

RESEARCH ON TAP: The Framingham Heart Study

**Three Generations, 78 Years of Data, 15,000
Participants, 2 Million Biosamples, and More to
Discover**

THURSDAY, APRIL 9 | 4-6 PM

bu.edu/research/events

Agenda

Opening Remarks

Kenneth Lutchen

Vice President and Associate Provost for Research

Donald Lloyd-Jones

Professor, Boston University Chobanian &
Avedisian School of Medicine

Presentations

Lindsay Farrer
Nicole Spartano
Jesse Mez
Gary Mitchell
Rhoda Au
Daniel Levy
Douglas Kiel
Jessica Fetterman
Alexander Stanisic
Matthew Naylor
Vanessa Xanthakis
George O'Connor
Joanne Murabito

Funding Opportunities

Sophie Reilly

Assistant Director, Foundation Relations

The Framingham Heart Study: 1 Town, 6 cohorts, 78 Years, 15,000 Participants, 2M Biosamples, Millions+ of Lives Saved, and So Much More to Do

Donald M. Lloyd-Jones, MD ScM
PI, Framingham Heart Study

BU Research on Tap
April 9, 2026



What is FHS? 1948-2031+



- Longest running, most famous study of its kind in the world
- After World War II, emerging epidemic of chronic diseases, especially CVD – accounting for 44% of US deaths
- But: “of the epidemiology of hypertensive or arteriosclerotic cardiovascular disease, almost nothing is known”
- Hypothesis: there was “not one cause, but rather multiple causes that work slowly within the individual to cause the disease over time”
- Therefore, need for an epidemiological study
- FHS defined the major risk factors for CVD: lipids, blood pressure, diabetes, smoking, adverse diet, sedentary lifestyle
- Still going strong; funded through 2031...

Dawber, 1951

Design



- ~20% of citizens of town in 1948 enrolled
 - Mostly European, diverse SES
 - Always more women than men
 - Families
 - Expanded to 3 generations of related individuals, and spouses, plus cohorts more representative of contemporary Framingham
- Repeated exams every 2-5 years: core measurements plus ancillary science
- Follow up for medical history annually, with adjudicated events
- Extensive data and biorepository



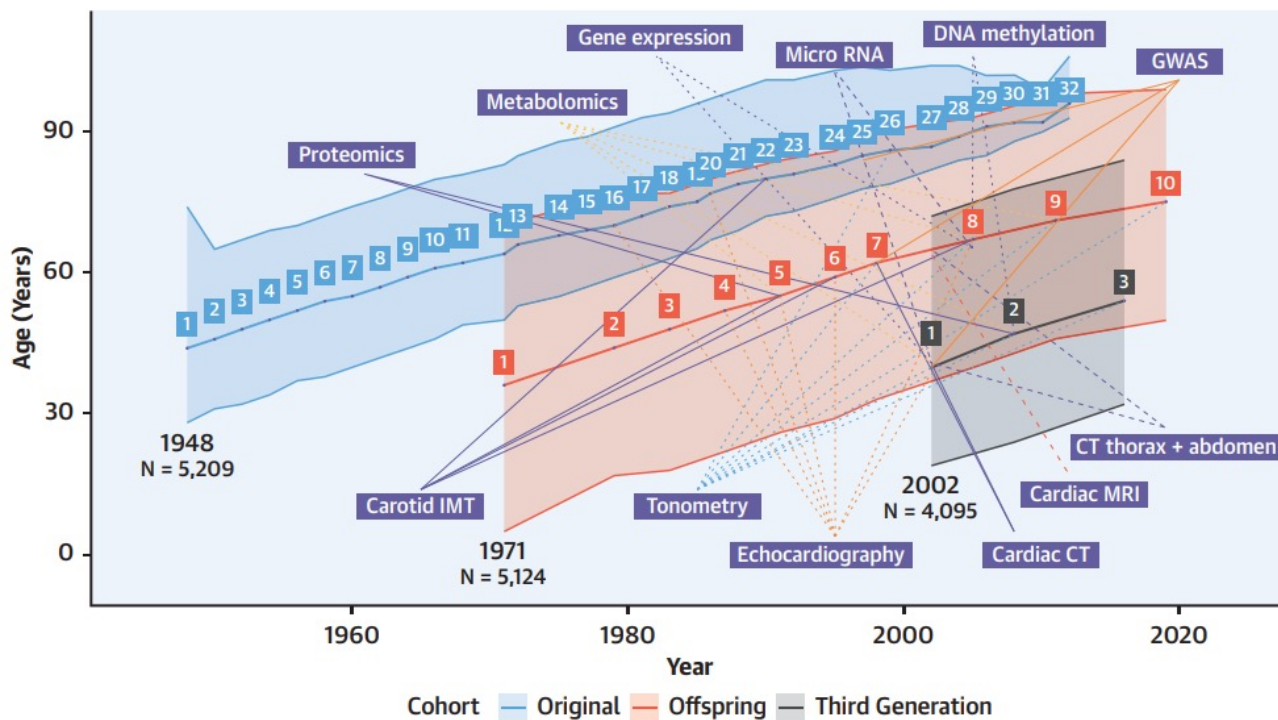
Structure of FHS Cohorts

Cohort	N	Ancestry	Exams Completed as of 4/2026
Original FHS, 1948	5,209 MW	Exclusively European	32
Offspring + Spouses, 1971	5,124 MW	Mostly European	10 (11 ongoing)
Gen 3, 2002	4,095 MW	Mostly European	4 (5 planned)
Omni-1, 1995	506 MW	Mixed/non-White	5 (6 ongoing)
Omni-2/New Offspring Spouses, 2002	513 MW	Mixed/non-White	4 (5 planned)
Total	15,447	~6300 surviving: ~3900 in MA; ~2300 in other states; ~40 abroad	

FHS Core Exams and Content



Cardiovascular Measurements



- Plus extensive and repeated deep phenotyping of brain/cognition, lung, kidney, bone, liver, functional status, ...
- Images
- 2M biosamples (plasma/serum, urine, WBC, iPSCs, DNA, brain and heart tissue)

Omics in FHS



- Existing (high-level summary)
 - Complex matrix across all cohorts – opportunistic with some strategic TOPMed fill-in: 7,215 WGS assays, 6,735 metabolomics assays, 3,991 methylation assays, 6,696 proteomics assays, and 5,052 RNASeq assays

Approach	Offspring	Gen3	Omni1	Omni2
WGS/Exome/GWAS	GWAS ~3600 Exome ~3400 WGS ~2700	GWAS ~3900 Exome ~4000 WGS ~3400	GWAS ~500 WGS ~300	GWAS ~400 WGS ~400
DNAm	Up to 2600 Exam 8	Up to 3000 Exam 2	~400 Exam 1	~400 Exam 1
RNA	Up to 2500 Exam 8	Up to 3200 Exam 2	~200 Exam 4	~300 Exam 2
Proteome	Up to 2100 Exam 7/8	Up to 3100 Exam 1/2	~250 Exam 3/4	~300 Exam 1/2
Metabolome	Variable	Up to 2000 Exam 2	~300 Exam 4	~300 Exam 2

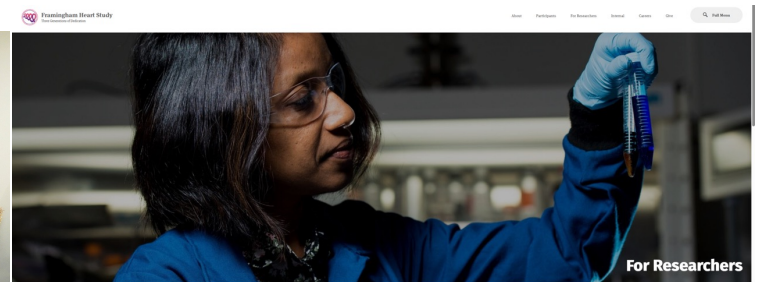
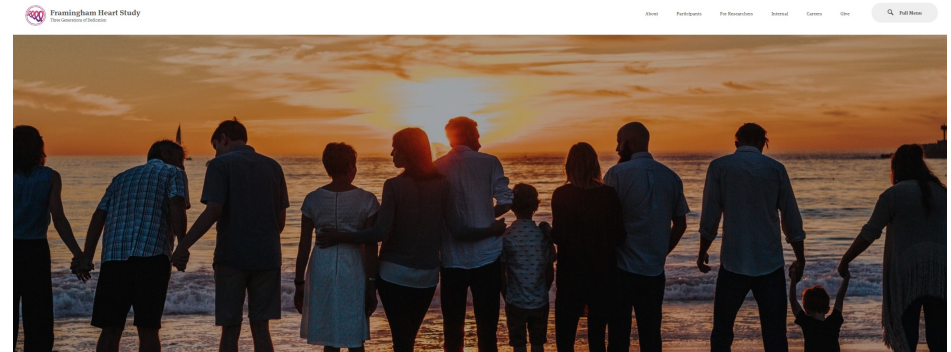
Seminal Contributions



- Identified major risk factors for CHD, HF, AF, stroke, dementia, and other forms of CVD
- Development and application of modern epidemiological and biostatistical methods
 - Training ground and inspiration for other cohort studies
- Repeated, longitudinal, deep phenotyping across the life course
 - Preclinical and clinical phenotypes, physiology, and basic biology
- Major contributions to cognitive aging and aspects of longevity
- Extensions beyond CVD to other phenotypes: environmental exposome; endocrine, renal, pulmonary health; bone and joint health; eye and ear; and; and much, much more
- Pioneering novel phenotyping and molecular epidemiology

If you'd like to learn more...

- www.framinghamheartstudy.org
- Email: fhs@bu.edu



Boston University Chobanian & Avedisian School of Medicine



Leveraging Genetic / Multi-omic and 75+ Years of Longitudinal Data in FHS for Alzheimer Disease Research



Lindsay A. Farrer, Ph.D.

Biomedical Genetics

Chobanian & Avedisian School of Medicine

Research on Tap

April 9, 2026

Advantages of Alzheimer Disease Research in the Framingham Heart Study

- > 15,000 subjects from 3 generations followed for up to 75 years
- Family-based design
- Wealth of clinical, laboratory, exposure and lifestyle data collected every 4-5 years
- AD relevant data include cognitive, neurological, AD biomarker, and neuroimaging (structural MRI and amyloid-PET) data
- Neuropathologically examined brains
- Genetic (GWAS, WGS, WES) data, and methylation, RNA-seq, proteomic and metabolomic data from blood and brain tissue
- FHS Brain Aging Program infrastructure for mentoring and promoting data sharing

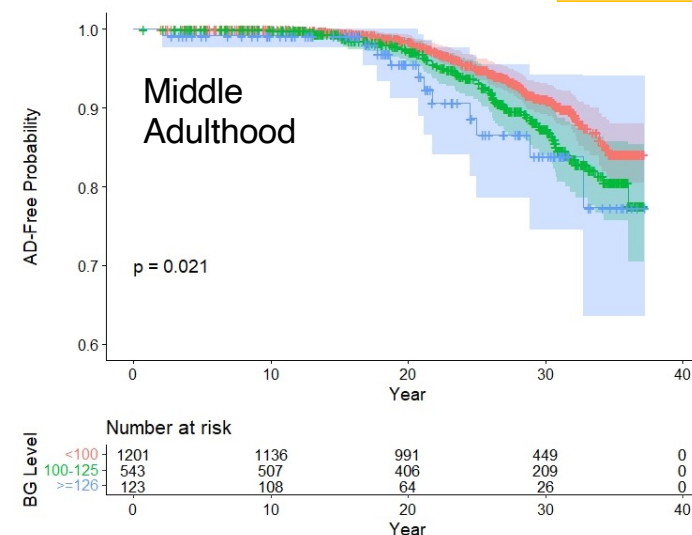
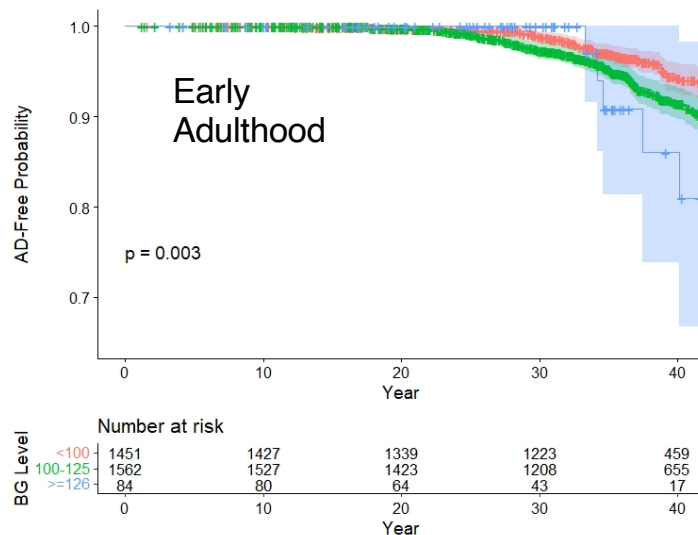
Association of blood lipids and glucose with incident Alzheimer disease in The Framingham Heart Study

Risk Factor	Group (age range in years) †											
	Early Adulthood (35-50)				Middle Adulthood (51-60)				Late Adulthood (61-70)			
	N	N events	HR*	P-value	N	N events	HR*	P-value	N	N events	HR*	P-value
HDL-C	2875	156	0.846	0.041	1803	163	0.821	0.014	1463	176	0.887	0.11
TG	2879	157	1.326	0.0013	1809	163	1.120	0.22	1470	176	1.048	0.57
Glucose	2820	154	1.067	0.39	1792	163	1.145	0.00029	1427	171	1.066	0.056

† Subjects may appear in multiple groups

* Hazard ratio for a 15 mg/dL increase

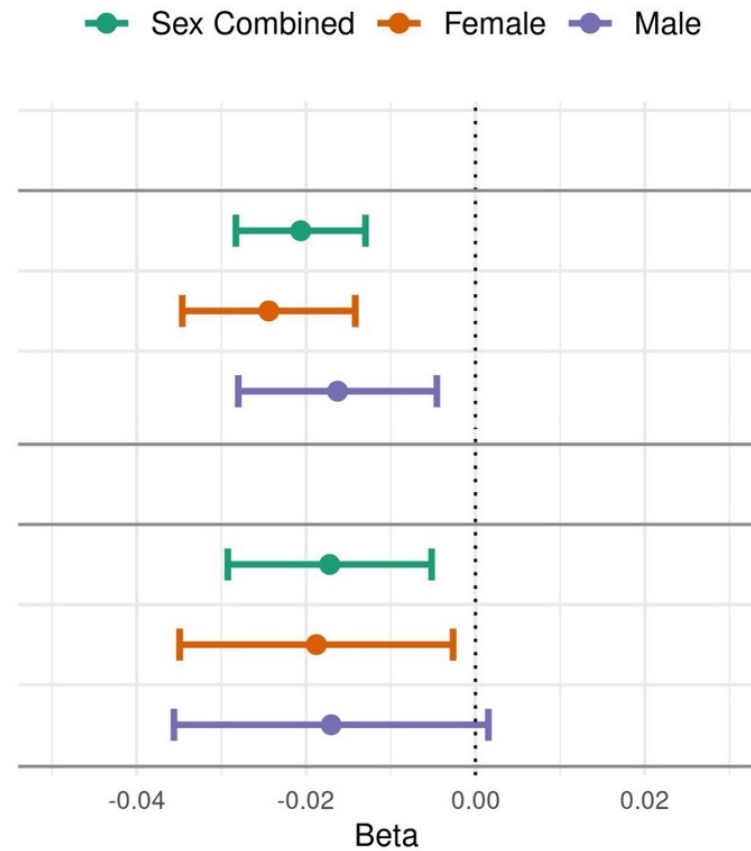
Zhang et al. *Alzheimer Dement.* 2023; 19:181-193



Association of an Alzheimer disease polygenic risk score with hippocampal volume



N	BETA [95% CI]	P
ADSP		
6568	-0.021 [-0.028;-0.013]	1.37×10^{-07}
3330	-0.024 [-0.035;-0.014]	3.14×10^{-06}
3238	-0.016 [-0.028;-0.005]	6.60×10^{-03}
FHS		
970	-0.017 [-0.029;-0.005]	5.23×10^{-03}
560	-0.019 [-0.035;-0.003]	2.33×10^{-02}
410	-0.017 [-0.036; 0.002]	7.32×10^{-02}



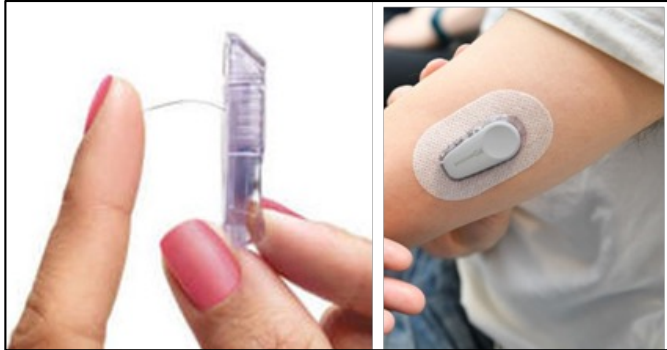
Using Continuous Glucose Monitoring (CGM) to Identify Hidden Dysglycemia in Individuals without Diabetes

Nicole Spartano, PhD

Assistant Professor

Department of Medicine, BUCASM

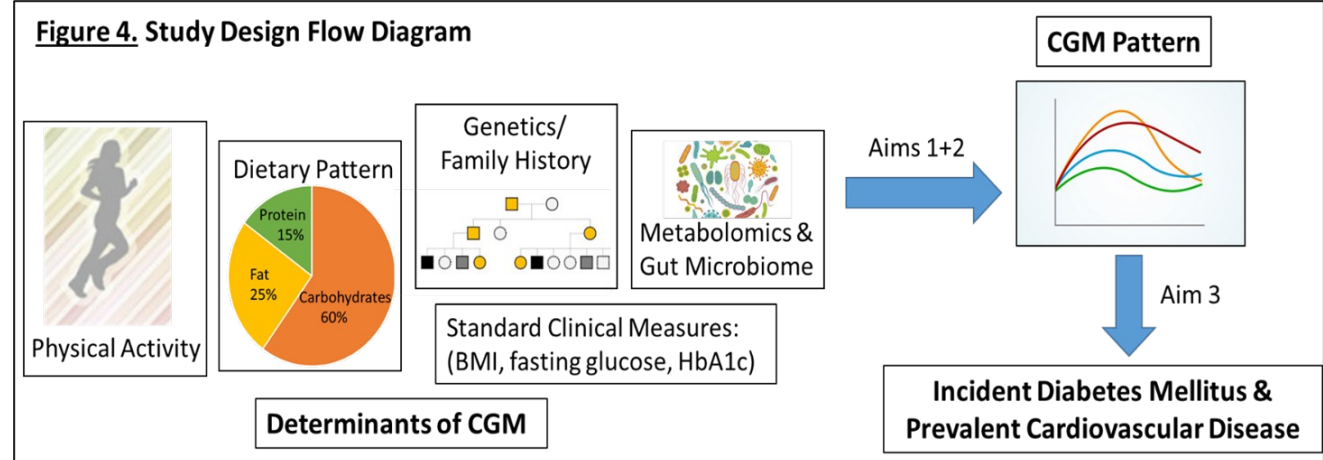
Our Goal: Use Continuous Glucose Monitoring (CGM) to predict diabetes development



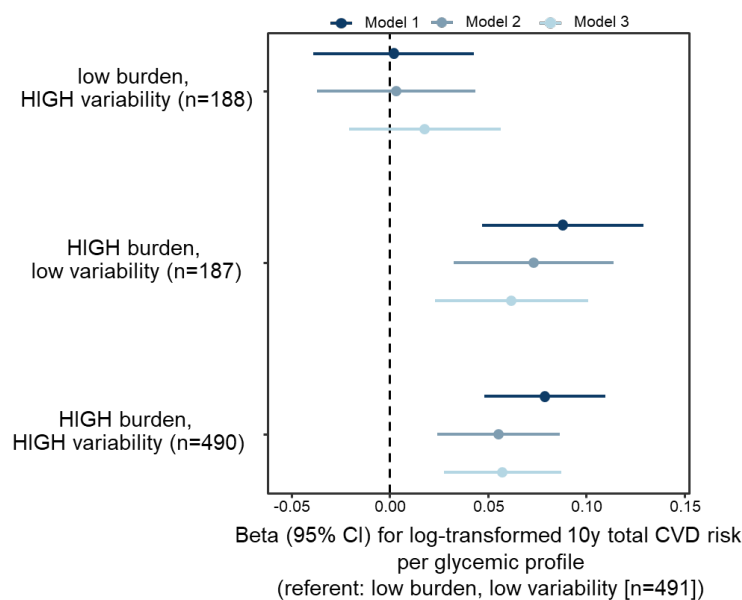
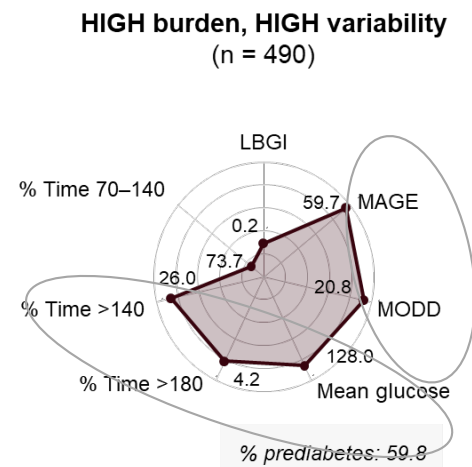
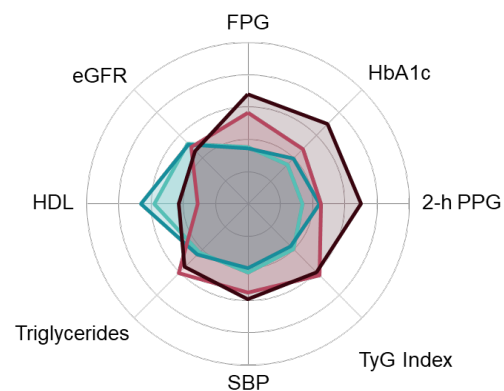
>2000 participants from the Framingham Heart Study wore a Dexcom G6 CGM for up to 10 days (2022-2025)

Records a glucose value every 5 minutes (288 values/day) from the interstitial space under the skin

11% of cohort had diabetes (or meds) at time of collection

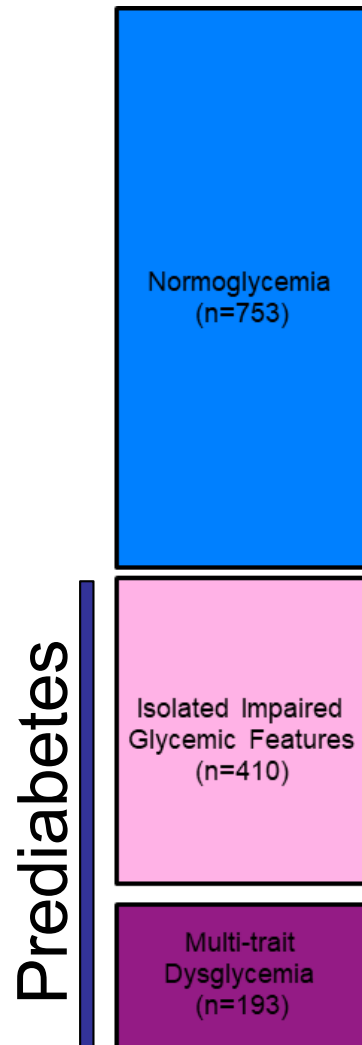


Do CGM-derived phenotypes inform cardiovascular risk? (n=1356)

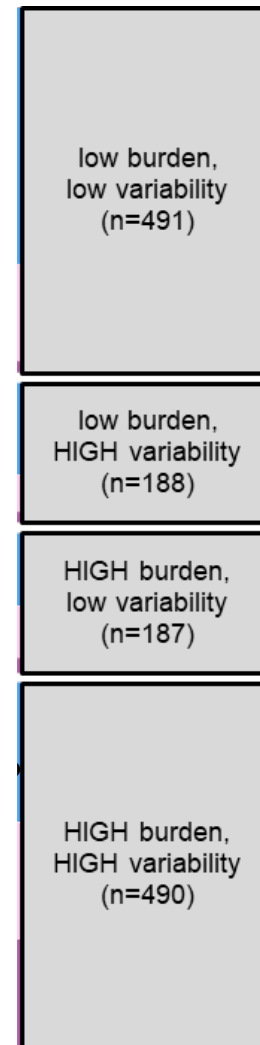


Can we use CGM to re-classify diabetes risk (n=1356?)

