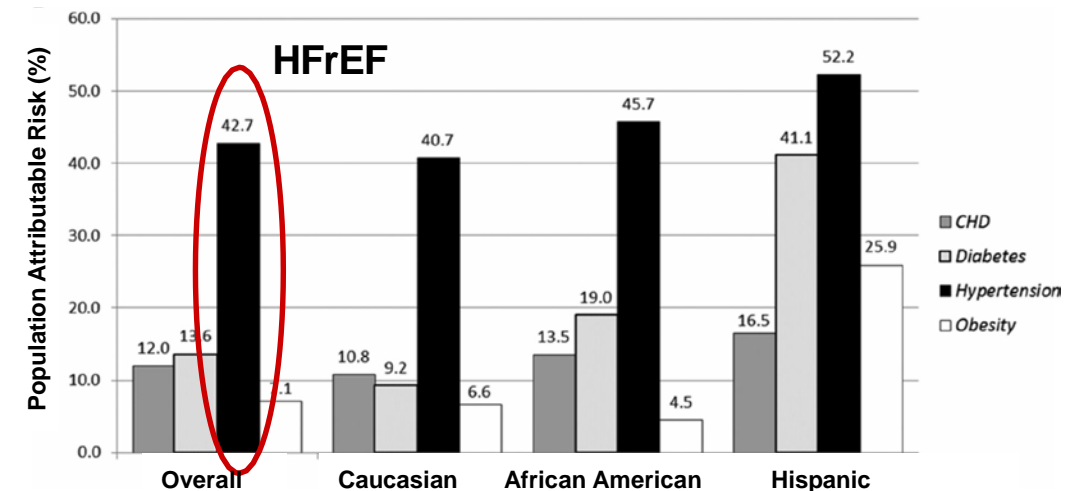
HTN occurs in more women than men. After 60 years, prevalence becomes higher in women than men, and gap widens with aging related to the large proportion of older women.



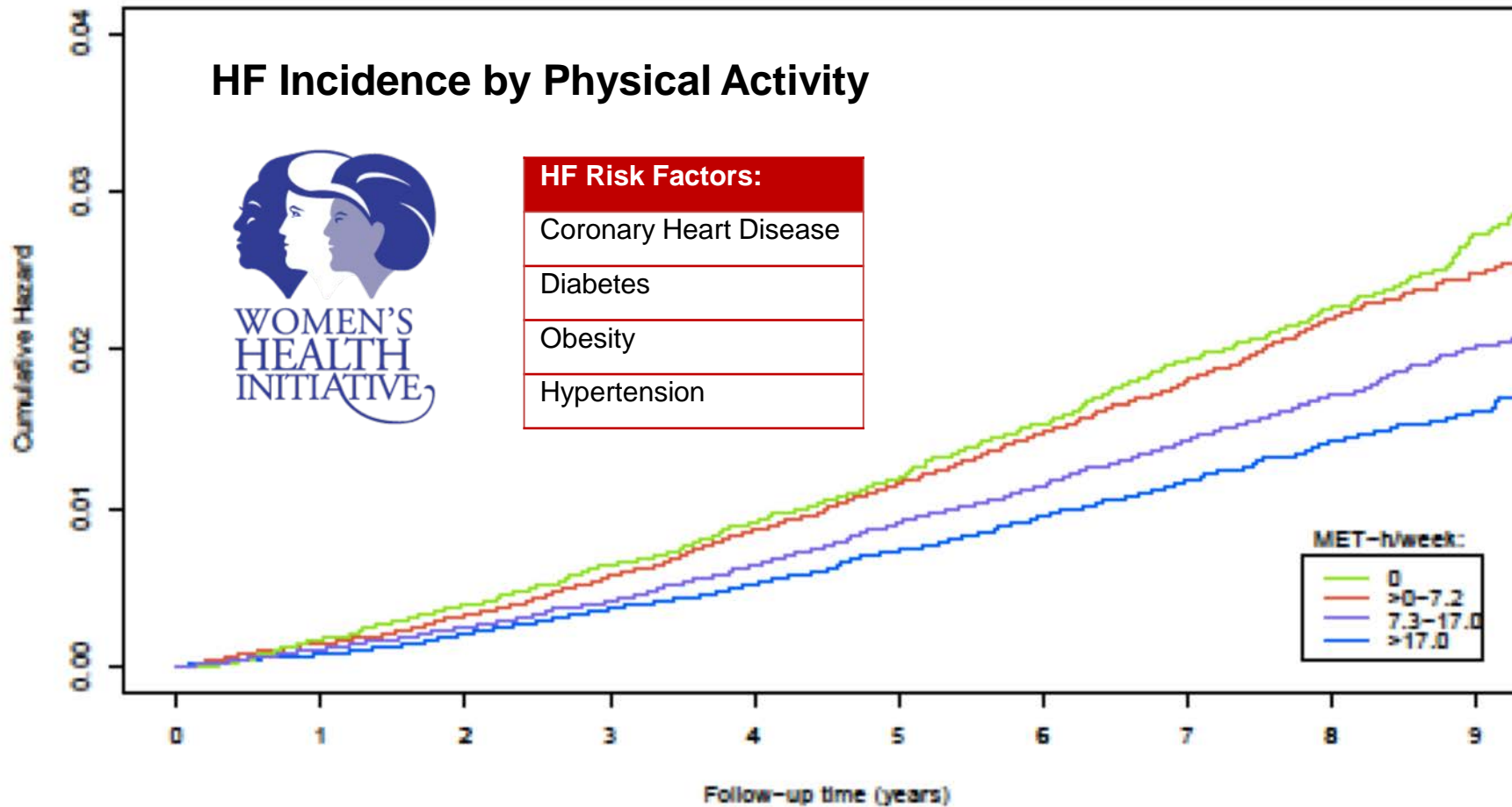
Heart Failure as a Complication of Hypertension: Increasing Prevalence with Age