Traditional classification



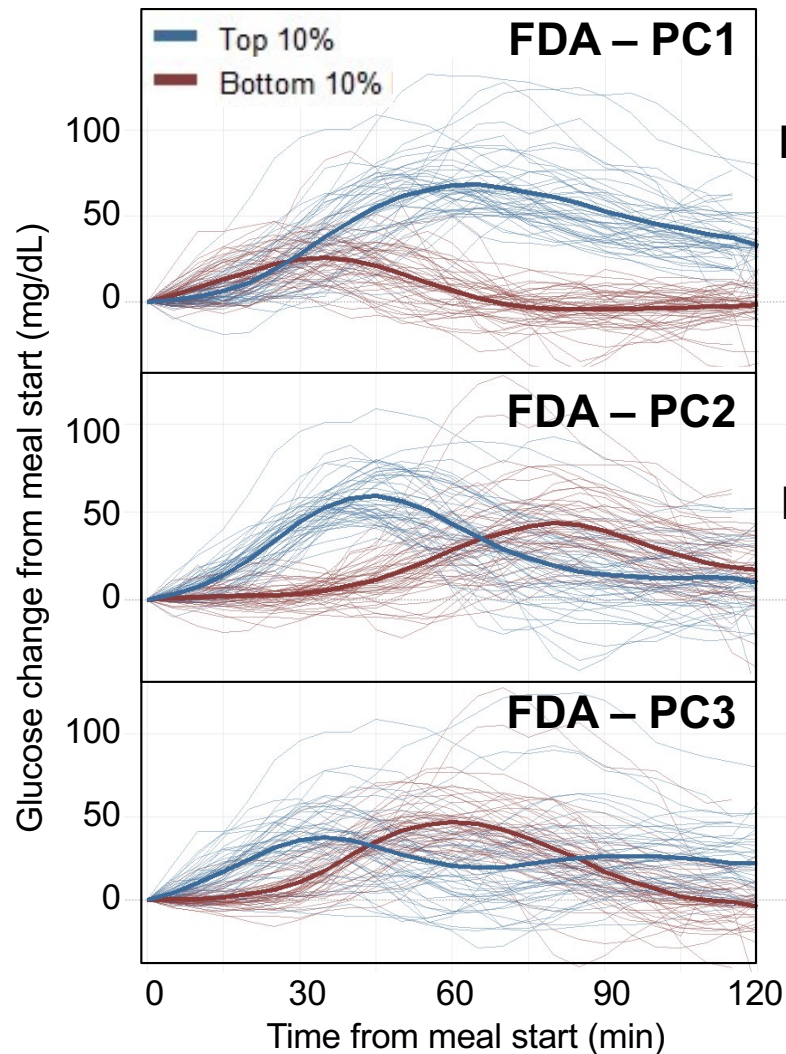
CGM phenotypes



Burden:
Time >140mg/dL

Variability:
Mean amplitude
of glycemic
excursions
(MAGE)

Functional data analysis allows for the analysis of curves/shapes in CGM postprandial periods (>30mg/dL rise)



PC1: large, sustained rise

- Dominant component — accounts for **60.3%** of between-person functional variation

PC2: early, sharp peak with rapid return

- Accounts for **19.8%** of variation

PC3: moderate, early rise with sustained plateau

- Accounts for **10.2%** of variation

NEWSLETTER

2026 WINTER EDITION



THE FRAMINGHAM
HEART STUDY

A project of the National Heart, Lung and blood
Institute and Boston University

Digital Health and Network Multiomics Lab

Maura Walker

Huimin Cheng

Nicola McKeown

Bahar Bakhshi **

Naznin Sultana **

Jung Lee

Suheng Yao

Yeji Han

Ye Eun (Christina) Koo

Nick Siegel

Jingxian Tang

Kimaya Gazula

Hannah Pratt

Ioanna Yiannakou

(Former Lab Members)

David Fei

Brenton Prescott

Daniel Cho

Hemant Singh

Vedika Srivastava

Noah Chigier

Menghan (Remi) Jin

Sruti Raman

**BOSTON
UNIVERSITY**

**GEN 2 & OMNI 1: START
YOUR EXAM ENGINES!**

Framingham Investigators

Honghuang Lin

Joanne Murabito

Matt Naylor

Vanessa Xanthakis

Donald Lloyd-Jones

Boston Medical Center

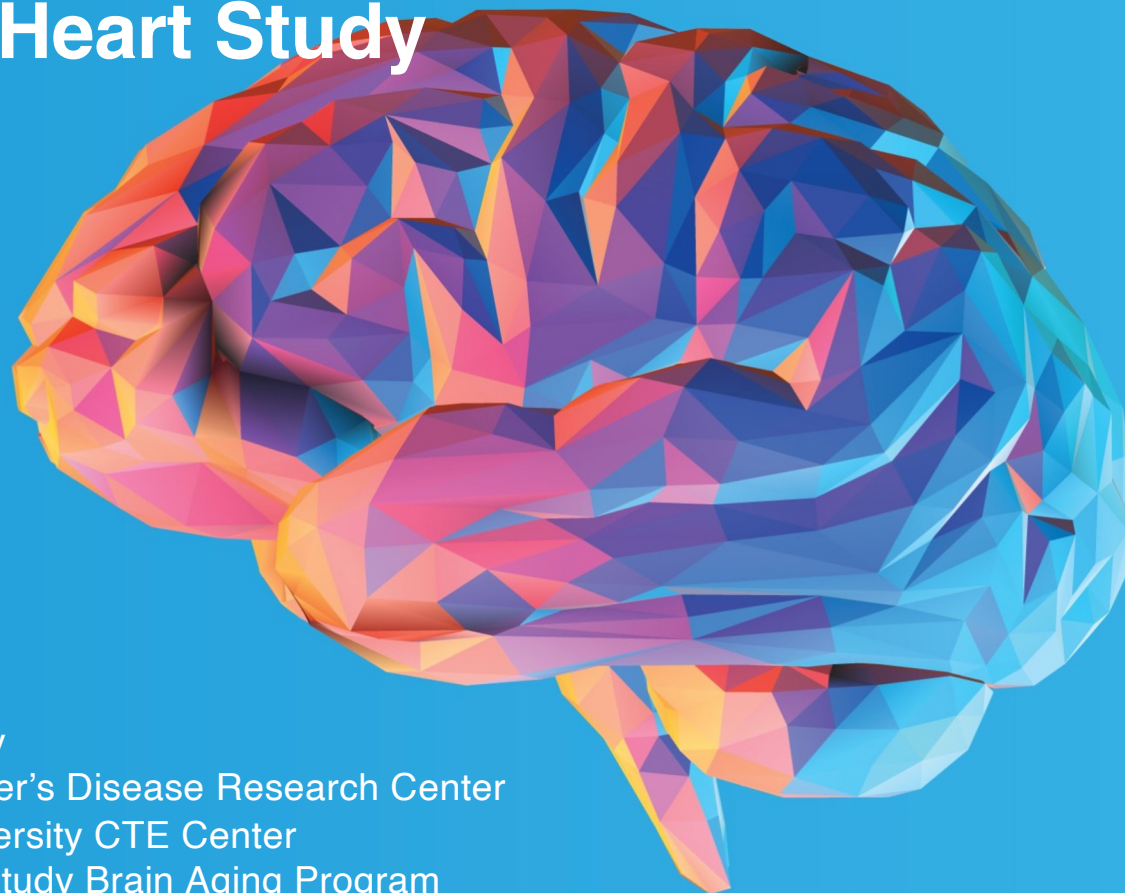
Devin Steenkamp

Howard Wolpert

Michael Cheney



Investigating brain trauma, Alzheimer's disease and related dementias in the Framingham Heart Study

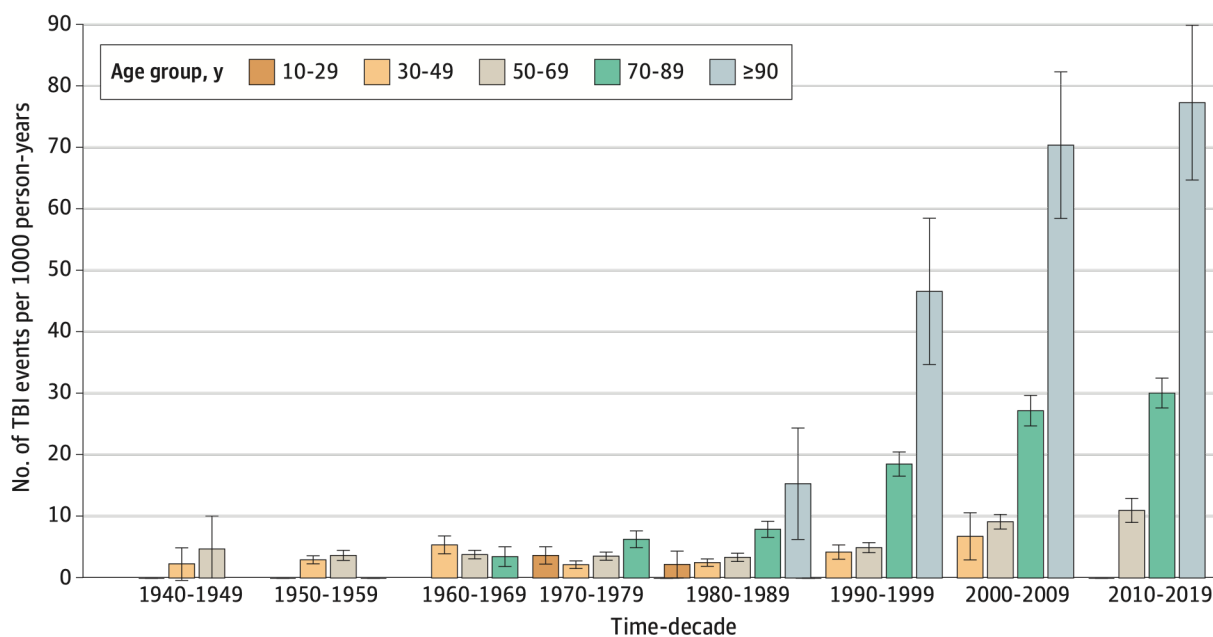


Jesse Mez, MD, MS

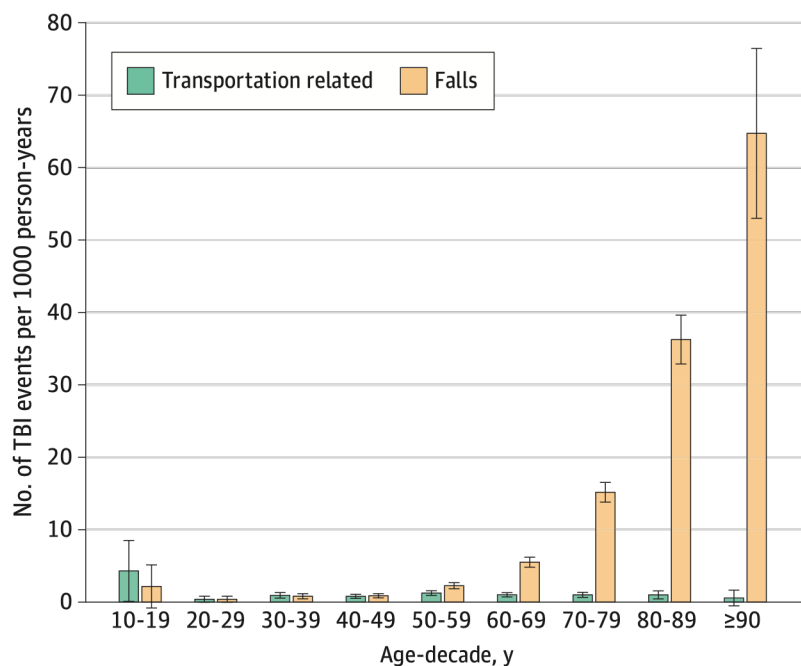
Associate Professor, Department of Neurology
Associate Director, Boston University Alzheimer's Disease Research Center
Co-Director of Clinical Research, Boston University CTE Center
Clinical Core Co-Leader, Framingham Heart Study Brain Aging Program

Traumatic brain injury (TBI) incidence across time-decades, age-decades and by mechanism in FHS

C TBI incidence stratified by time-decade and age group in the combined sample

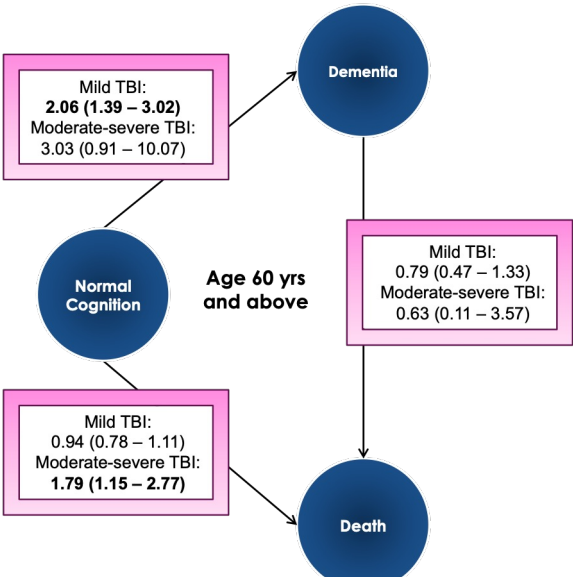
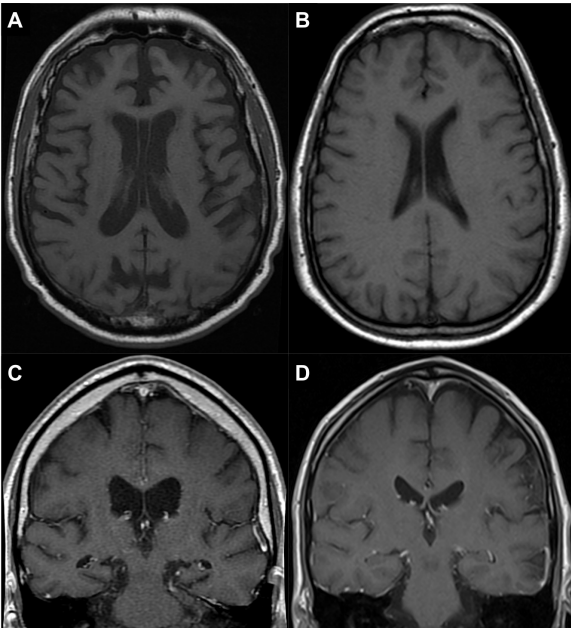
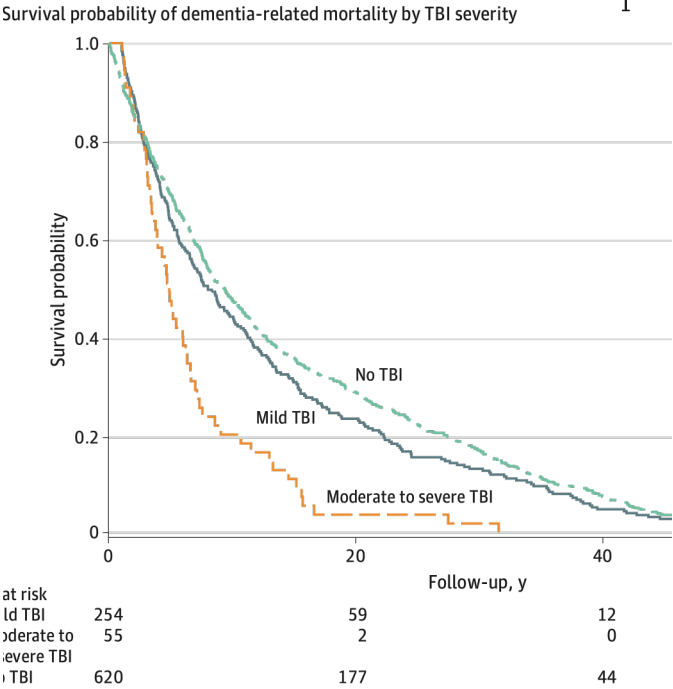
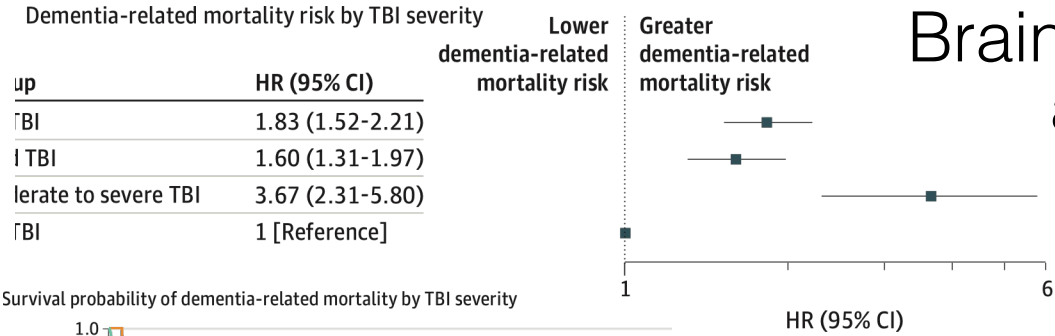


E TBI stratified by age-decade and mechanism: offspring cohort



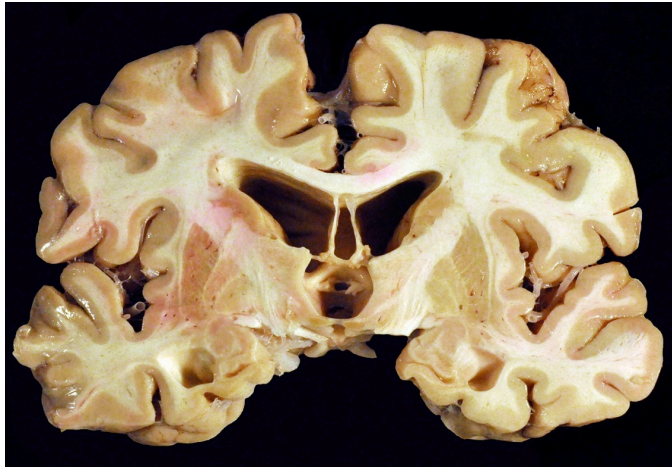
Burton et al. JAMA Open 2026

Brain trauma, mortality, dementia, and MRI imaging in FHS



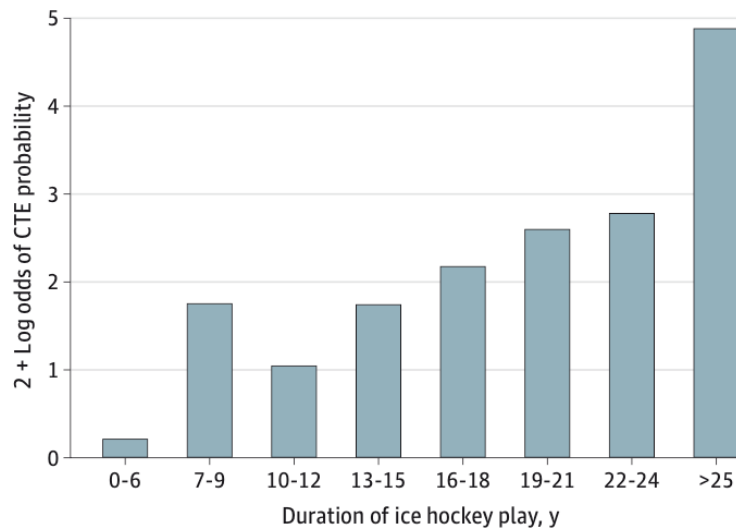
Burton et al. JAMA Open 2026

Alosco et al. Alz. Res. & Ther 2026
Farris et al. AAIC 2025

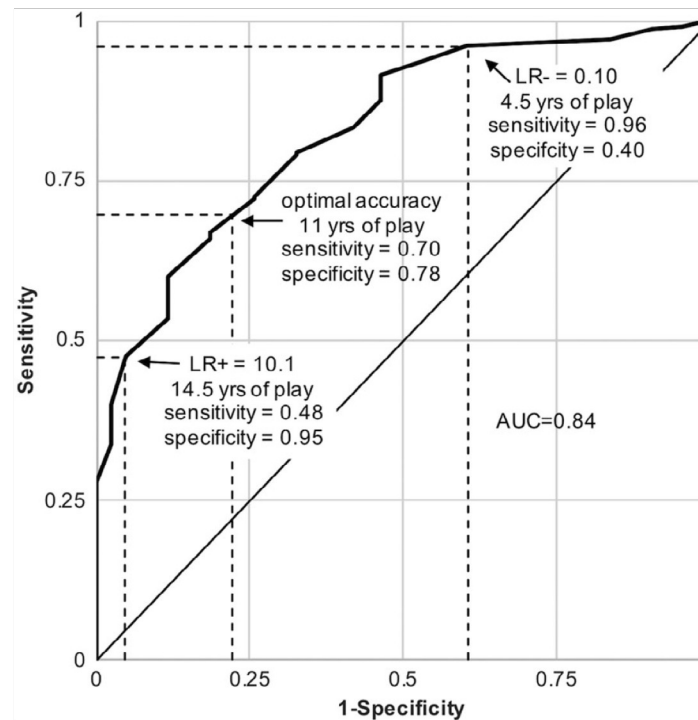


Leveraging FHS Brain Bank to investigate brain trauma – neuropathological relationships