Population-attributable risk by race and ethnicity for HF



Physical Activity in Women Associated with Reduced Risk of Heart Failure



Higher levels of physical activity and walking were associated with reduced risks of developing HF in later life. With continued growth in number of older women and challenges in treating HFpEF, physical activity may hold hope for HF prevention.

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The Heart-Brain Connection: Critical Intersection of Sex and Shared Risk Factors

Diabetes: Powerful risk factor, disproportionate increased risk of CHD for women vs. men.

Obesity: 41% of US women are obese; 10% extremely obese. Heaviest category with 4x risk for CV events.

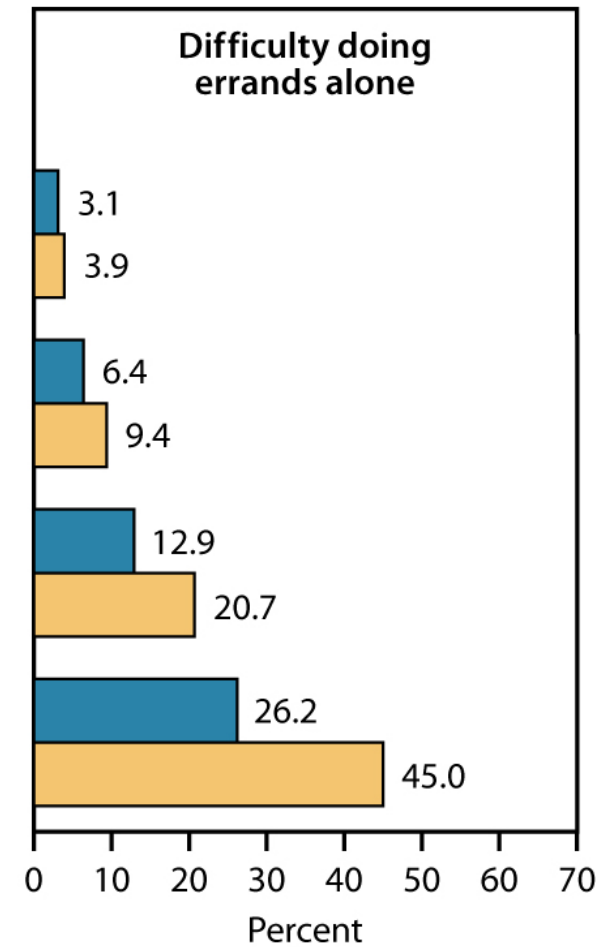
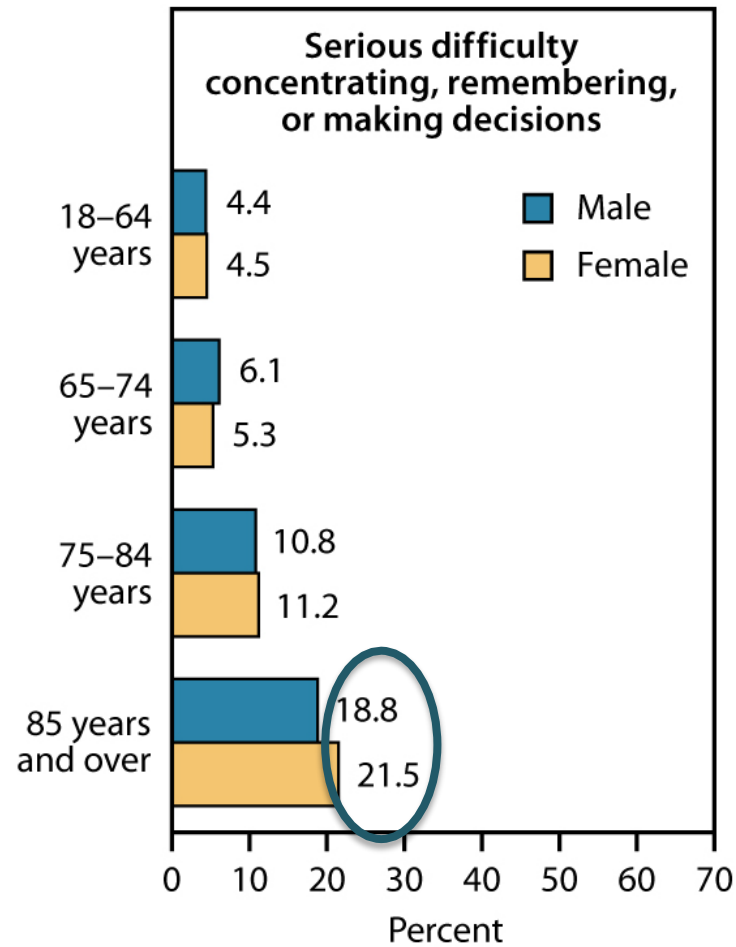
CVD and Broader
Health Implications

Hypertension: Antecedent to MI, Stroke, Heart Failure, Dementia. Prevalence increases with age.

Smoking: 25% increased CHD risk among female as compared to male smokers.

As Women Age

Challenges with Cognition and Independent Living Increase

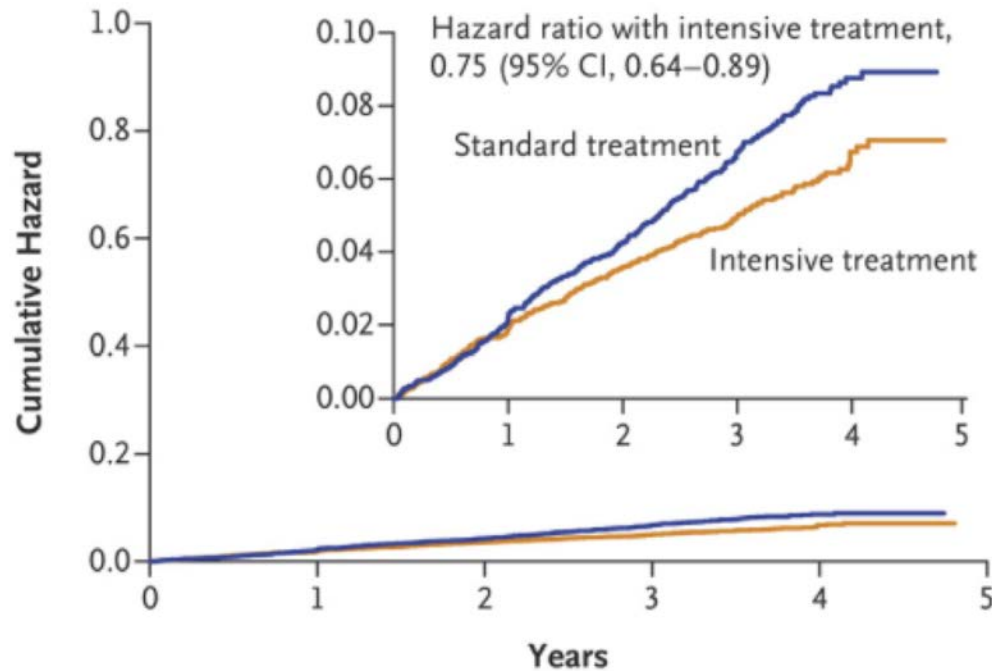


The Heart-Brain Connection: Addressing Shared Risk of Hypertension as Key Driver of CVD, Cognitive Decline, and Dementia



A Randomized Trial of Intensive
vs. Standard BP Control

SPRINT-MIND
Memory and Cognition in
Decreased Hypertension



Intensive management as compared to standard also reduced:

- Rate of incident mild cognitive impairment (MCI)
- MCI + dementia combined
- Smaller increases in white matter lesions on MRI