A Log odds of probability of CTE



Abdolmohammadi et al. JAMA Open 2025

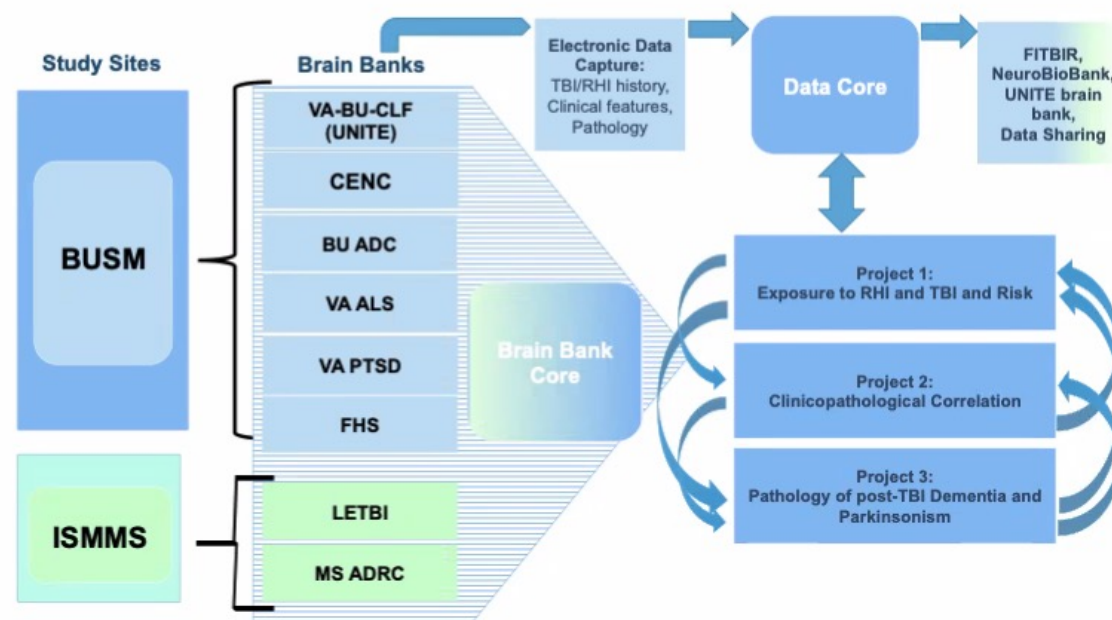


Mez et al. Annals of Neurology 2019



Harmonization of FHS data with other brain aging studies

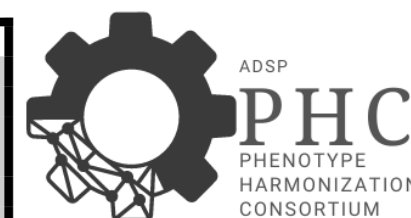
U54: Traumatic Brain Injury and Repetitive Head Impacts: Contributions to AD/ADRD and CTE Neuropathology and Resulting Clinical Syndromes



R01: Leveraging Existing Aging Research Networks to investigate TBI and AD/ADRD risk (LEARN TBI & AD)

Table 1. Summary of the five included studies

Study	<u>ACT</u>	<u>ROS</u>	<u>MAP</u>	<u>MARS</u>	<u>FHS</u>
Originating Year	1994-	1994-	1997-	2004-	1948/1971/1994
Participants	Seattle-area Kaiser Health members	Older religious clergy; >40 groups	Chicago-area older residents	Chicago-area African Americans	Framingham, MA residents
Visits	Biennial	Annual	Annual	Annual	Periodic waves
Health assessments	X	X	X	X	X
Cognitive evaluations	X	X	X	X	X
Questionnaires	X	X	X	X	X
Genomics	X	X	X	X	X
Total sample size (n)	5,280	1,407	1,927	736	10,333
Incident dementia	1,175	401	397	50	1439
Completed autopsies	738	730	747	48	222
Follow-up completion	97%	94%	93%	94%	99%

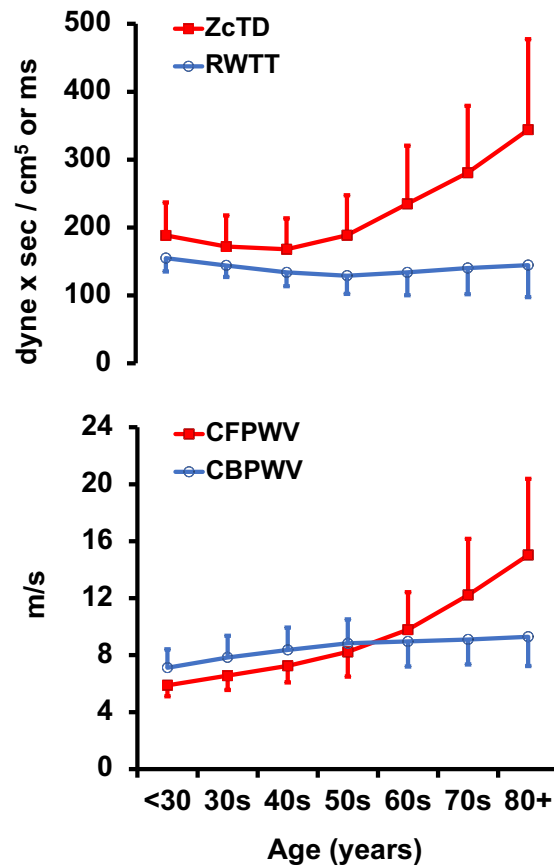
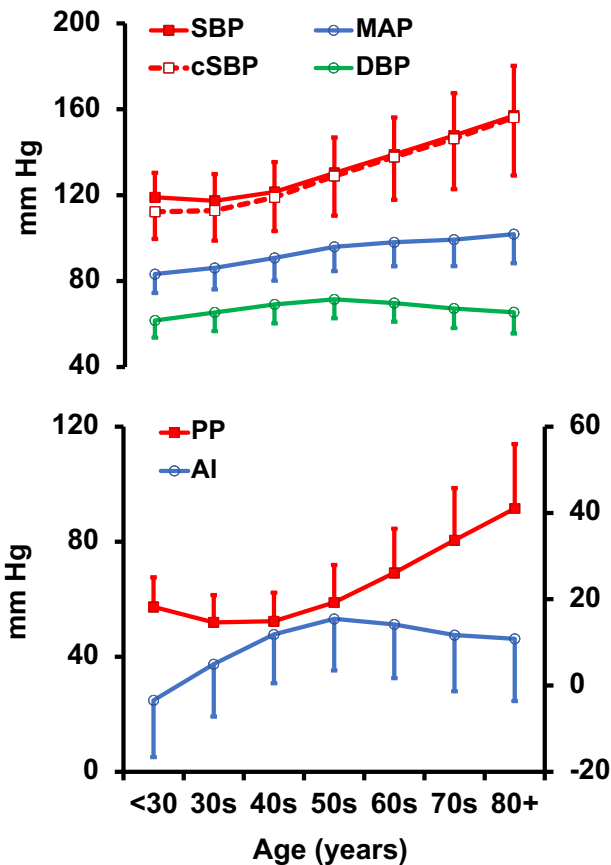
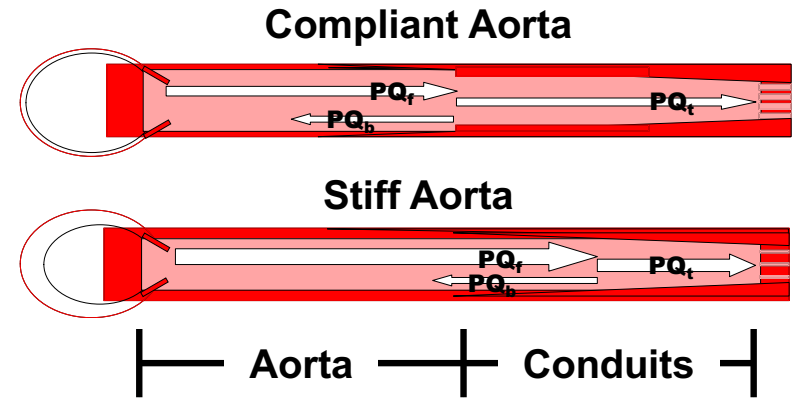
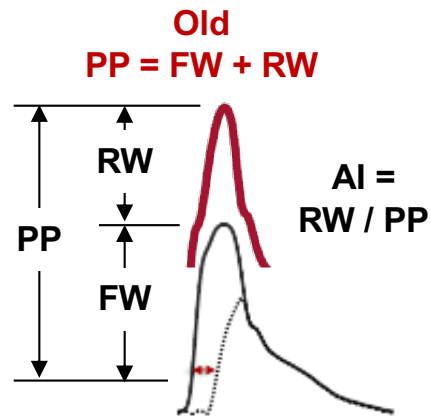
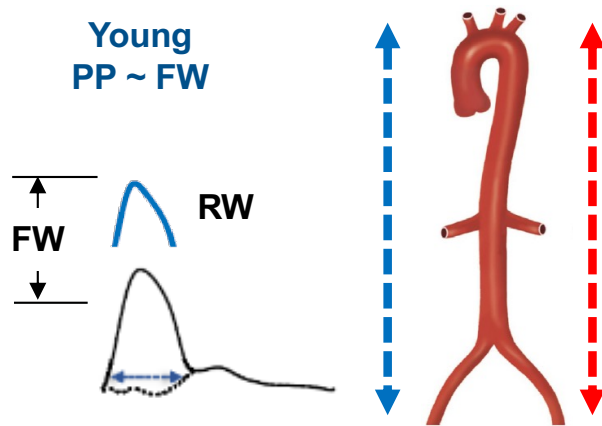


Vascular Function at FHS

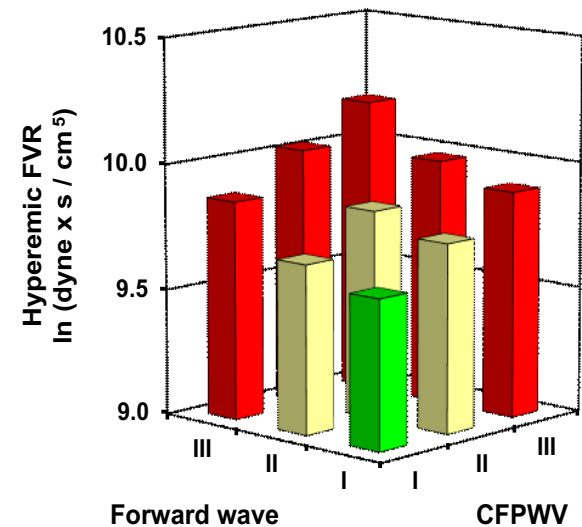
Gary F. Mitchell, MD

President, Cardiovascular Engineering, Inc.
Investigator, Framingham Heart Study

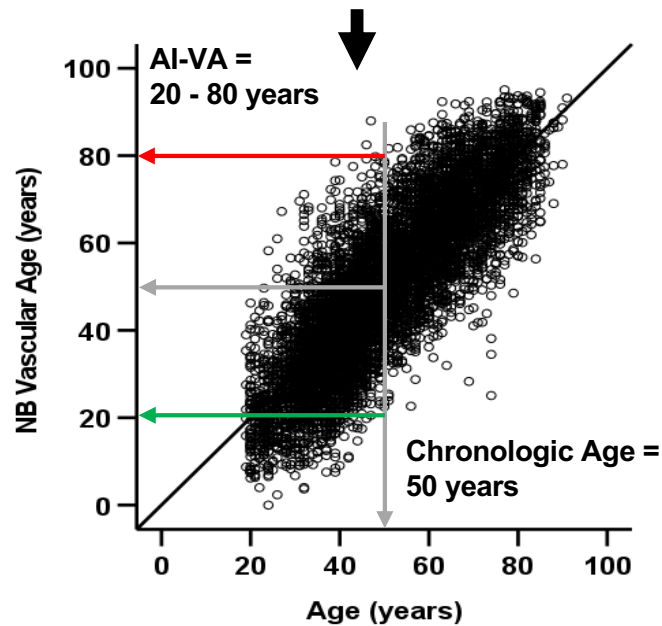
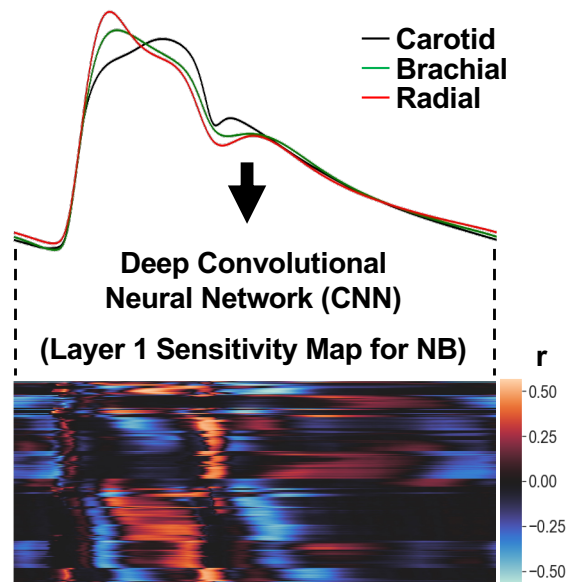
Wave Reflection: Not the Enemy!



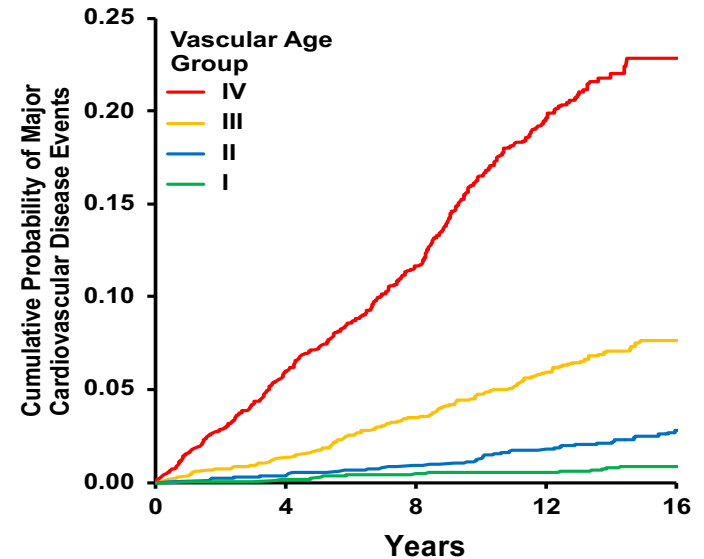
Hyperemic FVR (ln (dyne x s / cm⁵))



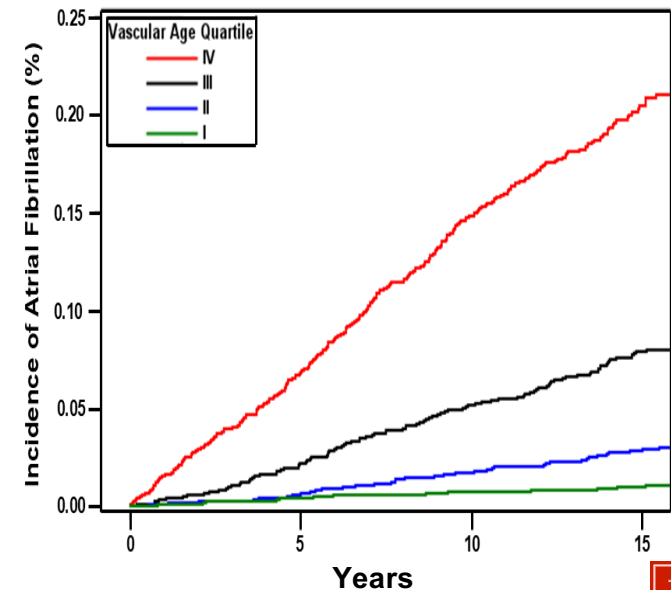
AI-VascularAge in FHS



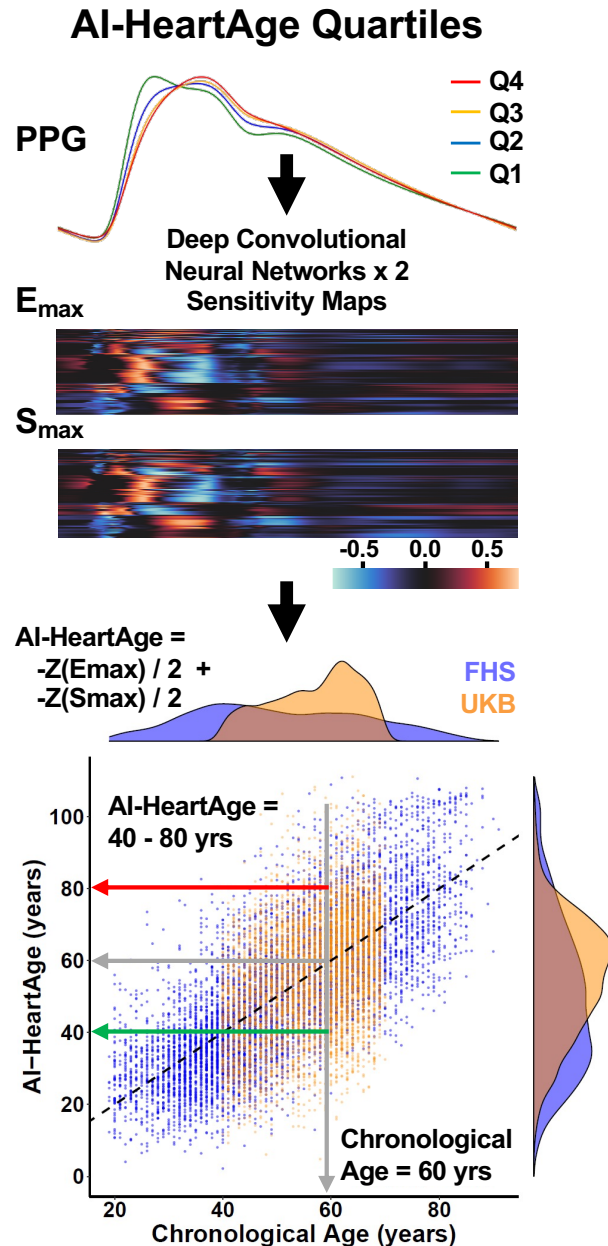
Incident CVD



Incident AF

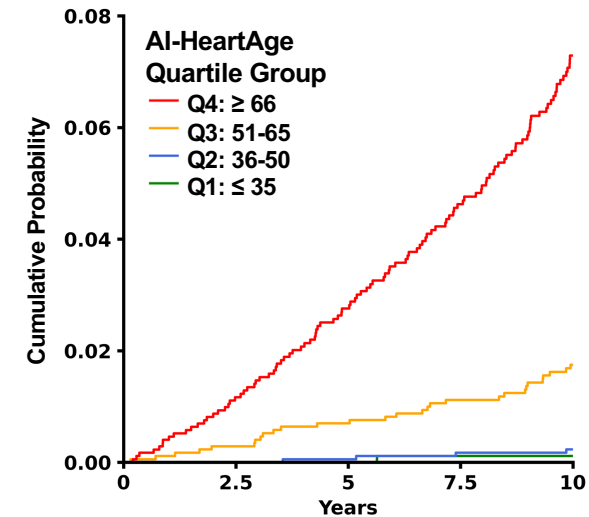


AI-HeartAge in FHS and UKB

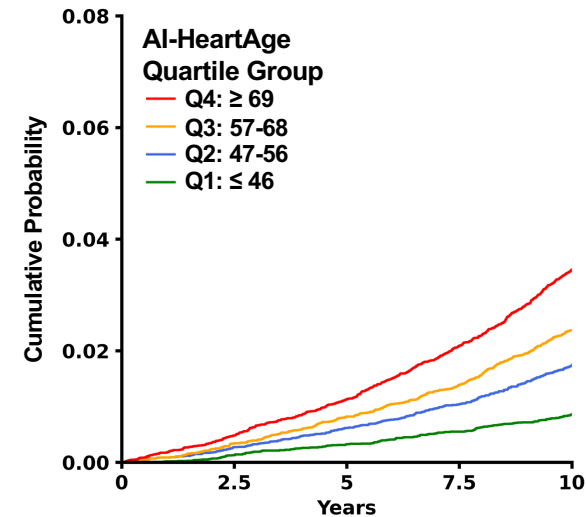


Incident Heart Failure

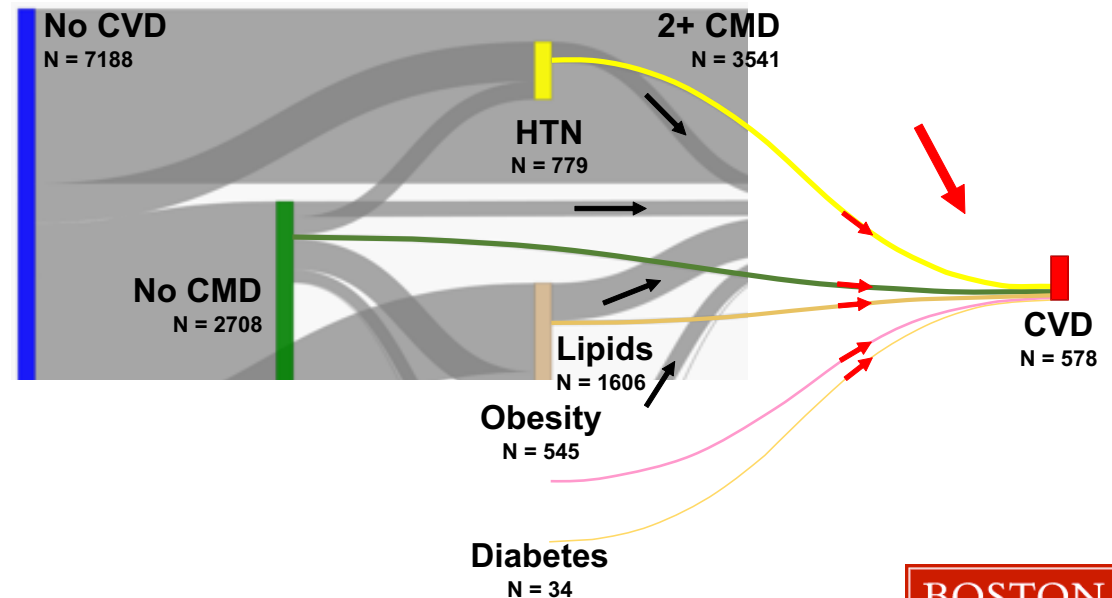
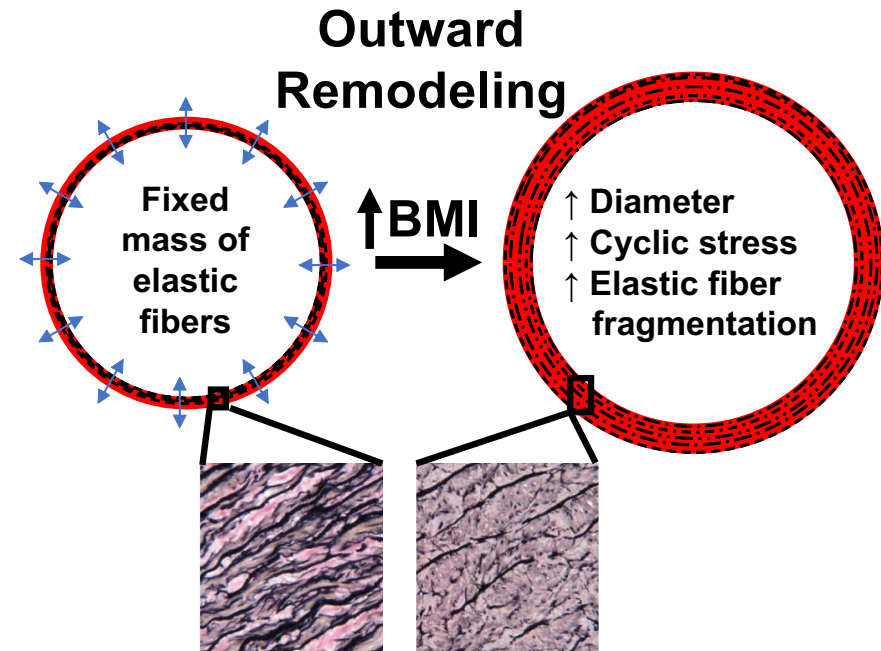
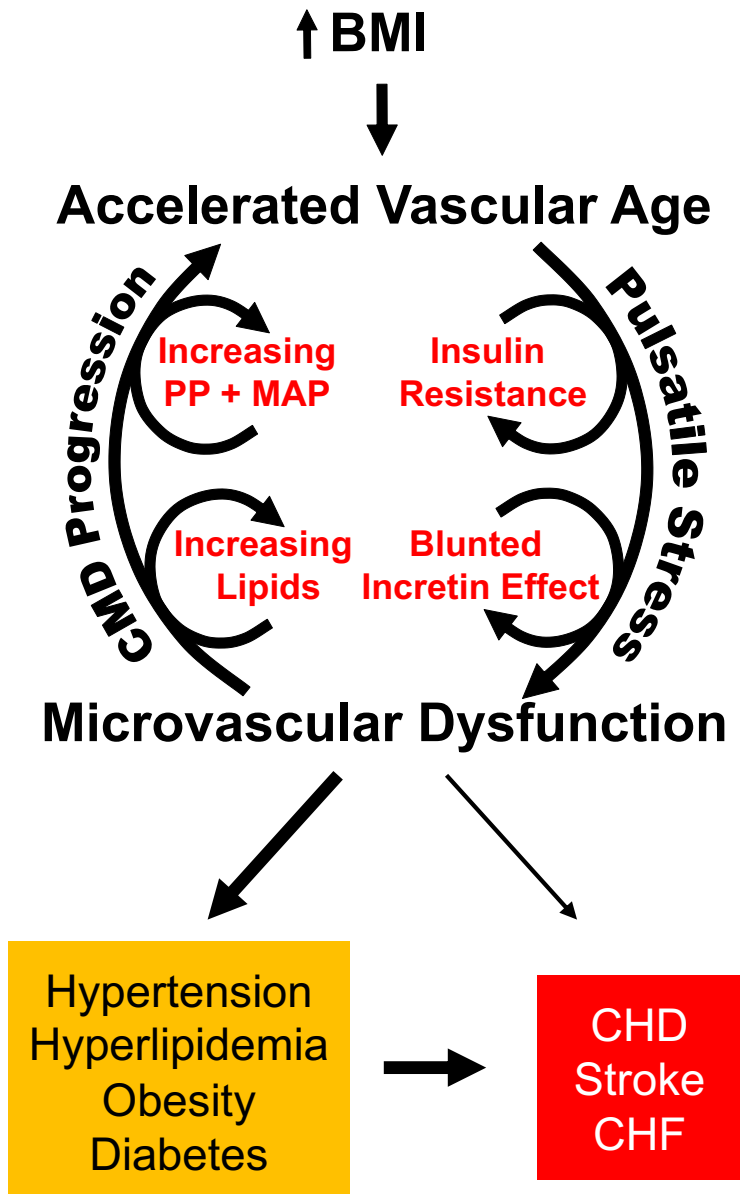
FHS