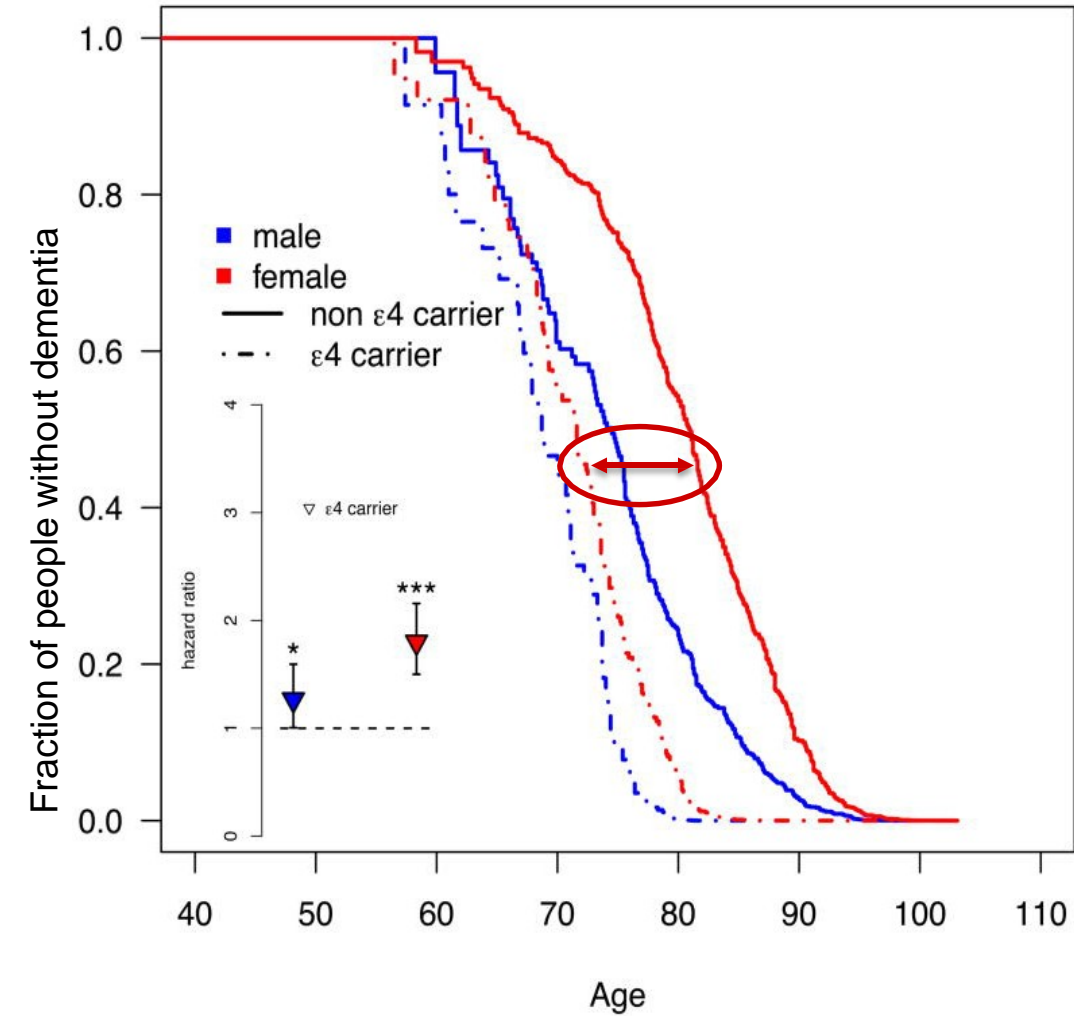
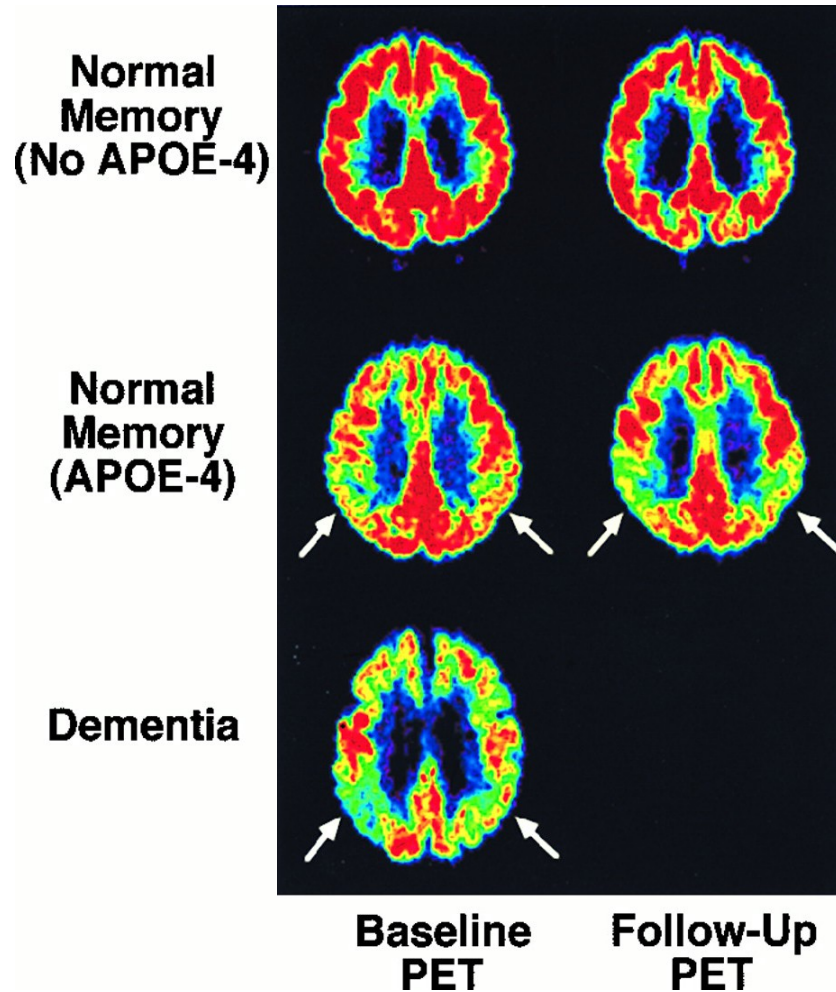
Intensive management of SBP to target <120 mmHg reduced complications of high BP by 25% and death by 27% as compared to SBP target <140 mm Hg.

The Overlapping Risk Profile of CVD and Dementia: Shared Genetic, Clinical, and Behavioral Factors

Vascular dementia and Alzheimer's disease share underlying disease mechanisms.

ApoE gene increases risk of both Alzheimer's disease and atherosclerosis.

The effect of ApoE on risk of dementia is stronger in women.



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Women's Health Research at NHLBI: Longstanding Legacy and New Directions

Initiatives/Programs

WISE

Women's Ischemia
Syndrome Evaluation



nuMOM2b

CHAP

Chronic Hypertension and Pregnancy



A program of the National
Institutes of Health

- **Physical Activity and CVD**
 - **Objective Physical Activity and CV Health (OPACH)**
 - **Both** light-intensity & moderate-vigorous PA associated with lower mortality
 - **WHI Strong and Healthy (WHISH)**
 - Trial of ~50K older women testing whether ↑PA will reduce CV events
 - **WHISH-2 Prevent Heart Failure Study**
 - RCT to evaluate effect of PA and strength training on HF in elderly women
- **CVD, sleep, and cognitive decline**
 - **WHI Memory Study**
 - CVD, high BP, and diabetes associated with cognitive decline in older women
 - **WHI Sleep Hypoxia Effects on Resilience (WHISPER)**
 - Impact of sleep-disordered breathing on CV events & cognition in older women
- **Future Directions**
 - **Precision Medicine**
 - **Healthy Aging and CV Health; Resilience**
 - **CVD Among Older Women (avg. age 83 years)**

In Utero

Childhood

Adolescence

Early
Adulthood

Middle
Adulthood

Late
Adulthood



National Heart, Lung,
and Blood Institute

Aligning Institute-Solicited Science with the Strategic Vision Goals & Objectives

Objective 1: Normal Biology
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Objective 2: Pathobiology, Onset,
& Progression of HLBS Diseases