UKB



AI-VA and Cardiometabolic Disease



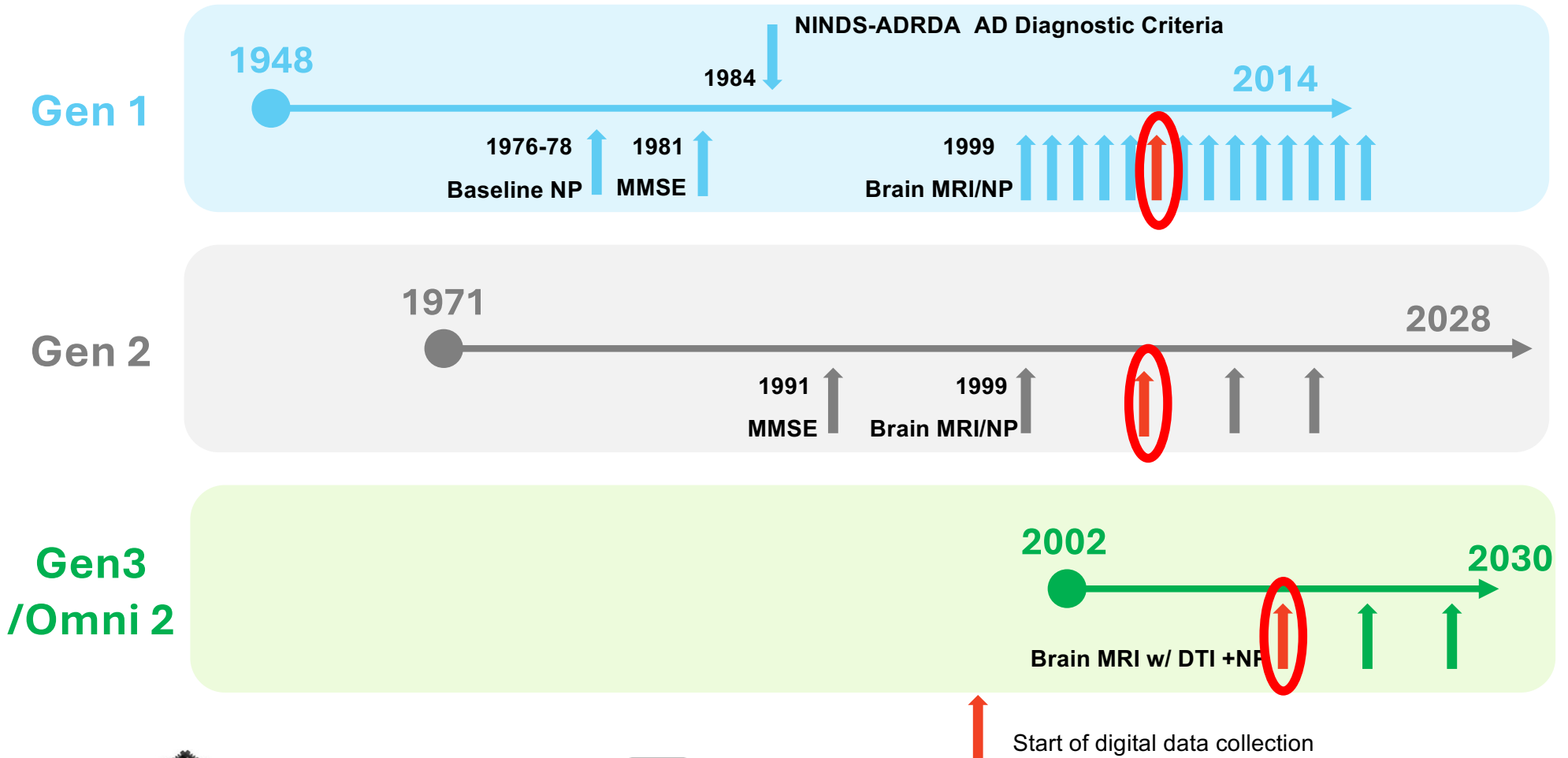
Embracing the Digital and AI Reality

Rhoda Au, PhD

Professor of Anatomy & Neurobiology, Neurology, Medicine & Epidemiology
Schools of Medicine & Public Health



FHS Brain Aging Program (FHS-BAP)



Digital Voice



Digital Pen



Smartphone

FHS Digital Voice

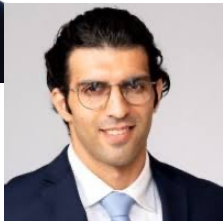


Acoustic features and NP tests related to AD plasma biomarkers

Biomarker	Measure	Significant features, <i>n</i>	Most significant feature	Beta	SE	<i>P</i> value
Total tau, pg/m	Acoustic	39	audspec_lengthL1norm (sum of auditory spectrum)	0.10	0.03	4.34E-04
	NP	2	Trails A	0.11	0.03	2.96E-04
p-tau181, pg/m	Acoustic	5	pcm_fftMag_fband1000-4000 (spectral feature, magnitude of frequency band 1-4 kHz (speech frequency band))	0.22	0.06	4.40E-04
	NP	3	Trails B	0.19	0.07	5.07E-03

NP=Neuropsychological Test; AD=Alzheimer's Disease

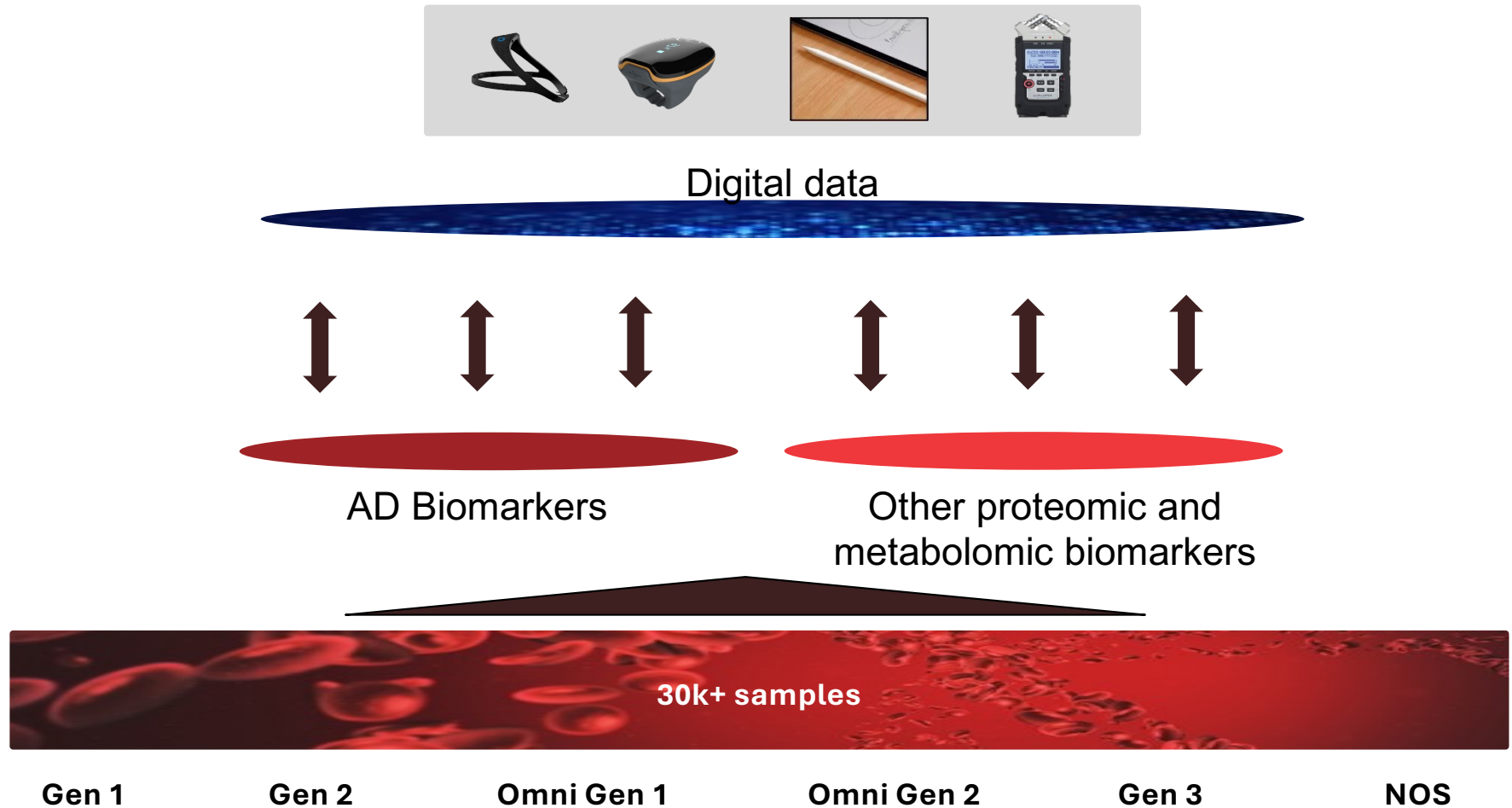
Text-based models predict AD progression within 6 years



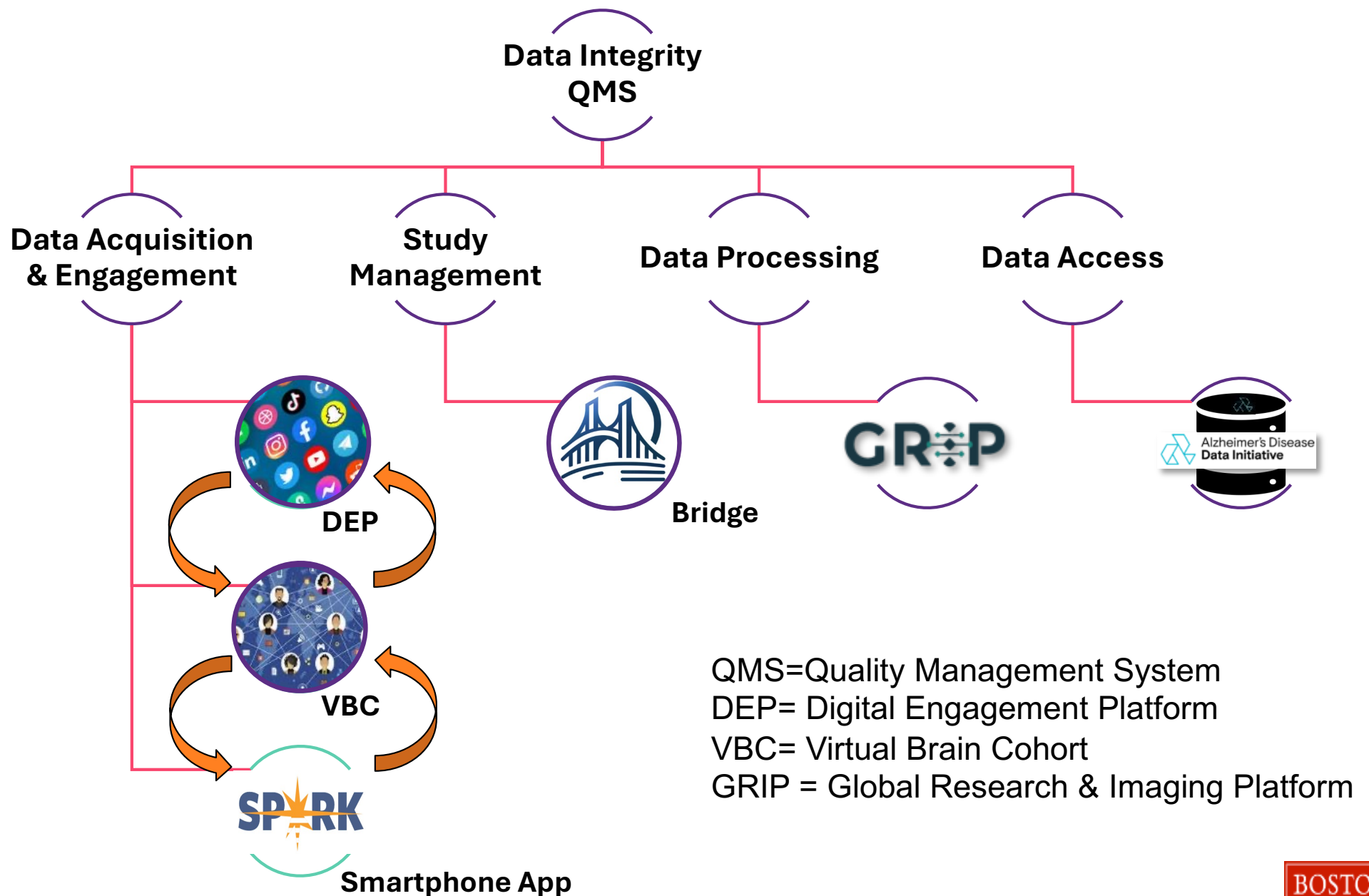
Methods	AUC %	Sensitivity %	Specificity %
Text+Dem+ApoE+Health	78.5 ± 3.9	80.6 ± 4.7	76.9 ± 4.7
Text	77.8 ± 3.9	81.1 ± 5.2	75.0 ± 4.1
Text+Dem	77.5 ± 3.7	81.1 ± 5.3	75.6 ± 4.2
Dem+ApoE	71.7 ± 4.0	77.8 ± 6.3	70.6 ± 7.0
NP scores	71.3 ± 4.1	77.2 ± 6.5	71.9 ± 5.6
Dem	68.8 ± 4.5	70.6 ± 6.1	70.6 ± 6.3
Health	66.2 ± 3.1	75.0 ± 6.6	66.9 ± 5.7
MMSE	60.7 ± 4.8	66.7 ± 5.9	58.8 ± 5.9

MMSE: Mini-Mental State Examination Dem: age, sex, educational level

Digital Biomarkers on the Horizon



FHS Going Forward and Beyond



Integrative Trans-Omics To Identify Molecular Clues to Disease

Daniel Levy, MD

NIH Distinguished Investigator
Chief, Population Sciences Branch,
National Heart, Lung, and Blood Institute
Senior Investigator, Framingham Heart Study
Professor of Medicine, Boston University

Research on Tap: The Framingham Heart Study

April 9, 2026

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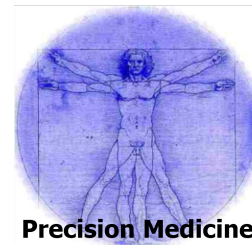
The NHLBI's TOPMed Program



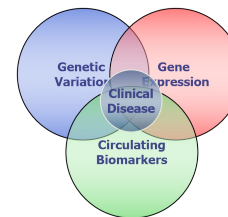
Aims:

- Apply trans-omics to identify new molecular signatures of heart, lung, and blood diseases using cutting-edge technologies
- Discover causal genes, pathways, and risk factors for disease
- Promote advances in precision medicine to predict, prevent, diagnose, and treat heart, lung, blood, and sleep disorders

Whole genome sequencing completed in ~200,000 people



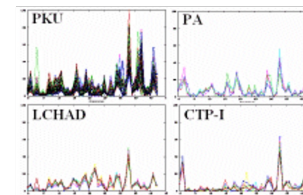
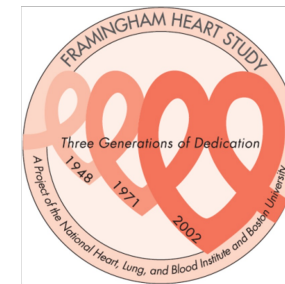
Precision Medicine



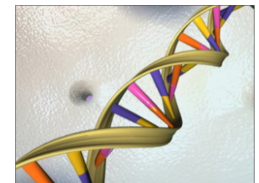
Systems Biology



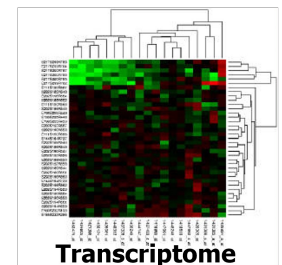
Population Research



Proteome/metabolome



Genome

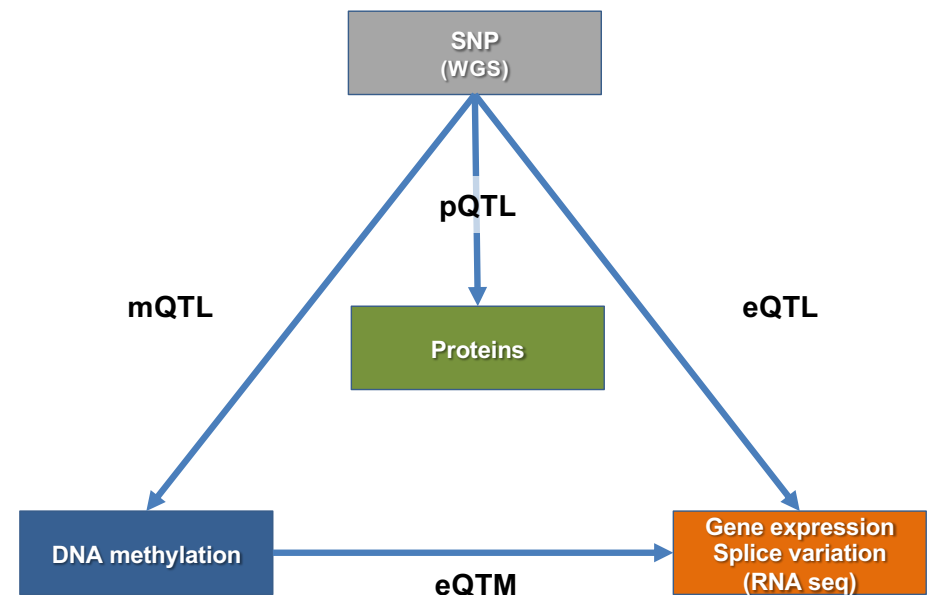


Transcriptome

Integrative Analyses using WGS, RNA Seq, DNA Methylation, and Proteomics

Integrative Trans-Omics

- To integrate genetic variation from WGS with gene expression profiling from RNA-seq, and with DNA methylation and proteomic profiling
- To characterize the genetic architecture of the human transcriptome, methylome, and proteome
- Apply these resources to understand molecular contributions to health and disease



WGS and RNA-seq Based eQTL, mQTL, and eQTM Studies

eQTL paper

Whole genome DNA and RNA sequencing of whole blood elucidates the genetic architecture of gene expression underlying a wide range of diseases

Chunyu Liu^{1,2,4,6,10}, Roby Joehanes^{2,3,11}, Jiantao Ma⁴, Yuxuan Wang⁴, Xianbang Sun⁴, Amena Keshawar², Meera Sooda^{2,3}, Tianxiao Huan⁴, Shih-Jen Hwang⁴, Helena Bui⁴, Brandon Tejada^{2,3}, Peter J. Munson^{2,3}, Cumhur Y. Demirkale⁴, Gina M. Peloso⁴, Michael Feolo⁴, Nancy L. Heard-Costa^{2,4}, Achilleas N. Pitsillides^{4,5,6}, Mike Feolo⁹, Nataliya Sharopova⁴, Ramachandran S. Vasan^{4,6,8}, Daniel Levy^{2,3,10}

To create a scientific resource of expression quantitative trait loci (eQTL), we conducted a genome-wide association study (GWAS) using genotypes obtained from whole genome sequencing (WGS) of DNA and gene expression levels from RNA sequencing (RNA-seq) of whole blood in 2622 participants in Framingham Heart Study. We identified 6,778,286 *cis*-eQTL variant-gene transcript (eGene) pairs at $p < 5 \times 10^{-4}$ (2,855,111 unique *cis*-eQTL variants and 15,982 unique eGenes) and 1,469,754 *trans*-eQTL variant-eGene pairs at $p < 1 \times 10^{-5}$ (526,056 unique *trans*-eQTL variants and 7233 unique eGenes). In addition, 442,379 *cis*-eQTL variants were associated with expression of 1518 long non-protein coding RNAs (lncRNAs). Gene Ontology (GO) analyses revealed that the top GO terms for *cis*-eGenes are enriched for immune functions (FDR < 0.05). The *cis*-eQTL variants are enriched for SNPs reported to be associated with 815 traits in prior GWAS, including cardiovascular disease risk factors. As proof of concept, we used this eQTL resource in conjunction with genetic variants from public GWAS databases in causal inference testing (e.g., COVID-19 severity). After Bonferroni correction, Mendelian randomization analyses identified putative causal associations of 60 eGenes with systolic blood pressure, 13 genes with coronary artery disease, and seven genes with COVID-19 severity. This study created a comprehensive eQTL resource via BioData Catalyst that will be made available to the scientific community. This will advance understanding of the genetic architecture of gene expression underlying a wide range of diseases.

mQTL paper

Elucidating the genetic architecture of DNA methylation to identify promising molecular mechanisms of disease

Jiantao Ma^{1,11,12,13}, Roby Joehanes^{2,3,11}, Chunyu Liu^{4,5,6}, Amena Keshawar^{2,3}, Shih-Jen Hwang^{2,3}, Helena Bui^{2,3}, Brandon Tejada^{2,3}, Meera Sooda^{2,3}, Peter J. Munson^{2,3}, Cumhur Y. Demirkale⁴, Paul Courchesne^{2,3}, Nancy L. Heard-Costa^{4,5,6}, Achilleas N. Pitsillides^{4,5,6}, Mike Feolo⁹, Nataliya Sharopova⁴, Ramachandran S. Vasan^{4,6,8}, Tianxiao Huan¹⁰ & Daniel Levy^{2,3,10}

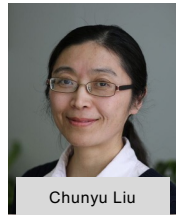
DNA methylation commonly occurs at cytosine-phosphate-guanine sites (CpGs) that can serve as biomarkers for many diseases. We analyzed whole genome sequencing data to identify DNA methylation quantitative trait loci (mQTLs) in 4126 Framingham Heart Study participants. Our mQTL mapping identified 94,362,817 *cis*-mQTL variant-CpG pairs (for 210,156 unique autosomal CpGs) at $P < 1 \times 10^{-7}$ and 33,572,145 *trans*-mQTL variant-CpG pairs (for 213,606 unique autosomal CpGs) at $P < 1 \times 10^{-14}$. Using *cis*-mQTL variants for 1258 CpGs associated with seven cardiovascular disease (CVD) risk factors, we found 104 unique CpGs that colocalized with at least one CVD trait. For example, cg11554650 (PPP1R1B) colocalized with type 2 diabetes, and was driven by a single nucleotide polymorphism (rs25163396). We performed Mendelian randomization (MR) analysis and demonstrated 58 putatively causal relations of CVD risk factor-associated CpGs to one or more risk factors (e.g., cg05337441 [APOB] with LDL; MR $P = 1.2 \times 10^{-99}$, and 17 causal associations with coronary artery disease (e.g., cg08129017 [SREBF1] with coronary artery disease, MR $P = 5 \times 10^{-13}$). We also showed that three CpGs, e.g., cg14893161 (PM20D1), are putatively causally associated with COVID-19 severity. To assist in future analyses of the role of DNA methylation in disease pathogenesis, we have posted a comprehensive summary data set in the National Heart, Lung, and Blood Institute's BioData Catalyst.

eQTM paper

Expression quantitative trait methylation analysis elucidates gene regulatory effects of DNA methylation: the Framingham Heart Study

Amena Keshawar^{1,2}, Helena Bui^{1,2}, Roby Joehanes^{1,2}, Jiantao Ma^{1,3}, Chunyu Liu^{1,4}, Tianxiao Huan^{1,5}, Shih-Jen Hwang^{1,2}, Brandon Tejada^{1,2}, Meera Sooda^{1,2}, Paul Courchesne^{1,2}, Peter J. Munson^{1,2}, Cumhur Y. Demirkale⁴, Chen Yao¹, Nancy L. Heard-Costa^{1,7}, Achilleas N. Pitsillides^{1,4}, Honghuang Lin^{1,8}, Ching-Ti Liu^{1,4}, Yuxuan Wang^{1,4}, Gina M. Peloso^{1,4}, Jessica Lundin⁹, Jeffrey Haessler⁹, Zhaohui Du⁹, Michael Cho^{10,11}, Craig P. Hersh^{10,11}, Peter Castaldi^{10,12}, Laura M. Raffield¹³, Jia Wen¹³, Yun Li^{13,14}, Alexander P. Reiner^{15,9}, Mike Feolo¹⁶, Nataliya Sharopova¹⁶, Ramachandran S. Vasan^{1,7}, Dawn L. DeMeo^{10,11}, April P. Carson¹⁸, Charles Kooperberg⁹ & Daniel Levy^{1,2,10}

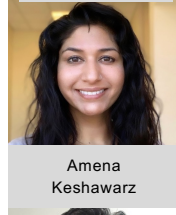
Expression quantitative trait methylation (eQTM) analysis identifies DNA CpG sites at which methylation is associated with gene expression. The present study describes an eQTM resource of CpG-transcript pairs derived from whole blood DNA methylation and RNA sequencing gene expression data in 2115 Framingham Heart Study participants. We identified 70,047 significant *cis* CpG-transcript pairs at $p < 1 \times 10^{-7}$ where the top most significant eGenes (i.e., gene transcripts associated with a CpG) were enriched in biological pathways related to cell signaling, and for 1208 clinical traits (enrichment false discovery rate [FDR] ≤ 0.05). We also identified 246,667 significant *trans* CpG-transcript pairs at $p < 1 \times 10^{-14}$ where the top most significant eGenes were enriched in biological pathways related to activation of the immune response, and for 1191 clinical traits (enrichment FDR ≤ 0.05). Independent and external replication of the top 1000 significant *cis* and *trans* CpG-transcript pairs was completed in the Women's Health Initiative and Jackson Heart Study cohorts. Using significant *cis* CpG-transcript pairs, we identified significant mediation of the association between CpG sites and cardiometabolic traits through gene expression and identified shared genetic regulation between CpGs and transcripts.



Chunyu Liu



Jiantao Ma



Amena Keshawar



Roby Joehanes

Whole Genome Sequencing and RNA Sequencing to Characterize Genetic Architecture of plice Variation

nature communications



Article

<https://doi.org/10.1038/s41467-025-64336-8>

Integrating whole genome and transcriptome sequencing to characterize the genetic architecture of isoform variation

Received: 26 November 2024

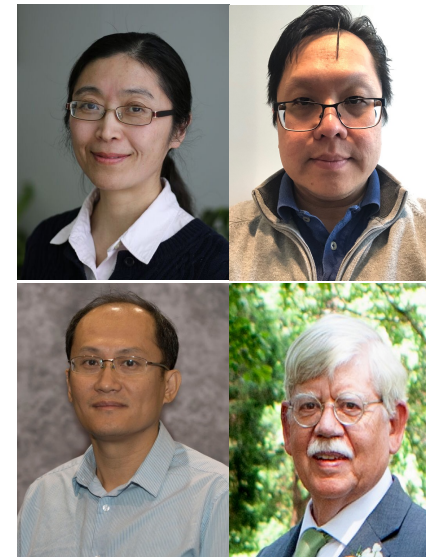
Accepted: 15 September 2025

Published online: 22 November 2025

Check for updates

Chunyu Liu^{1,2,30} , Roby Joehanes^{3,20} , Jiantao Ma^{4,20}, Jiuyong Xie⁵, Jian Yang⁶, Mengyao Wang¹, Tianxiao Huan³, Shih-Jen Hwang³, Jia Wen⁶, Quan Sun^{7,8,9}, Cumhur Y. Demirkale¹⁰, Nancy L. Heard-Costa^{2,11}, Peter Orchard¹², April P. Carson¹³, Jeffrey W. Haessler¹⁴, Laura M. Raffield⁶, Alex P. Reiner^{14,15}, Nora Franceschini^{6,16}, Paul L. Auer¹⁷, Charles Kooperberg¹⁴, Yun Li⁷, George O'Connor^{2,18}, Joanne M. Murabito^{2,19}, Peter Munson³ & Daniel Levy^{2,3}

We present a whole-blood isoform ratio QTL (irQTL) resource by analyzing genome-wide isoform-to-gene expression ratios using sequencing data. In Framingham Heart Study (FHS, $n = 2622$) discovery, we identify over 11 million *cis*-irQTLs (minor allele frequency [MAF] ≥ 0.01 , ± 1 Mb of 10,883 isoform transcripts, $P < 5 \times 10^{-8}$) across 4,971 genes. Among 11,425 sentinel *cis*-irQTLs, 72% replicate ($P < 1 \times 10^{-4}$) in the Women's Health Initiative (WHI; $n = 2005$). Notably, 20% of *cis*-irQTLs have no significant association with overall gene expression, indicating isoform-specific regulation. These variants are enriched at splice donor/acceptor sites and genome-wide association study loci ($P < 1 \times 10^{-10}$). We also identify 1870 sentinel *trans*-irQTLs (MAF ≥ 0.01 , $P < 1.5 \times 10^{-13}$) for 1,084 isoforms across 590 genes, and 2327 rare *cis*-irQTLs ($0.003 < \text{MAF} < 0.01$) for 2467 isoforms of 1428 genes in FHS, with external replication rates of 61% and 41% in WHI, respectively. We highlight rs12898397 in *ULK3*, which alters splice site usage and reduces expression of a full-length isoform. Mendelian randomization supports a causal role between this isoform shift and reduced diastolic blood pressure. These findings highlight the power of irQTL mapping to uncover transcript-specific regulatory mechanisms underlying complex traits.



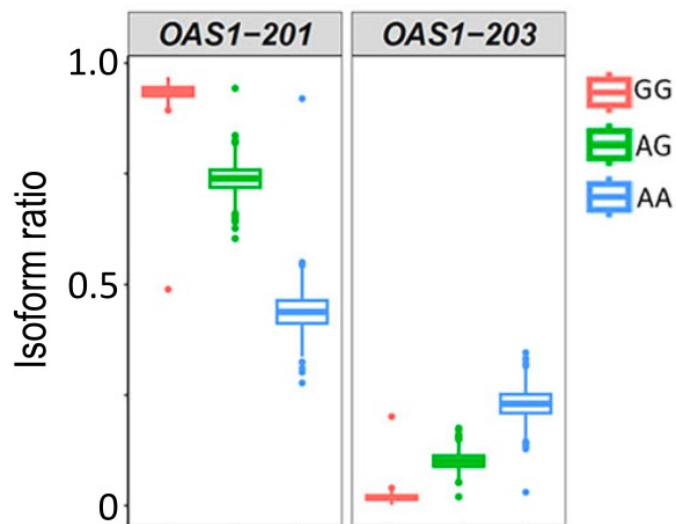
BOSTON
UNIVERSITY

Nature Communications
2025

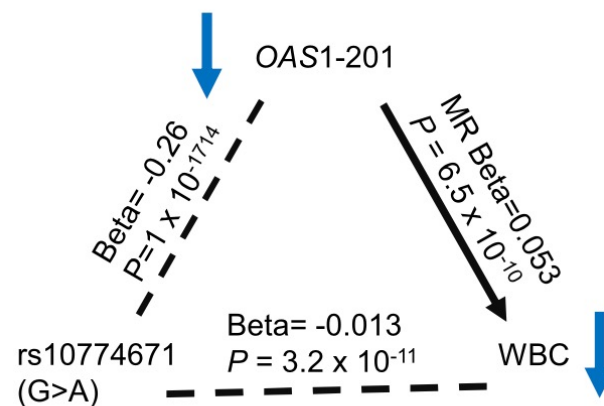
National Heart, Lung,
and Blood Institute

Splicing Variation in *OAS1* Protects Against Severe COVID

A recent study identified a genetic variant, rs10774671 G>A, associated with alternative splicing of *OAS1*, for which the “G” allele leads to a full-length protein that is protective against severe COVID (Huffman, JE, *et al. Nat Genet* 54, 125–127. 2022).



rs10774671 G>A genotype explains 95% of inter-individual variation in expression of *OAS1* isoforms 201 and 203



rs10774671 AA genotype suppresses isoform 201 expression, and reduces WBC count

Musculoskeletal Research in the Framingham Study

So Much More than the Bare Bones

Douglas P. Kiel, MD, MPH

Professor of Medicine, Harvard Medical School

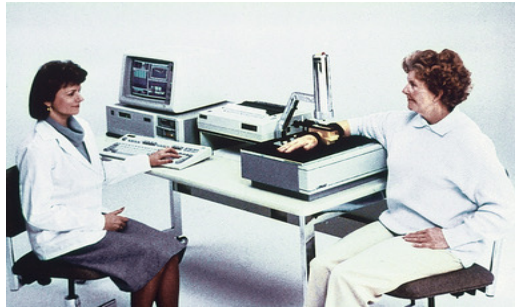
Director Musculoskeletal Research

Marcus Institute for Aging Research

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Measuring Bone Density and Structure Through the Years at FHS



1986-1990
Original Cohort
Exam 20



1990-1994
Original Cohort
Exam 20 and
22, 23



1996-2001
Offspring
Exam 6-7

2005-2008
Offspring
Exam 8



2011-2014
2019-2022
Offspring
Exam 9 & 10

2016-2019
2022-2025
Gen 3
Exam 3 & 4



Nutrition Findings from the Framingham Osteoporosis Study

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 6, 2009
Published online on January 5, 2009; doi: 10.1359/JBMR.090102
© 2009 American Society for Bone and Mineral Research

Protective Effect of Total Carotenoid and Lycopene Intake on the Risk of Hip Fracture: A 17-Year Follow-Up From the Framingham Osteoporosis Study

Shivani Sahni,¹ Marian T. Hannan,² Jeffrey Blumberg,³ L. Adrienne Cupples,⁴ Douglas P. Kiel,² and Katherine L. Tucker¹

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 19, Number 2, 2004
Published online on December 16, 2003; doi: 10.1359/JBMR.0301225
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Dietary Silicon Intake Is Positively Associated With Bone Mineral Density in Men and Premenopausal Women of the Framingham Offspring Cohort

Ravin Jugdaohsingh,^{1,6} Katherine L. Tucker,^{2,6} Ning Qiao,² L. Adrienne Cupples,³ Douglas P. Kiel,⁴ and Jonathan J. Powell^{1,5}

 The American Journal of Clinical Nutrition
Volume 93, Issue 5, May 2011, Pages 1142-1151

Protective effects of fish intake and interactive effects of long-chain polyunsaturated fatty acid intakes on hip bone mineral density in older adults: the Framingham Osteoporosis Study 1, 2, 3

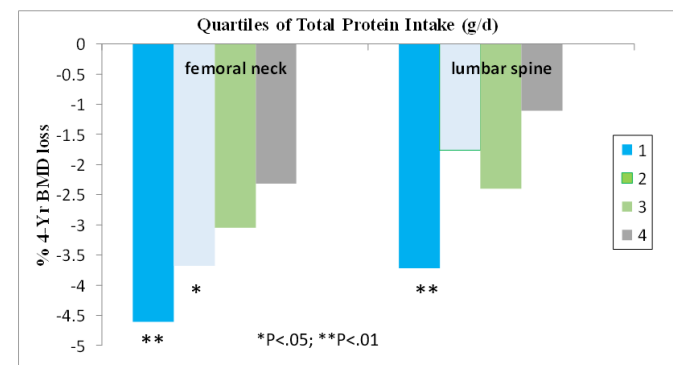
Farina Emily K, Kiel Douglas P, Roubenoff Ronenn, Schaefer Ernst J, Cupples L, Adrienne, Tucker Katherine L

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Homocysteine as a Predictive Factor for Hip Fracture in Older Persons

Robert R. McLean, M.P.H., Paul F. Jacques, D.Sc., Jacob Selhub, Ph.D., Katherine L. Tucker, Ph.D., Elizabeth J. Samelson, Ph.D., Kerry E. Broe, M.P.H., Marian T. Hannan, D.Sc., L. Adrienne Cupples, Ph.D., and Douglas P. Kiel, M.D.



Hannan MT et al JBMR 2012

Boston University Office of Research

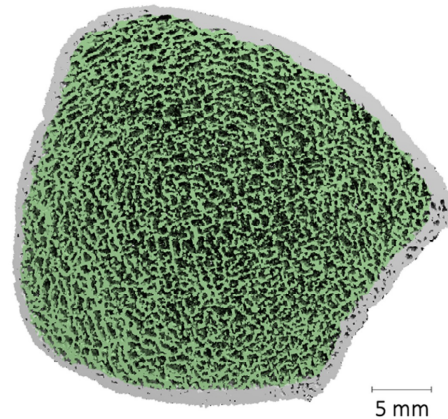
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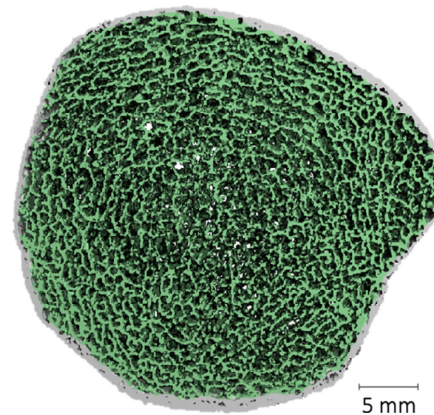
 BOSTON
UNIVERSITY

The Framingham Osteoporosis Study Uses High Resolution Skeletal Imaging

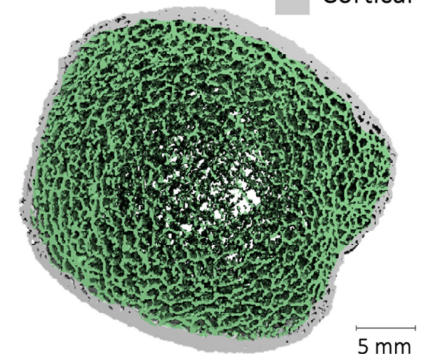
b



Healthy phenotype
(male, 49 years)



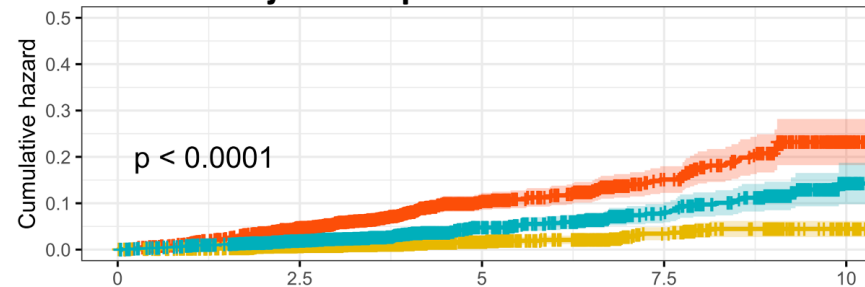
Low density phenotype
(female, 75 years)



Low volume phenotype
(female, 79 years)

Bone structure
■ Trabecular
■ Cortical

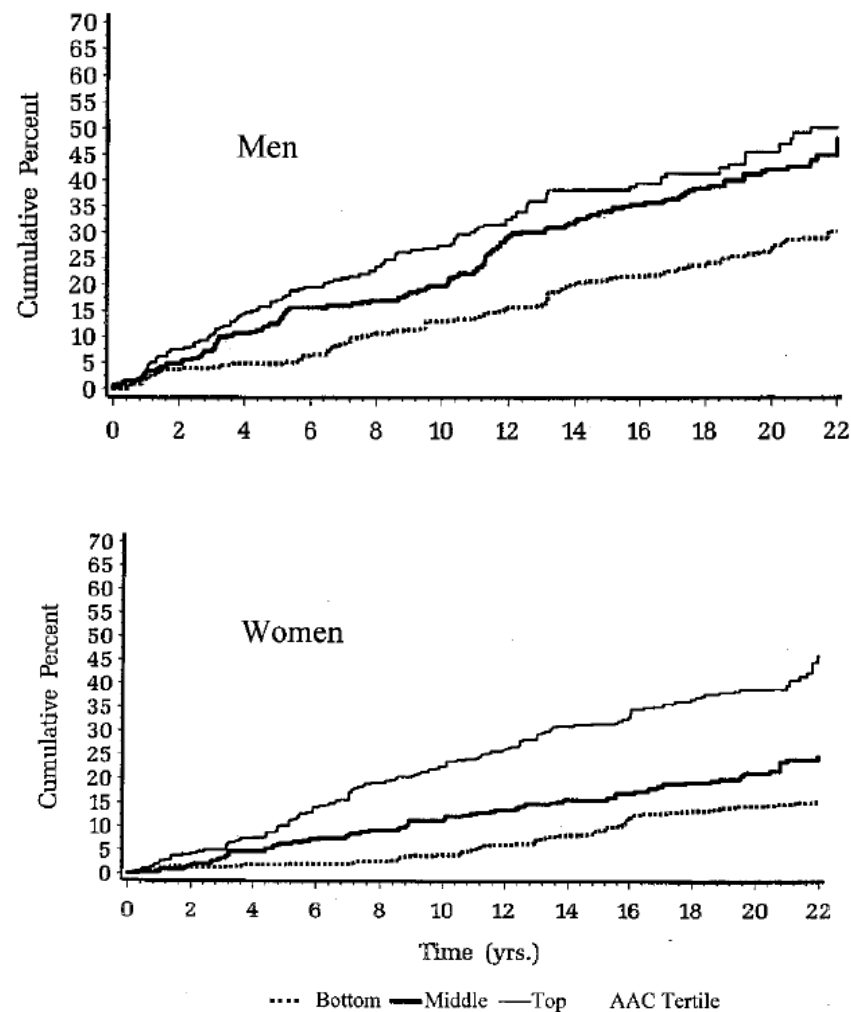
Incident major osteoporotic fracture



Strata	LD	2021	1711	530	285	26
	Healthy	1806	1558	694	424	22
	LV	2046	1813	582	309	53
		0	2.5	5	7.5	10



Using Spine Radiographs to Predict Incident CHD



Bone-Omics

nature
genetics

Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture

LETTER

doi:10.1038/nature141

Whole-genome sequencing identifies *EN1* as a determinant of bone density and fracture

ORIGINAL ARTICLE

Metabolomics Insights into Osteoporosis Through Association With Bone Mineral Density

Xiaoyu Zhang,¹ Hanfei Xu,¹ Gloria HY Li,² Michelle T Long,^{3,4} Ching-Lung Cheung,⁵ 
Ramachandran S Vasan,^{4,6,7} Yi-Hsiang Hsu,^{8,9,10} Douglas P Kiel,^{8,9,10}  and Ching-Ti Liu¹ 

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ARTICLE

DOI: 10.1038/s41467-017-00031-7

OPEN

Large meta-analysis of genome-wide association studies identifies five loci for lean body mass

M. Carola Zillikens et al.[#]

RESEARCH



OPEN ACCESS

Assessment of the genetic and clinical determinants of fracture risk: genome wide association and mendelian randomisation study

Katerina Trajanoska,^{1,2} John A Morris,^{3,4} Ling Oei,^{1,2} Hou-Feng Zheng,^{5,6} David M Evans,^{7,8}
Douglas P Kiel,^{9,10} Claes Ohlsson,¹¹ J Brent Richards,^{3,4} Fernando Rivadeneira,^{1,2} on behalf of
the GEFOS/GENOMOS consortium and the 23andMe research team

 frontiers | Frontiers in Endocrinology

A two-cohort study on the association between the gut microbiota and bone density, microarchitecture, and strength

Paul C. Okoro¹, Eric S. Orwoll², Curtis Huttenhower^{3,4,5,6},
Xochitl Morgan⁴, Thomas M. Kuntz⁴, Lauren J. McIver⁴,
Alyssa B. Dufour^{1,7}, Mary L. Bouxsein^{8,9}, Lisa Langsetmo^{10,11},
Samaneh Farsijani^{12,13}, Deborah M. Kado^{14,15}, Roberto Pacifici¹⁶,
Shivani Sahni^{1,7} and Douglas P. Kiel^{1,7*}