Objective 3: Population
Differences

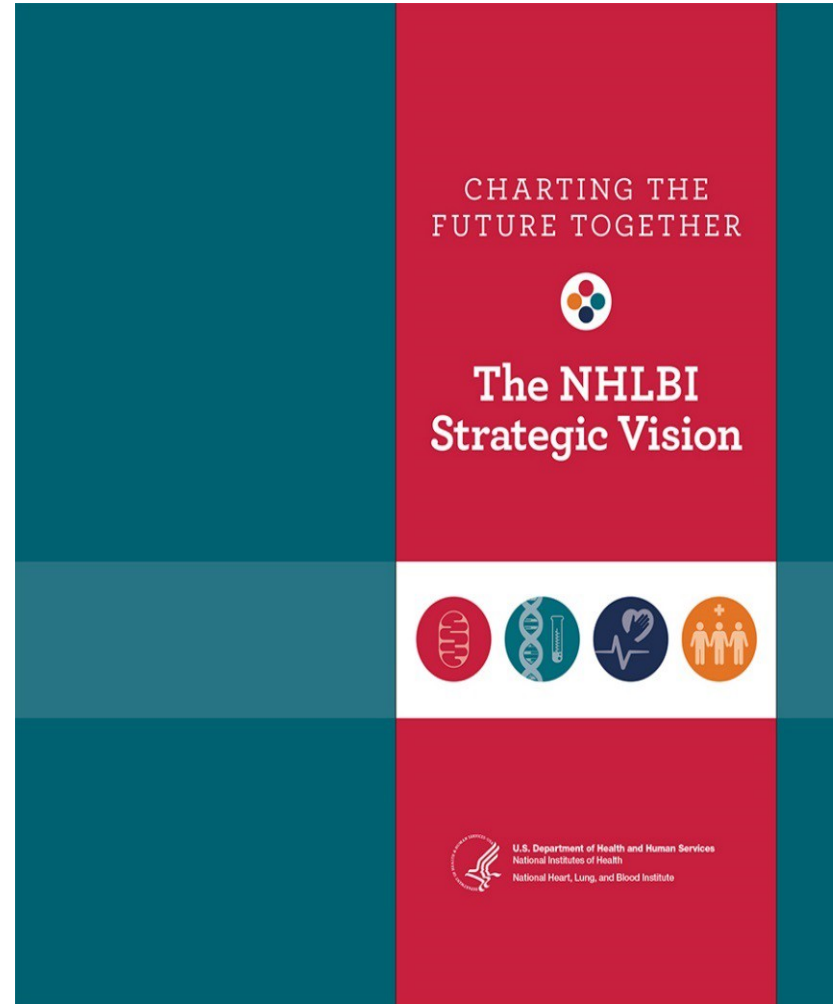
Objective 4: Precision Medicine

Objective 5: Novel Diagnostics
& Therapeutics

Objective 6: Clinical &
Implementation Research

Objective 7: Data Science
Objective 7: Data Science

Objective 8: Workforce &
Resources



In Utero

Childhood

Adolescence

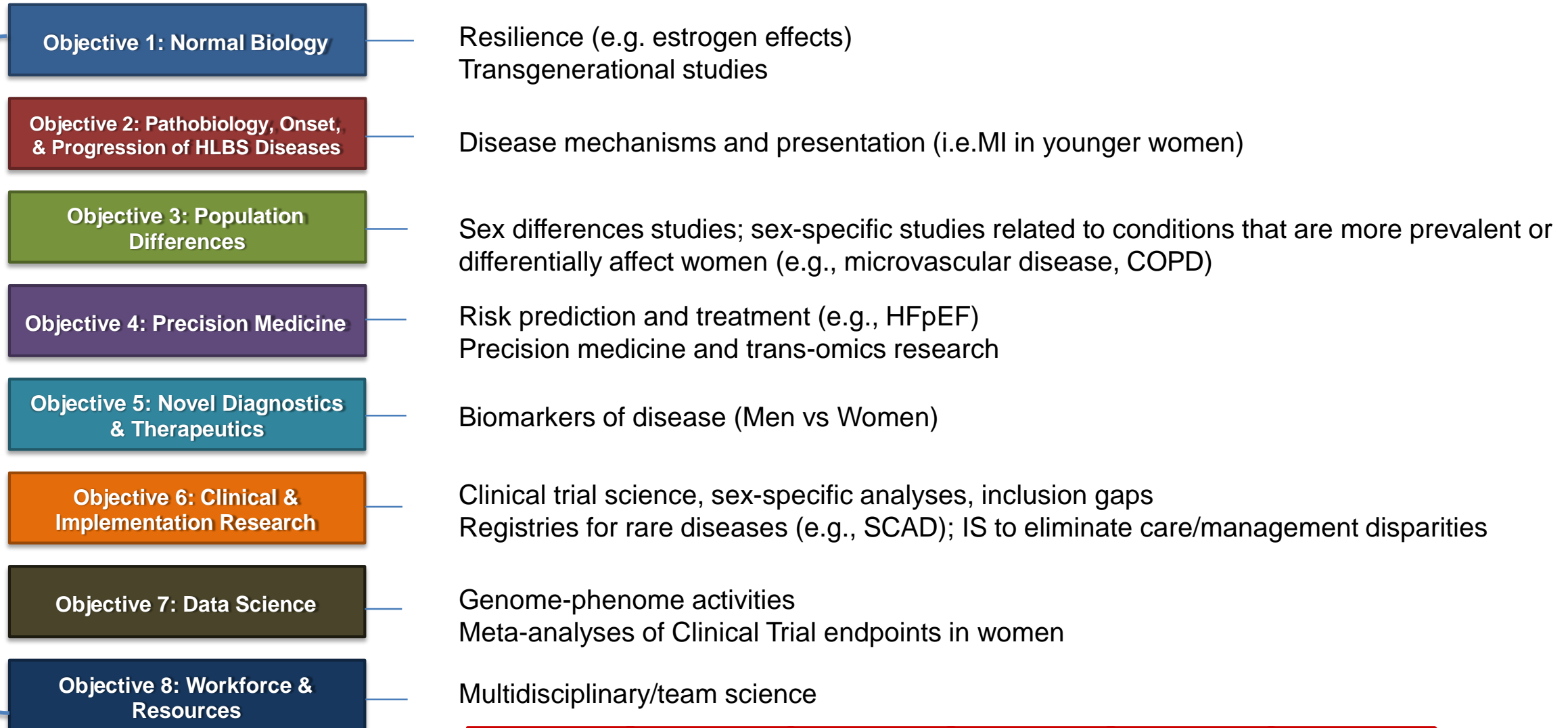
Early
Adulthood

Middle
Adulthood

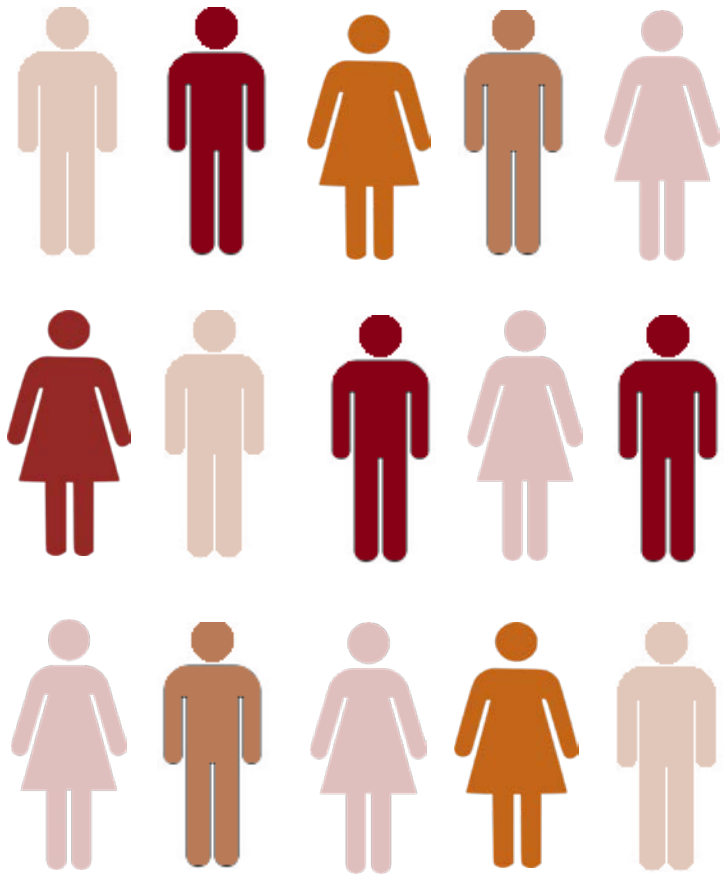
Late
Adulthood

Aligning Institute-Solicited Science with the Strategic Vision Goals & Objectives