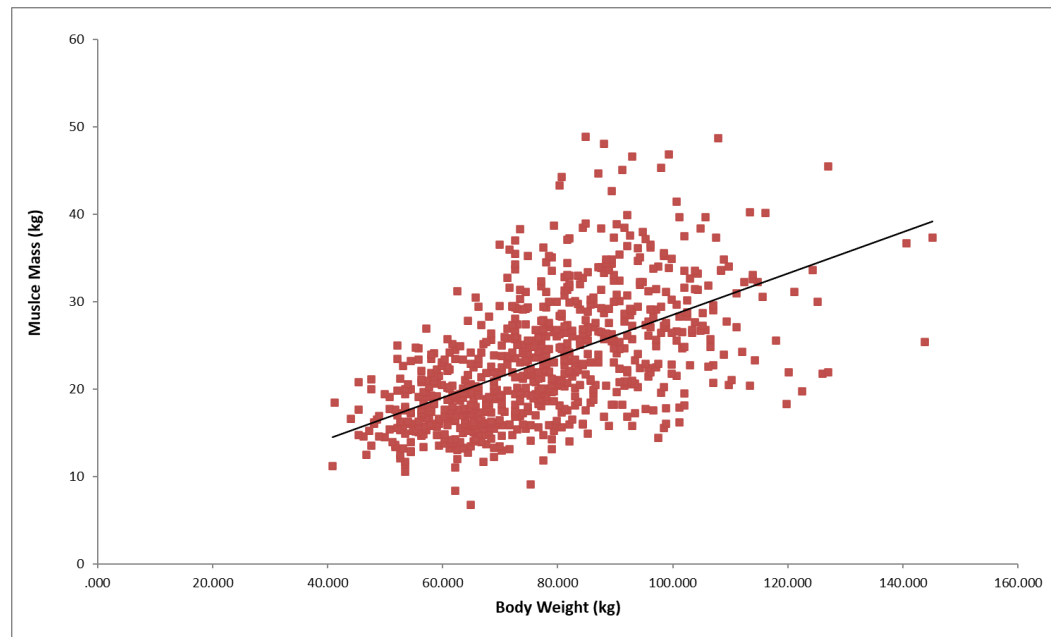
BOSTON
UNIVERSITY

Framingham Muscle Study – Offspring Cohort



D₃-creatine dilution

1. Orally dose with D₃-creatine
2. Reach isotopic steady state (3 days)
creatine → creatinine
D₃-creatine → D₃-creatinine
3. Fasting morning spot urine: measure
D₃-creatinine & creatinine
4. Calculate creatine pool size
5. Calculate total body muscle mass



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Acknowledgments

Collaborators

Marian Hannan	David Felson
Robert McLean	Bess Dawson-Hughes
Lisa Samelson	Eric Orwoll
Mary Bouxsein	Steven Boyd
Shivani Sahni	Ronenn Roubenoff
David Karasik	Tamara Harris
Yi-Hsiang Hsu	Harry Genant
Michelle Yau	Peggy Cawthon
Courtney Millar	William Evans
Sarah Berry	Mahalakshmi Shankaran
Alyssa Dufour	Zsu Zsu Chen
Thomas Trivison	Lisa Langsetmo
Paul Jacques	Curtis Huttenhower
Katherine Tucker	Xochitl Morgan
Bess Dawson-Hughes	
Paul Okoro	

Collaborators (BU and FHS)

Adrienne Cupples
Josee Dupuis
Serkalem Demissie
Ching-Ti Liu
Peter Wilson
Christopher O'Donnell
Kathy Lunetta
Joanne Murabito
Vasan Ramachandran
Daniel Levy

Other Collaborators

GEFOS consortium
CHARGE Musculoskeletal
Working Group
TOPMed Bone Mineralization
Working Group



Boston University Office of Research



Lifelong Endowment for Genomic
and Cellular Discovery

Jessica L. Fetterman, PhD
Deepa M. Gopal, MD, MS

Department of Medicine, Chobanian & Avedisiant School of Medicine

NHLBI R01HL176818

Tissue is the Issue

- ~70% of cardiovascular disease events are attributable to risk factor burden
- FHS & others have been pivotal in identifying cardiovascular disease risk factors but are limited to circulating cells/plasma
- NCI's Cancer Genome Atlas with disease-relevant tissue has led to new discoveries connecting genetic aberrations with cellular dysfunction using multiomics
 - Improved classification & prognostication
 - Identification of novel therapeutic targets
- Existing cardiac biobanks:
 - Lack adequate antecedent phenotyping of risk factors
 - Restricted to cardiovascular diseases in which cardiac procedures are performed
 - Bereft of participant & tissue diversity



Our objective is to build a cardiovascular tissue biobank consisting of whole hearts and major blood vessels collected at the time of death from participants in FHS who provide consent.

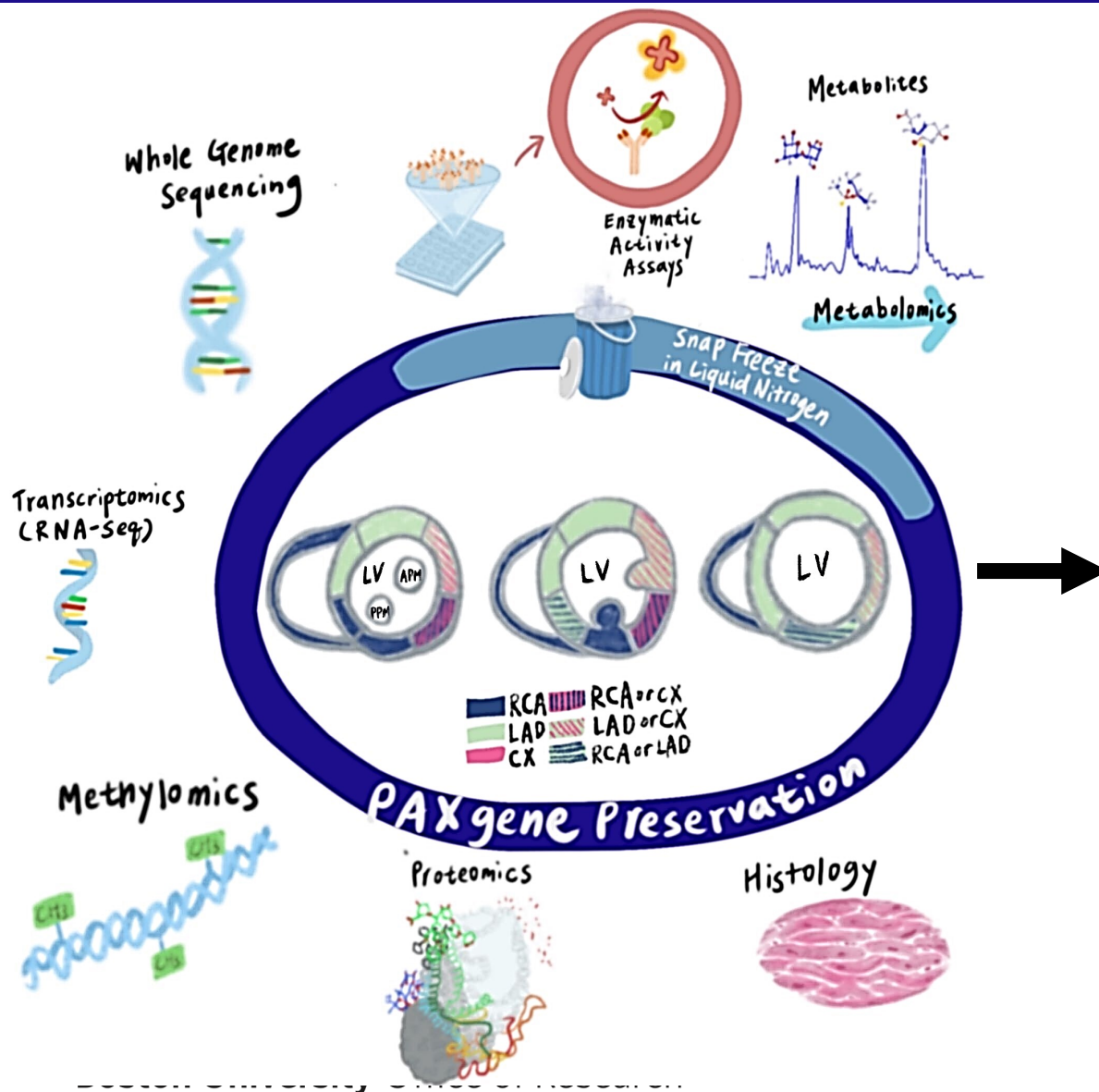


FHS LEGACY Biobank & Atlas: Study Design



“From my wife: "I love your heart. It's the greatest thing about you ♡. Just tell them they'll need an extra large case to put it in."

Transformative Research Afforded by LEGACY



- ✓ Circulating omics
- ✓ Cardiovascular imaging
- ✓ Cardiopulmonary & vascular function data
- ✓ Cardiovascular risk factors
- ✓ Outcomes
- ✓ iPSCs

The Bidirectional Association of Atrial Fibrillation and Cancer in the Framingham Heart Study

Alexander Stanisic

Resident Physician
Internal Medicine, Boston Medical Center

Supported by:

Framingham Heart Study Pathway

NHLBI R01HL092577

BU BIRCWH K12AR085635

75N92025D00012

Thank you to my mentors:

Sarah Preis, ScD, MPH, Emelia Benjamin, MD, ScM, & Celestin Hategeka, MD, PHD

The Bidirectional Association of AF and Cancer

Introduction

- Both AF & Cancer
 - Significant morbidity and mortality
 - Increasing incidence
 - Improved treatment and survival

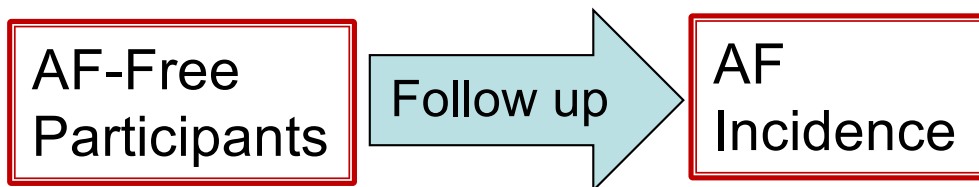
Hypotheses

- Positive bidirectional association between AF & cancer
- Increase in all-cause mortality when both AF & cancer are present

The Bidirectional Association of AF and Cancer

Results – Incidence Analyses

AF Sample



Exposure:	HR(95%)	P-value
<u>Cancer Status:</u>		
- Prevalent	0.95 (0.81,1.12)	0.52
- Interim	1.66 (1.37,2.00)	<0.001
- No cancer	1.00 (referent)	--

Cancer Sample



Exposure:	HR(95%)	P-value
<u>AF Status:</u>		
- Prevalent	0.89 (0.71,1.12)	0.33
- Interim	1.16 (0.93,1.45)	0.19
- No AF	1.00 (referent)	--

- Interim cancer, but not prevalent cancer, was associated with increased AF incidence
- AF was **not** associated with cancer incidence

The Bidirectional Association of AF and Cancer

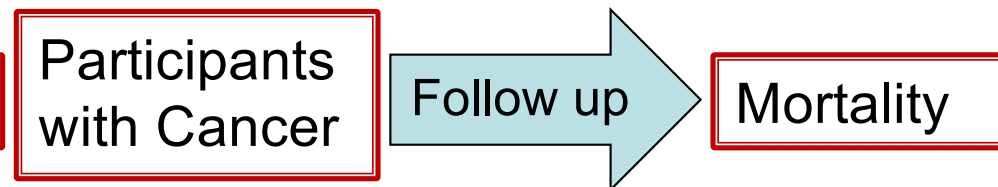
Results – Mortality Analyses

AF Sample



Exposure:	HR(95%)	P-value
<u>Cancer Status:</u>		
- Prevalent	1.70 (1.49,1.95)	<0.001
- Interim	2.24 (1.86,2.70)	<0.001
- No cancer	1.00 (referent)	--

Cancer Sample



Exposure:	HR(95%)	P-value
<u>AF Status:</u>		
- Prevalent	1.53 (1.30,1.80)	<0.001
- Interim	2.41 (2.08, 2.79)	<0.001
- No AF	1.00 (referent)	--

- The presence of AF and cancer was associated with higher mortality than either condition alone

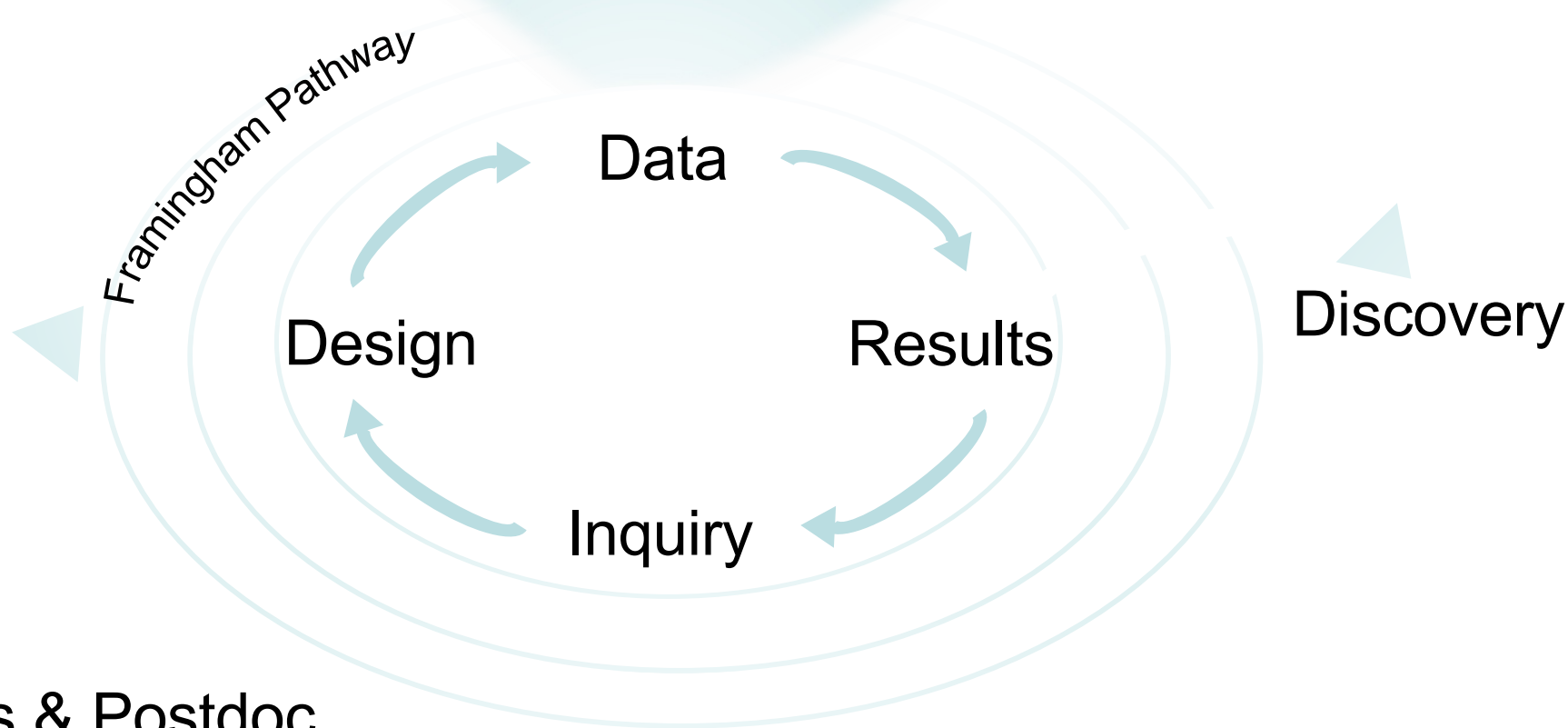


The Bidirectional Association of AF and Cancer

Framingham Heart Study

1948

2026



Trainees & Postdoc

Cardiometabolic Resilience in the Framingham Heart Study

Matthew Naylor, MD, MPH

Associate Professor of Medicine

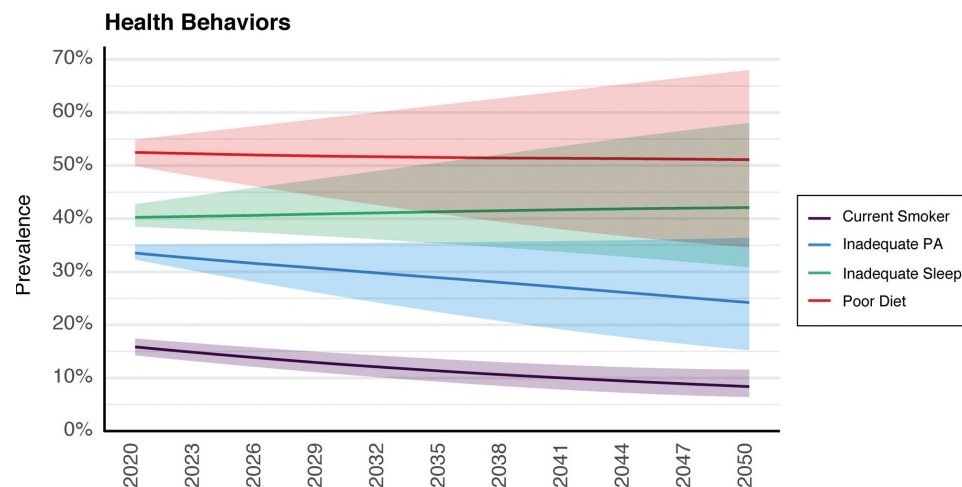
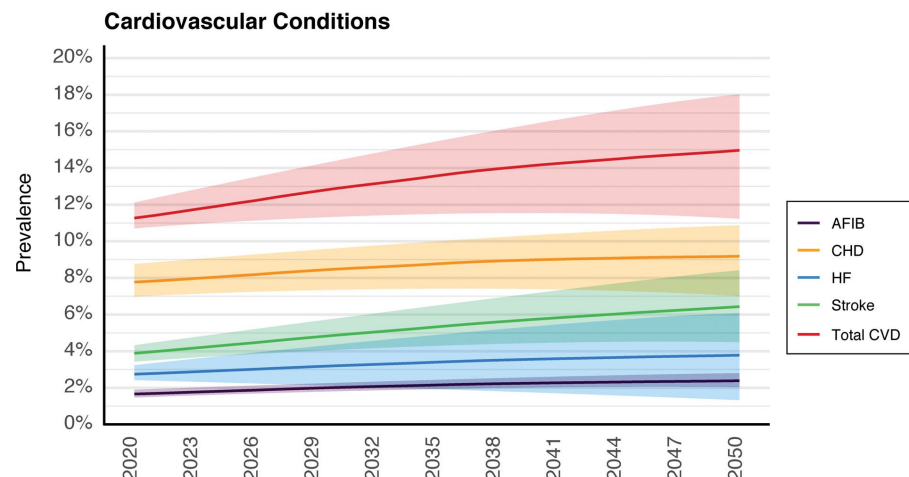
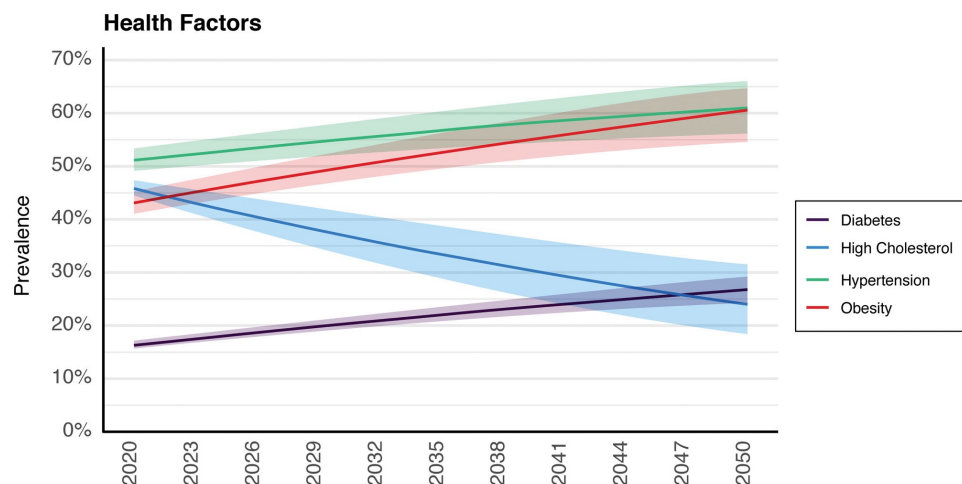
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Heart Failure Cardiologist, Boston Medical Center

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Worsening metabolic health in the US calls for new approaches to disease prevention

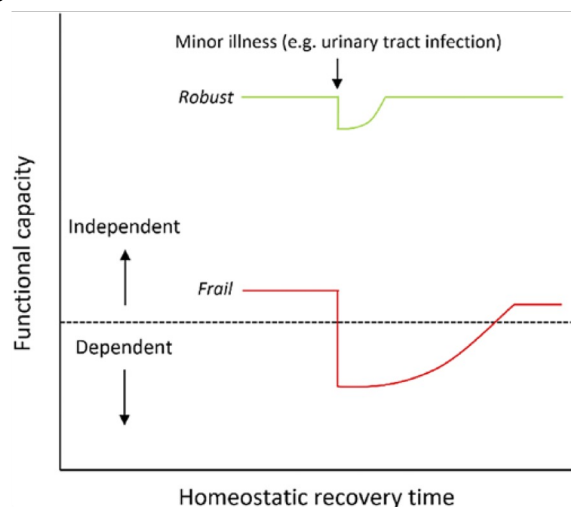
- Rates of CVD mortality have plateaued over the last decade
- Shift in cardiometabolic risk factors toward obesity and diabetes



Emphasis on defining and promoting health

Definitions of cardiometabolic health

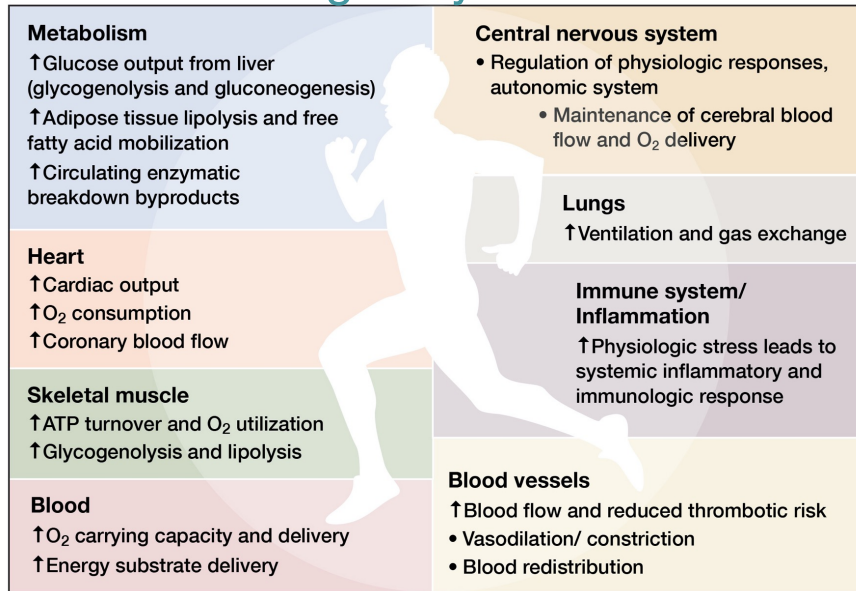
- 1) Health is the presence of healthy behaviors coupled with the absence of diseases or risk factors
- 2) Physiological health is demonstrated by the presence of resilience to stress



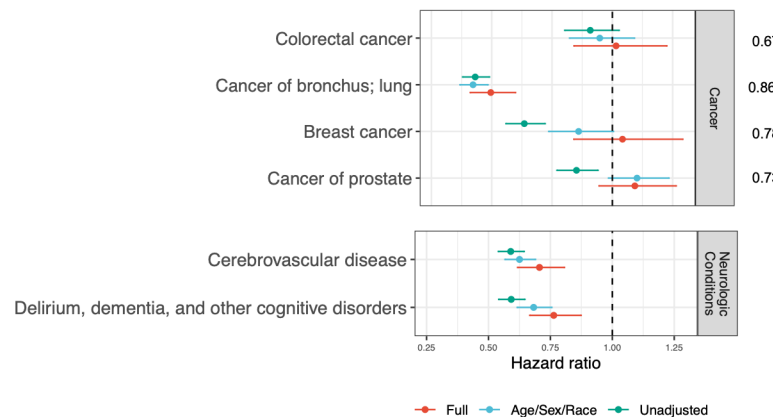
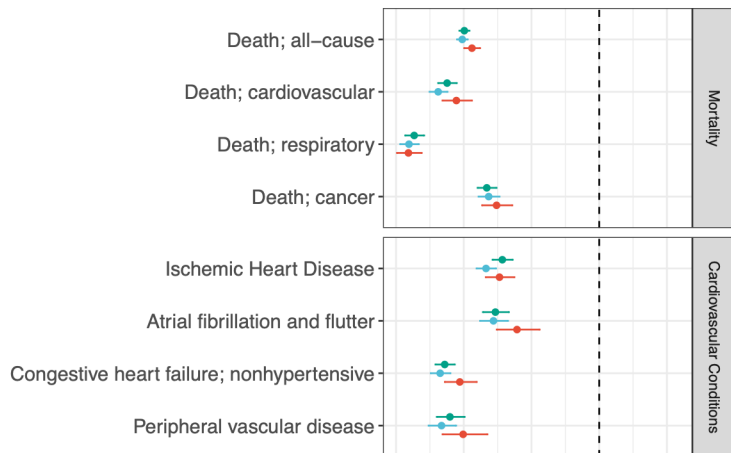
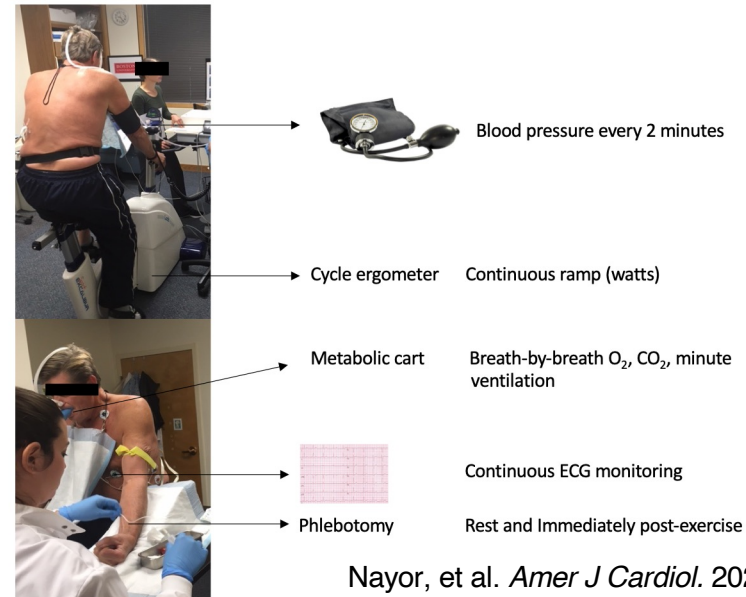
“Ecological resilience [is] the capacity of an ecosystem to absorb disturbances—whether natural or human-made—while maintaining its essential functions...”

Resilience phenotype 1: EXERCISE

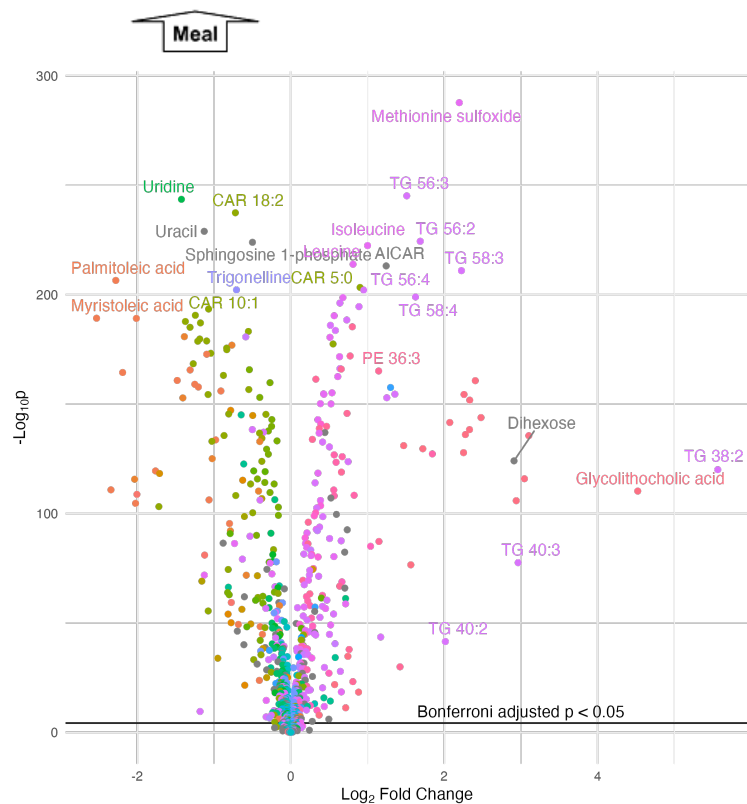
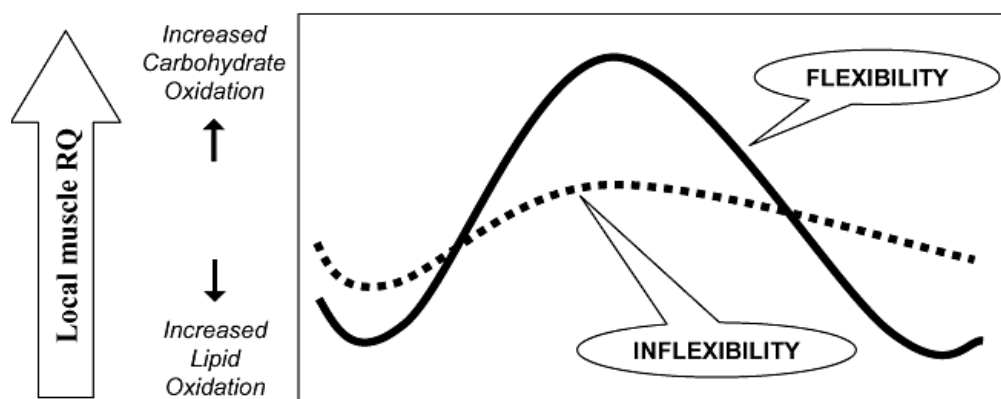
Exercise exerts stress on multiple organ systems



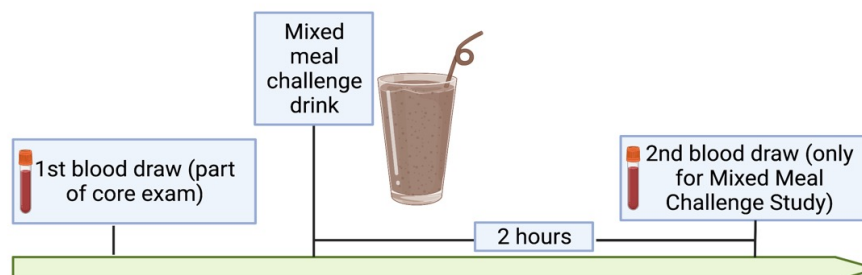
Gold standard cardiopulmonary exercise tests in >3000 FHS participants



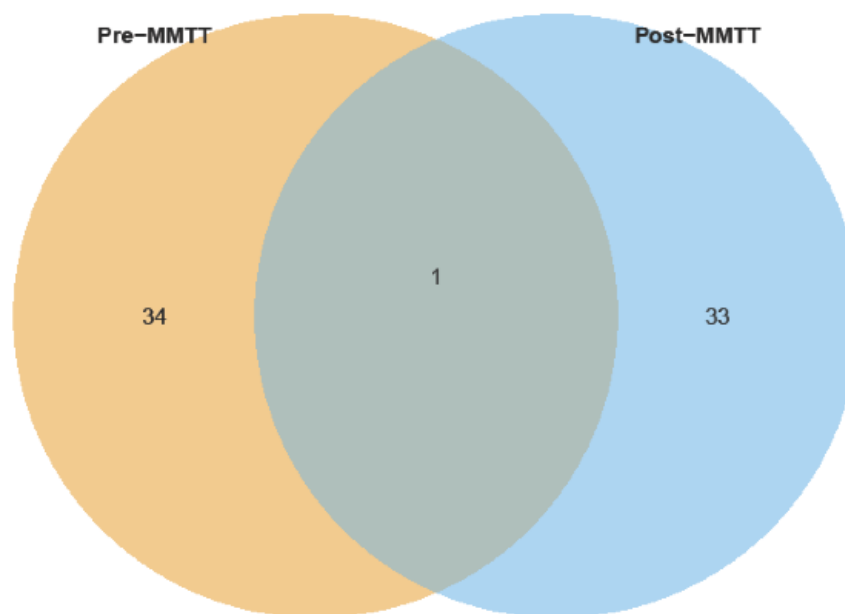
Resilience phenotype 2: NUTRITIONAL STRESS

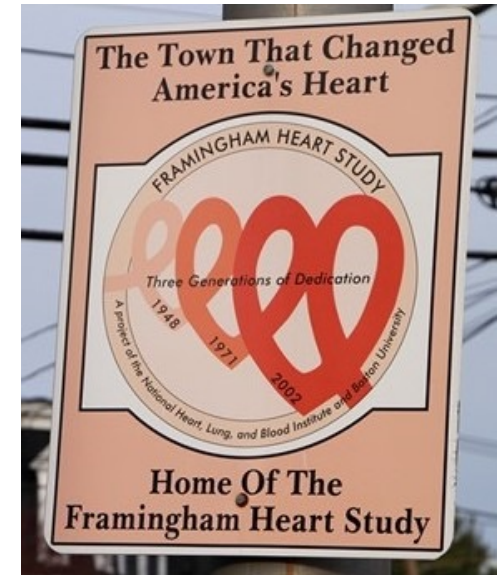


Mixed meal study, N=2400



Muscle Skeletal - Glucose





Vanessa Xanthakis, PhD FAHA

Associate Professor of Medicine and Biostatistics

Section of Preventive Medicine and Epidemiology

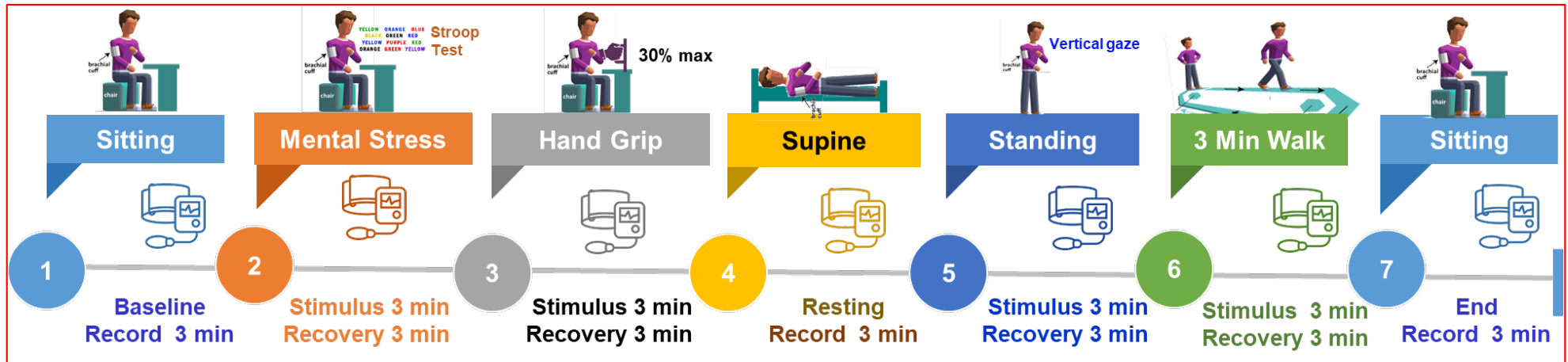
Department of Medicine

Chobanian and Avedisian School of Medicine

Department of Biostatistics, School of Public Health

Cardiovascular Resiliency Evaluation

Responses to activities in a typical day



- SBP, DBP, MAP
- Heart Rate
- Respiratory Rate
- Oxygen saturation
- Accelerometer data (in motion)
- Continuous ECG recording

ECG monitor on chest



Pulse Oximeter



HR Finger Monitor

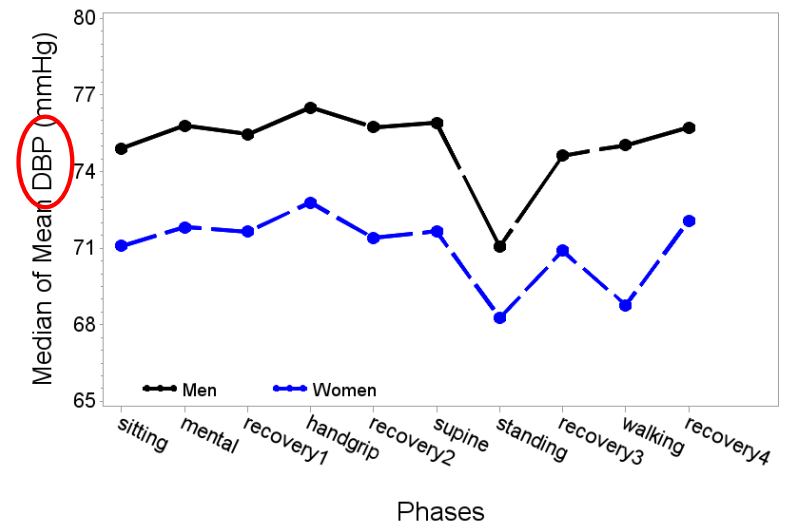
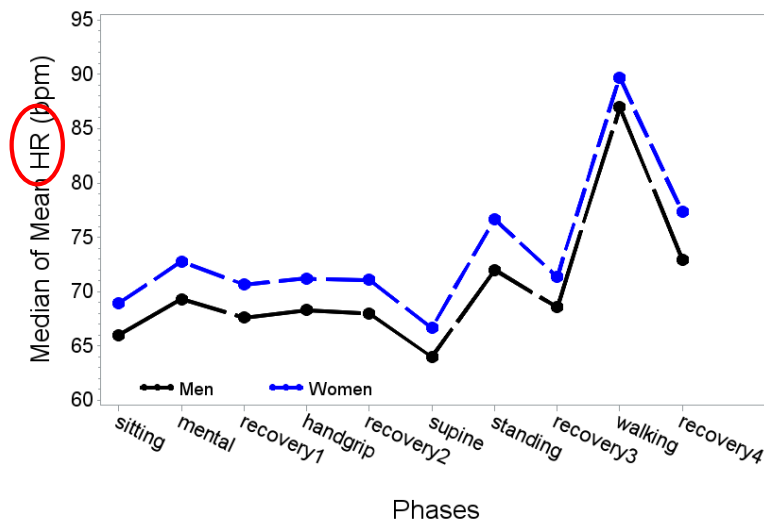
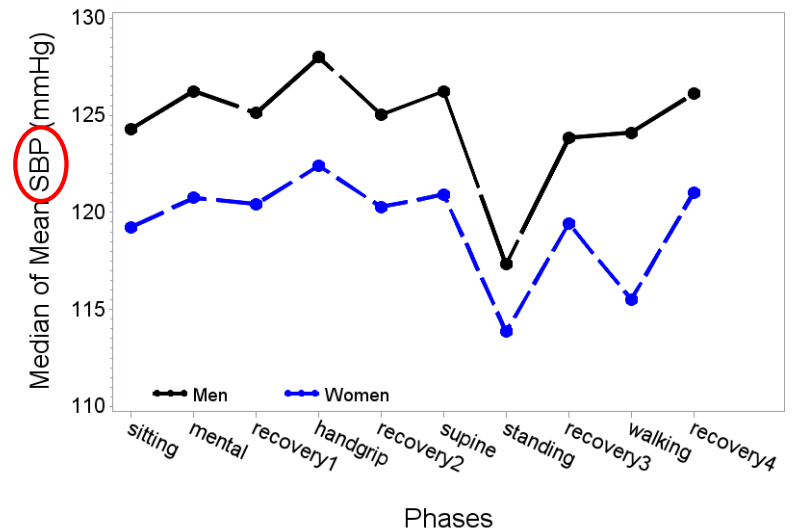


Cardiovascular Resiliency Evaluation

Responses to activities in a typical day

≥ 1 observation per second
>180 observations for each
3-min stressor
~1300 observations/ppt
for each variable

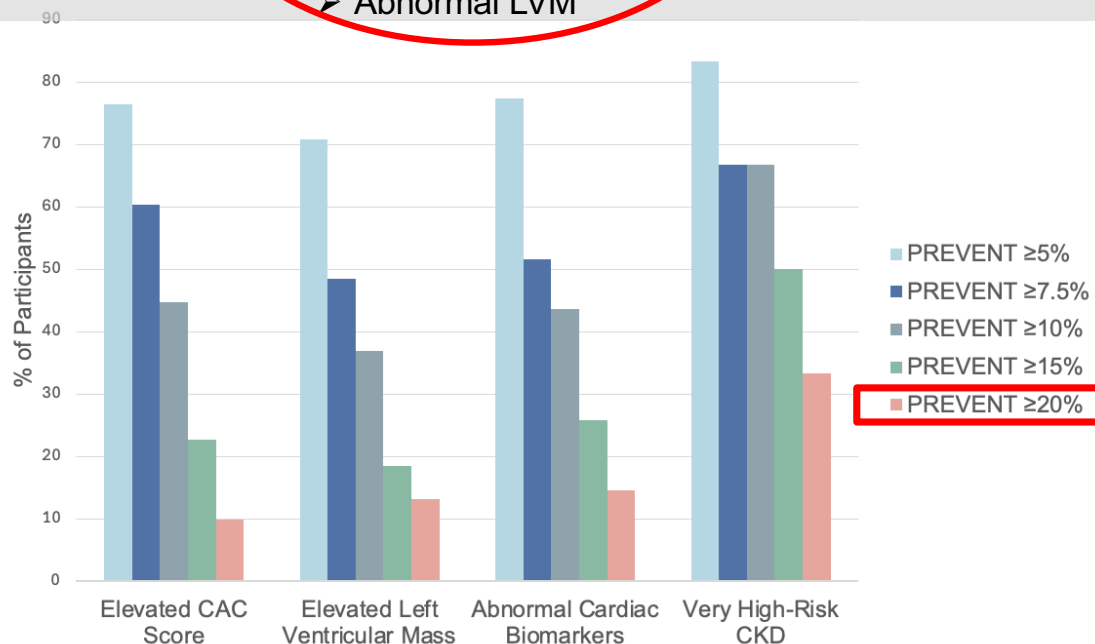
Dynamic Indicators Of
Resilience (DIORs)
mean, SD, Interpercentile range
(P95-P5), and average change



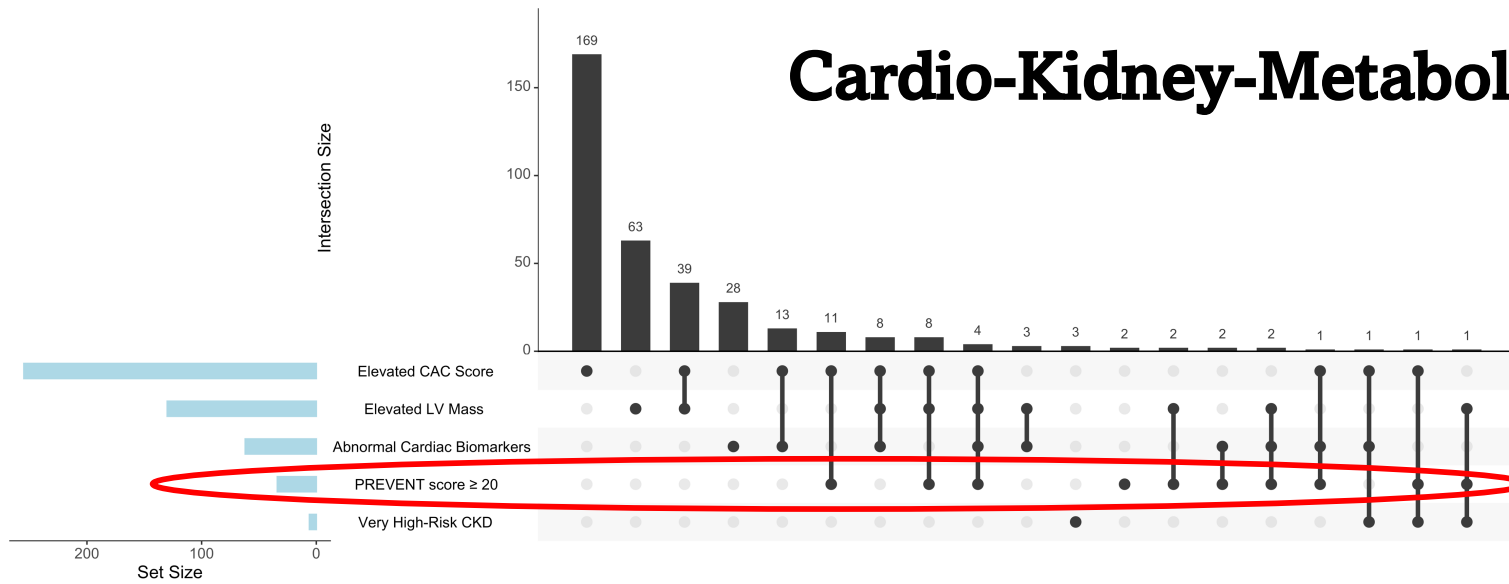
Cardio-Kidney-Metabolic (CKM) Stages

<u>Stage 0</u>	<u>Stage 1</u>	<u>Stage 2</u>	<u>Stage 3</u>	<u>Stage 4</u>
No risk factors	Excess or dysfunctional adipose tissue	Metabolic Risk Factors, mod-high risk CKD	Subclinical ASCVD or subclinical HF	Clinical CVD or CKD
At least one of: ➤ Healthy BMI or ➤ Healthy WC	At least one of: ➤ BMI ≥ 25 kg/m ² ➤ WC ≥ 88 cm/102cm in women/men ➤ HbA1c 5.7-6.4% or FBG 100-124 mg/dL	➤ At least one of: Abnormal triglycerides, BP, HgbA1c or glucose ➤ Metabolic syndrome, ≥ 3 of: Abnormal WC, HDL, TGs, BP, glucose ➤ Moderate-High risk CKD (abnormal GFR, albuminuria)	At least one of: ➤ PREVENT score $\geq 20\%$ (10-yr) ➤ Abnormal CAC ➤ Abnormal cardiac biomarkers (BNP, NT-proBNP, hsTnI) ➤ Very high-risk CKD (GFR, albuminuria) ➤ Abnormal LVM	Must have one of: ➤ CHD, HF, Stroke, PAD, AF ➤ GFR ≤ 29 mL/min/1.73m ²

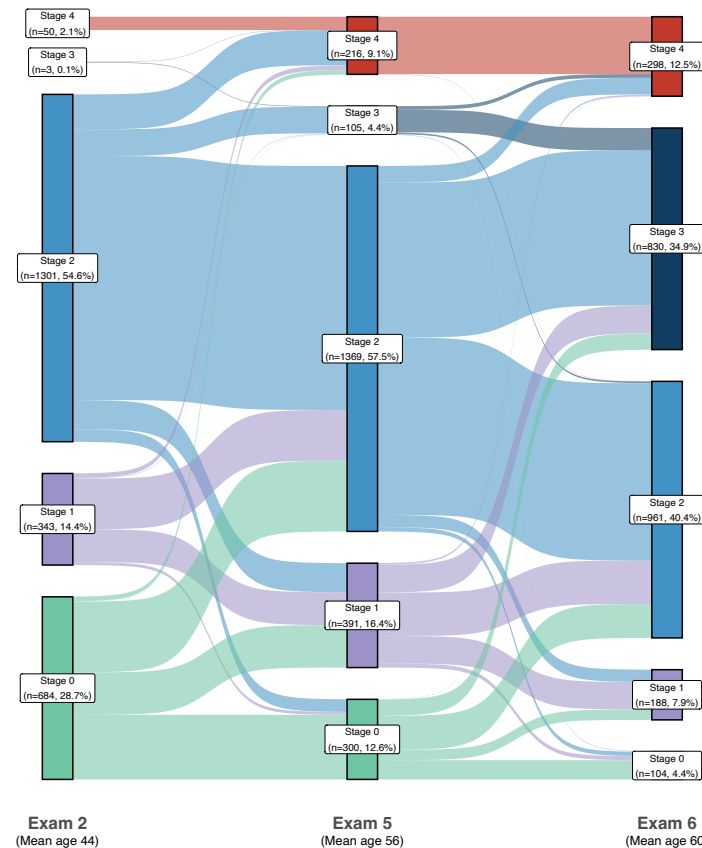
Using only PREVENT $\geq 20\%$ to define Stage 3 CKM, **41%** of sample was misclassified as Stage 0-2.