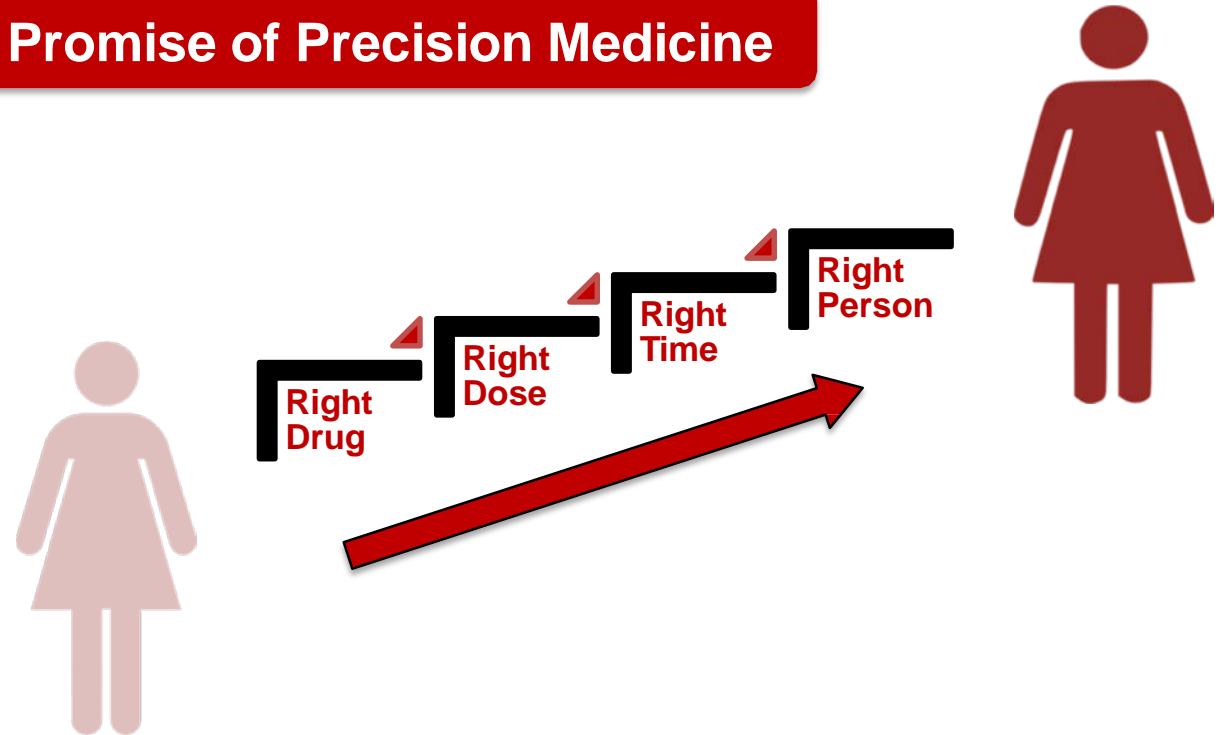
Women's Health Priorities Span Every Objective of the NHLBI Strategic Vision



Sex as the Highest Order of Precision Medicine



Promise of Precision Medicine



How do clinical factors interact with exposures, differential risk factors, and their potency, genetic susceptibility, and lifestyle and social determinants of health in pathways of heart, lung, blood, and sleep dysfunction?

Advancing Precision Medicine Science: Early vs. Late Postmenopausal Hormone Therapy

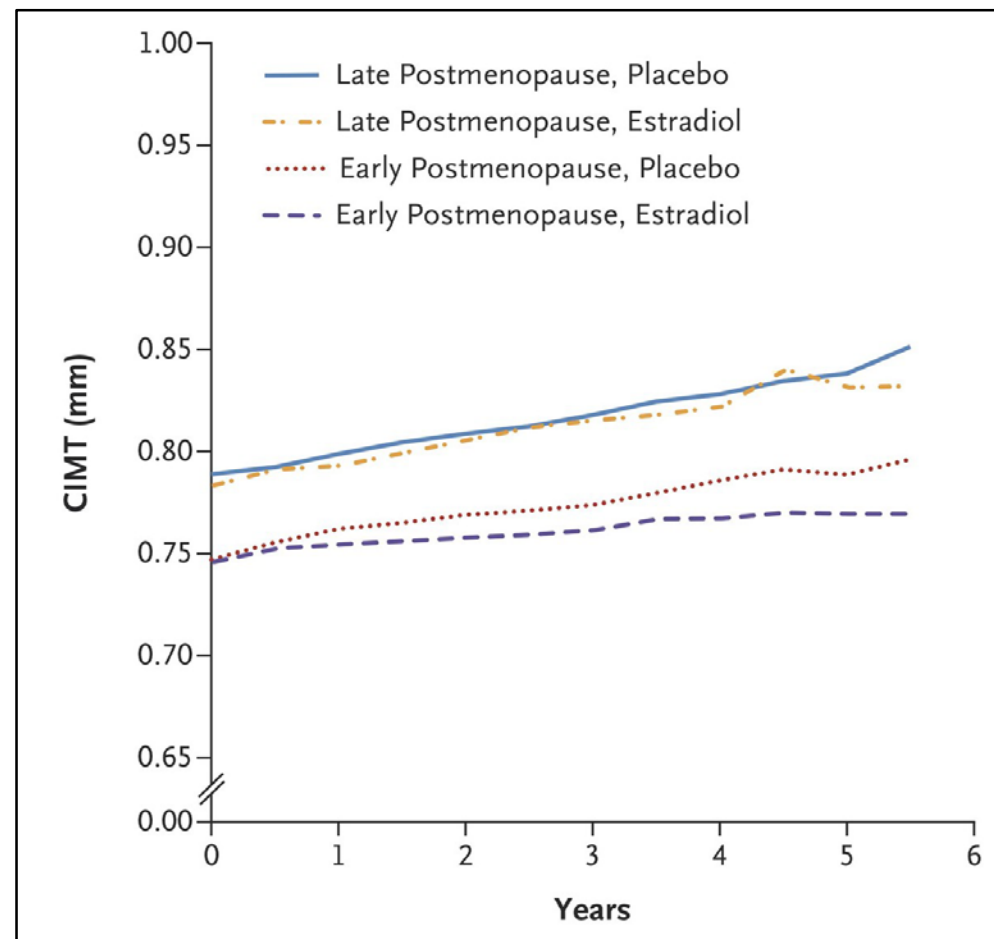
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol

Howard N. Hodis, M.D., Wendy J. Mack, Ph.D., Victor W. Henderson, M.D., Donna Shoupe, M.D., Matthew J. Budoff, M.D., Juliana Hwang-Levine, Pharm.D., Yanjie Li, M.D., Mei Feng, M.D., Laurie Dustin, M.S., Naoko Kono, M.P.H., Frank Z. Stanczyk, Ph.D., Robert H. Selzer, M.S., and Stanley P. Azen, Ph.D., for the ELITE Research Group*

Effects of estradiol on progression of atherosclerosis, assessed as CIMT, differed according to the time of initiation of therapy, with benefit when initiated at <6 years past menopause but not when initiated ≥ 10 years past menopause



In Utero

Childhood

Adolescence

Early Adulthood

Middle Adulthood

Late Adulthood

TOPMed: A Diverse Genome-Phenome Resource Enabling Data Science for an Innovative Women's Health 2.0 Agenda

Objective 4: Precision Medicine

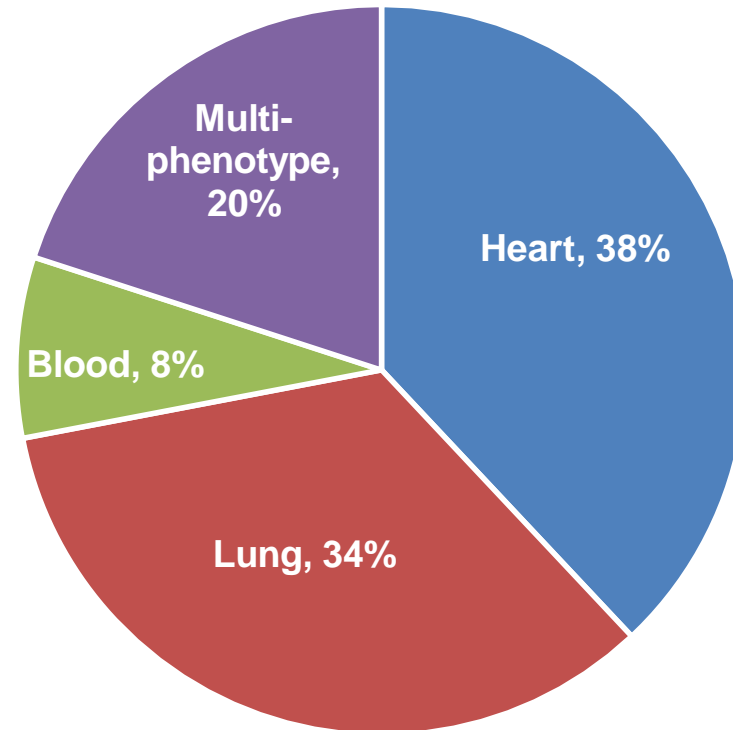
58% women in WGS samples publicly available for research



TOPMed



WOMEN'S
HEALTH
INITIATIVE



Phenotype Diversity

Hypertension
MI CAD
Stroke
Small Vessel Disease
CHD
Afib
CAC
Adiposity
CHF

Hemophilia
SCD
Platelets
Lipids
VTE

Asthma
COPD
IPF
Sarcoidosis
ILD
Sleep

An expansive data resource, with rich phenotype and population diversity, for scientific exploration, including **sex-specific and sex-difference** analyses.

Phenotype Diversity represents 144K WGS samples from Phase 1-4 X01s.

Addressing the Cardiovascular Health of Women



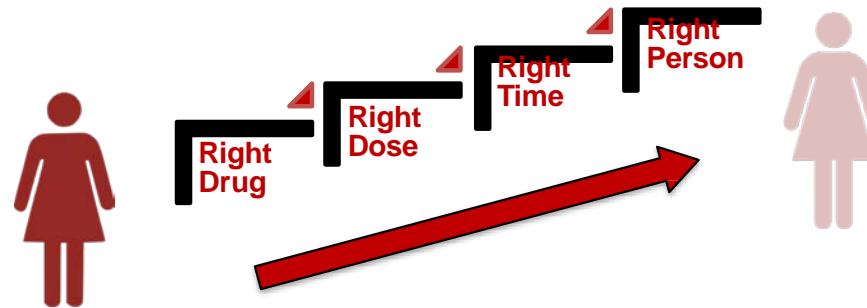
TOPMed

What if We Could Leverage Deep Characterization, Genomics, and Data Science for Transformative Impacts on the Health of Women?



Protective effects of estrogen in early life and post-menopausal transitions that confer vascular risk

Targets of intervention early in life to portend improved long-term CVD and cognitive outcomes for women



The promise of precision medicine, when fully realized embraces...

- Sex as the highest order of risk assessment, prevention, diagnosis, and treatment
- Diagnostics that reflect contribution of sex-based biomarkers
- Tailored therapeutics that address hormone and age-related influences on health and disease
- Clinical research that advances sex-specific analyses to eliminate gaps in evidence-based care of women



National Heart, Lung,
and Blood Institute