Cardio-Kidney-Metabolic (CKM) Stages



- lower PREVENT threshold
- or
- enhance screening with CAC, echo, biomarkers



Genetics of chronic obstructive pulmonary disease (COPD)

George O'Connor, MD, MS

Professor of Medicine

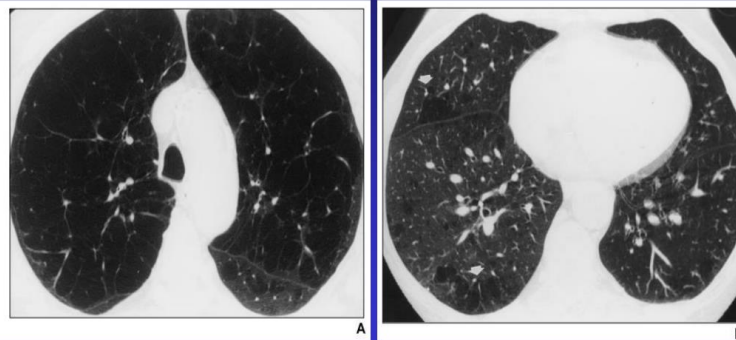
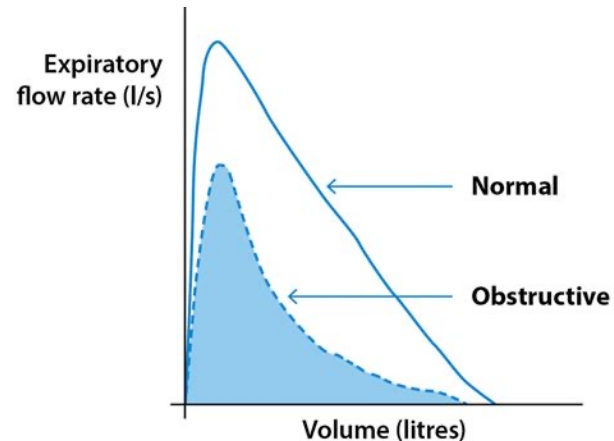
Section of Pulmonary, Allergy, Sleep, and Critical Care Medicine

Pulmonary Center

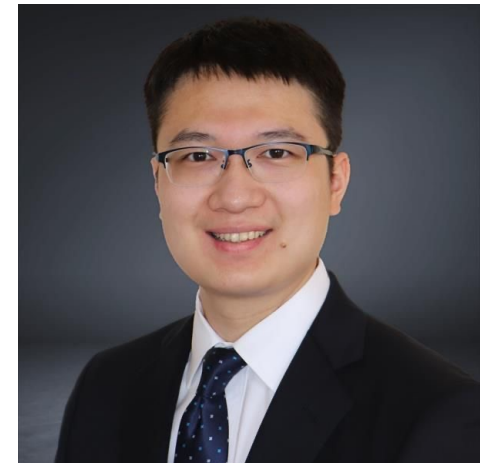
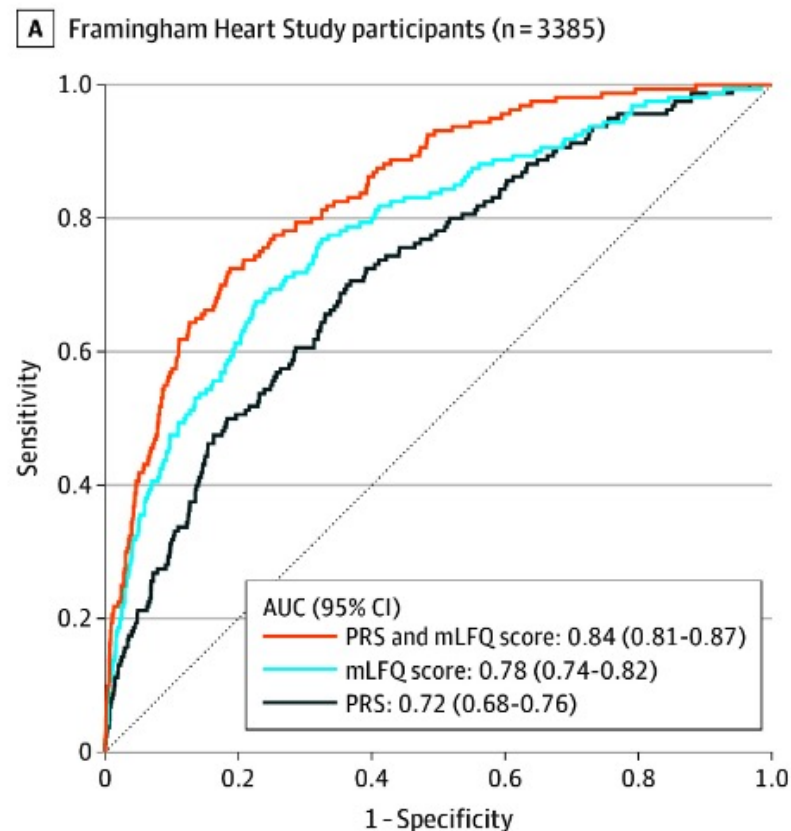
BU Chobanian and Avedisian School of Medicine

Features of COPD

- Global prevalence ~ 8%
- 6th leading cause of death in US
- A leading cause of health care expenditures and disability



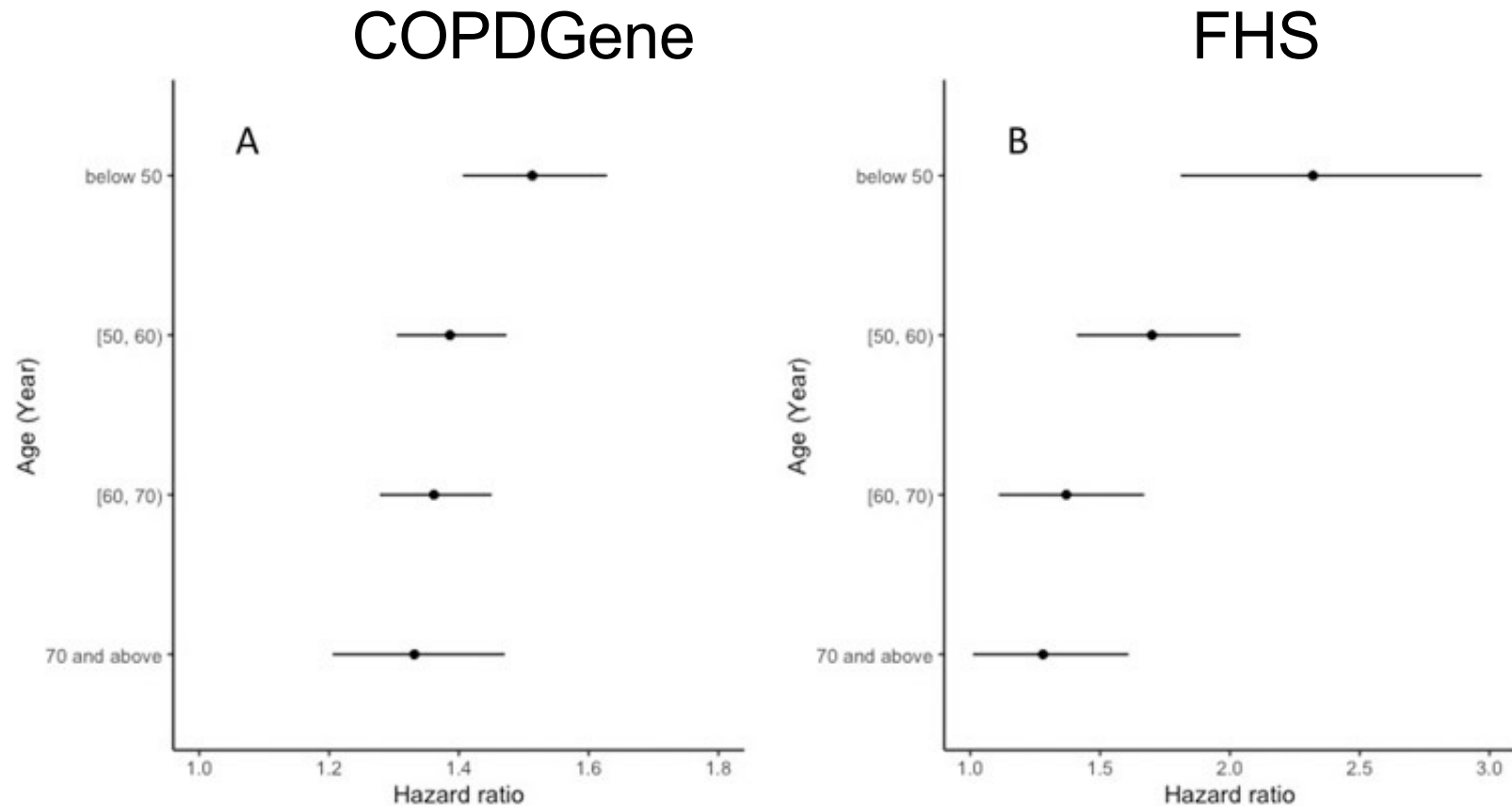
- COPD is a complex genetic trait.
- Screening (not recommended by USPSTF) vs. case-finding



ROC Curve and Area Under the Curve for the PRS, mLFQ Score, and Combined PRS + mLFQ Score in Predicting Moderate to Severe COPD

(Zhang J et al. JAMA. 2025;333:784-792)

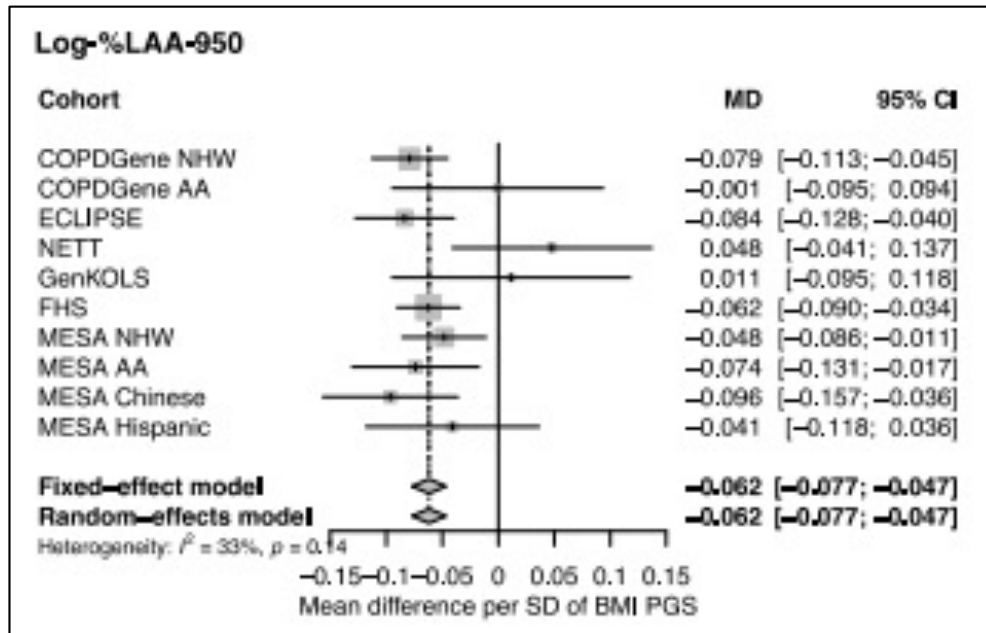
COPD polygenic risk score is associated with age of onset of disease.



Hazard ratios (95% CI) for associated of COPD PRS (per SD) for incident COPD by age interval

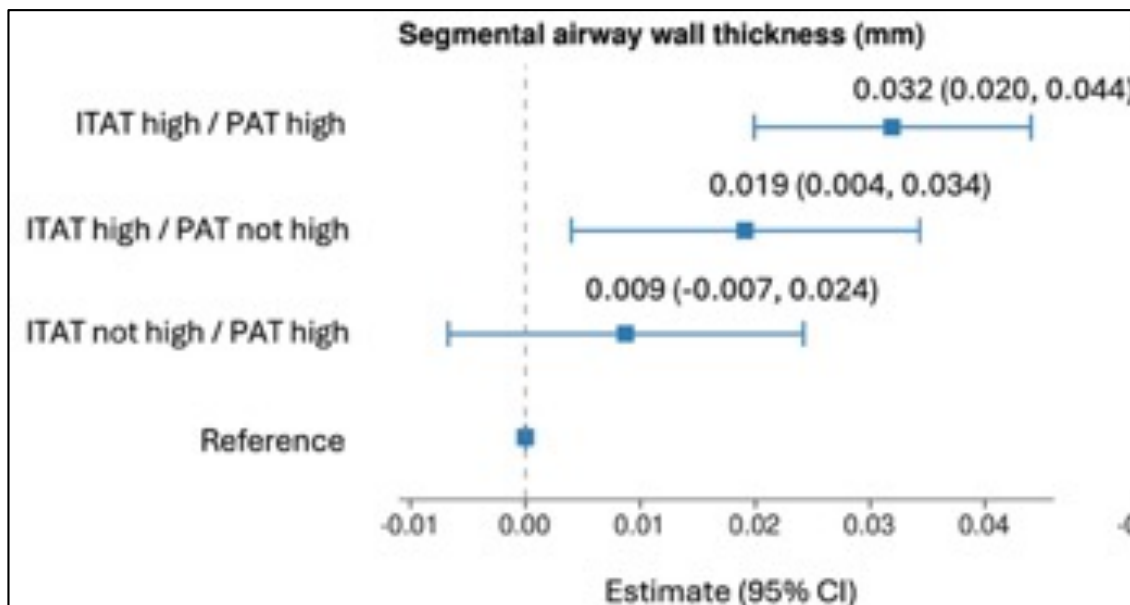
Zhang J et al, Eur Respir J. 2022 Sep 15;60:2101954.

Obesity / adiposity and COPD?



Association of BMI polygenic score with CT emphysema

Zhang J et al., Ann Am Thorac Soc. 2026 Feb 21. Epub ahead of print.



Intrathoracic Adipose Tissue and Airway Phenotypes in FHS

Zhang J et al. (In preparation)

Inflammation and Immune Health in Healthy Aging: Framingham Heart Study

Joanne Murabito, MD ScM

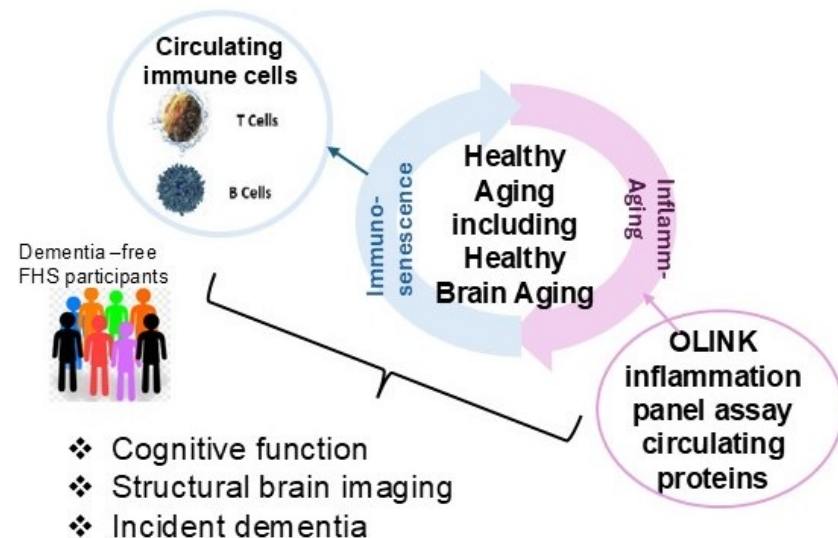
Professor of Medicine

Department of Medicine, Section of General Internal Medicine
BU Chobanian and Avedisian School of Medicine

Hallmarks of aging: biologic mechanisms

- Understanding biologic mechanisms of aging may lead to interventions to slow aging, delay the onset of multiple chronic diseases and extend healthy years of life

Chronic Inflammation: one hallmark of aging

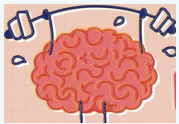


Funding:
NIA R01AG067457
MPIs: Murabito, Lunetta,
Doyle

Circulating inflammatory proteins associate with cognitive function, brain imaging and Alzheimer's Disease

Cognitive function

Higher levels of inflammatory proteins

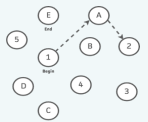


Full sample most proteins associated with lower (worse) executive function (EF)

❖ 12 proteins

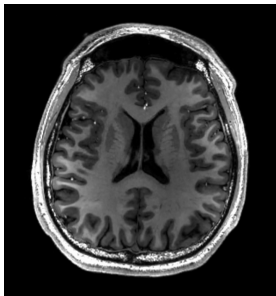
High risk APOE E4 subgroup proteins associated with EF & memory including:

- ❖ 1 protein associated with higher EF
- ❖ 2 proteins associated with higher memory
- ❖ 5 proteins associated with lower EF or memory



Protective inflammatory protein: TWEAK

- ❖ TWEAK involved in wide range of cellular activities and vascular processes including angiogenesis and endothelial cell proliferation
- ❖ Better EF and memory cognitive testing
- ❖ Bigger total cerebral brain volume
- ❖ Lower incidence of Alzheimer's Dementia



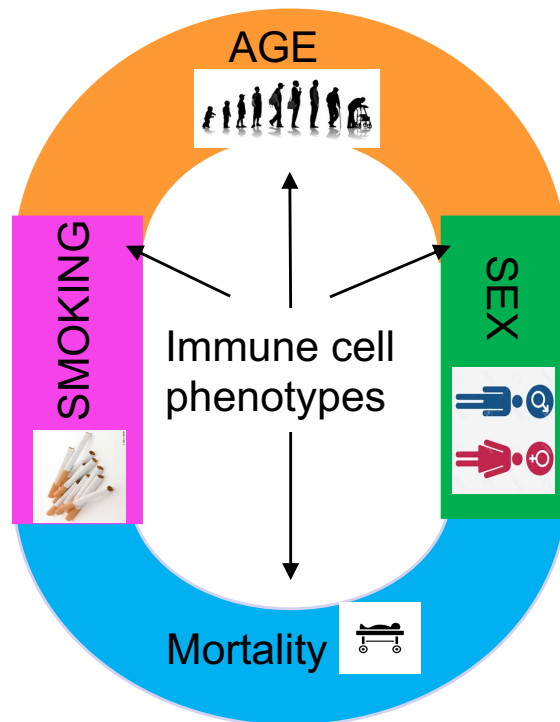
Higher levels:

2 inflammatory proteins → larger total brain volume

7 inflammatory markers → smaller brain volume

Chen J, et al Alz & Dementia 2024; Chen J et al Aging Cell 2023

Circulating immune cells associate with important outcomes



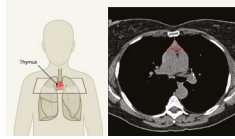
Immune cells associated with brain volumes

- ❖ Multiple immune cell phenotypes (T cell subtypes) associated with higher total gray and frontal gray volumes

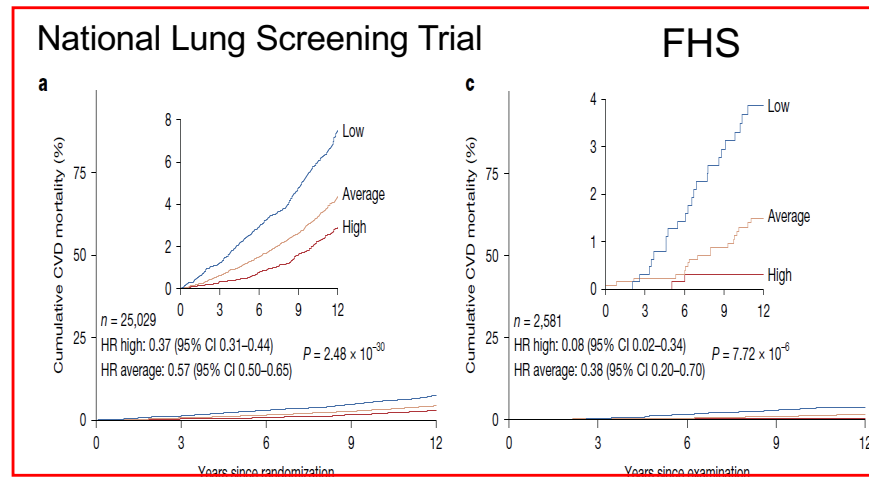
No association between immune cells and cognitive function or incident dementia

Fang Y et al Aging 2023; Ragab AAY et al Immunity and Aging 2024; Cao Y, et al J Geront 2025

Thymic Health associates with longevity and lower disease incidence



Thymus generates T cells
(a type of immune cells)



In FHS, lower thymic health associated with higher levels of risk factors:

- ❖ Metabolic risk factors
- ❖ Smoking
- ❖ Inflammatory proteins

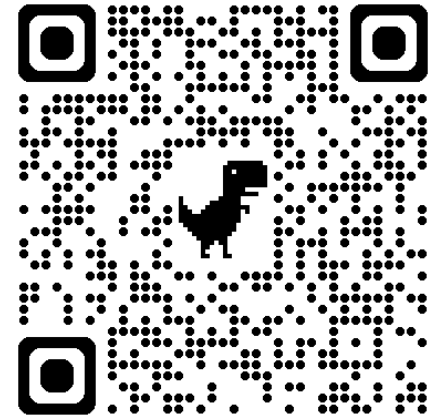
Inflammation and the immune system play a complex but important role in healthy aging

Bernatz S et al Nature 2026



Foundation Funding Opportunities

- Alfred P. Sloan Foundation
- American Federation for Aging Research
- Alzheimer's Association
- Brain & Behavior Research Foundation
- American Parkinson Disease Foundation
- Rita Allen Foundation
- Alzheimer's Drug Discovery Foundation
- Richard and Susan Smith Foundation
- American Heart Association
- Leducq Foundation



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other grant programs is
available on our website.

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Upcoming Events

Research How-to

4/16 Positive Media Presence
Thursday.

4/27 Meet the Funded: Building
Authentic Relationships with Foundations

4/29 Meet the Funder: RRF Foundation

4/29 Find Funding: Updates to BU's
Internal Limited Submissions Process



bu.edu/research/events

Thank you!