OHBM 2024 educational course on normative modeling

Characterizing brain-body relationships using normative modeling

Ye Ella Tian, PhD

NHMRC Research Fellow

Department of Psychiatry

The University of Melbourne

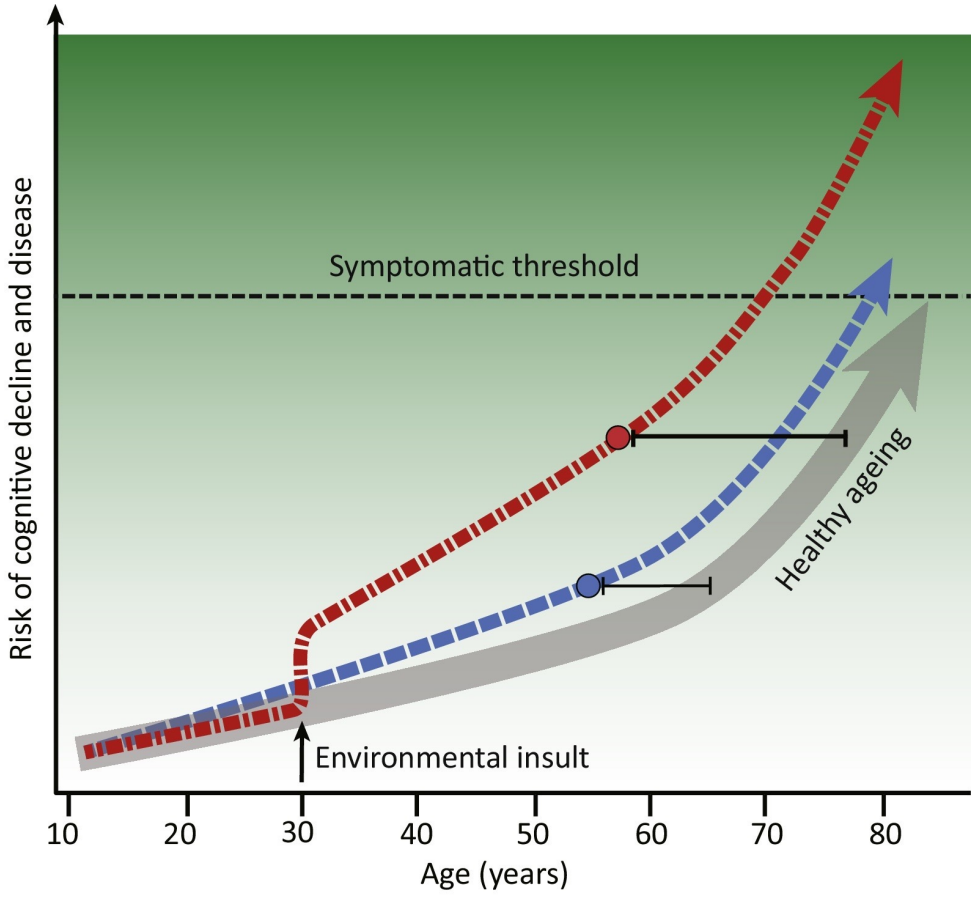
Outline

Part 1: Estimating the biological age of brain and body systems using normative modeling

Part 2: Evaluating brain-body health in mental illness using normative modeling

Part 1: Biological age

Trajectories of biological aging

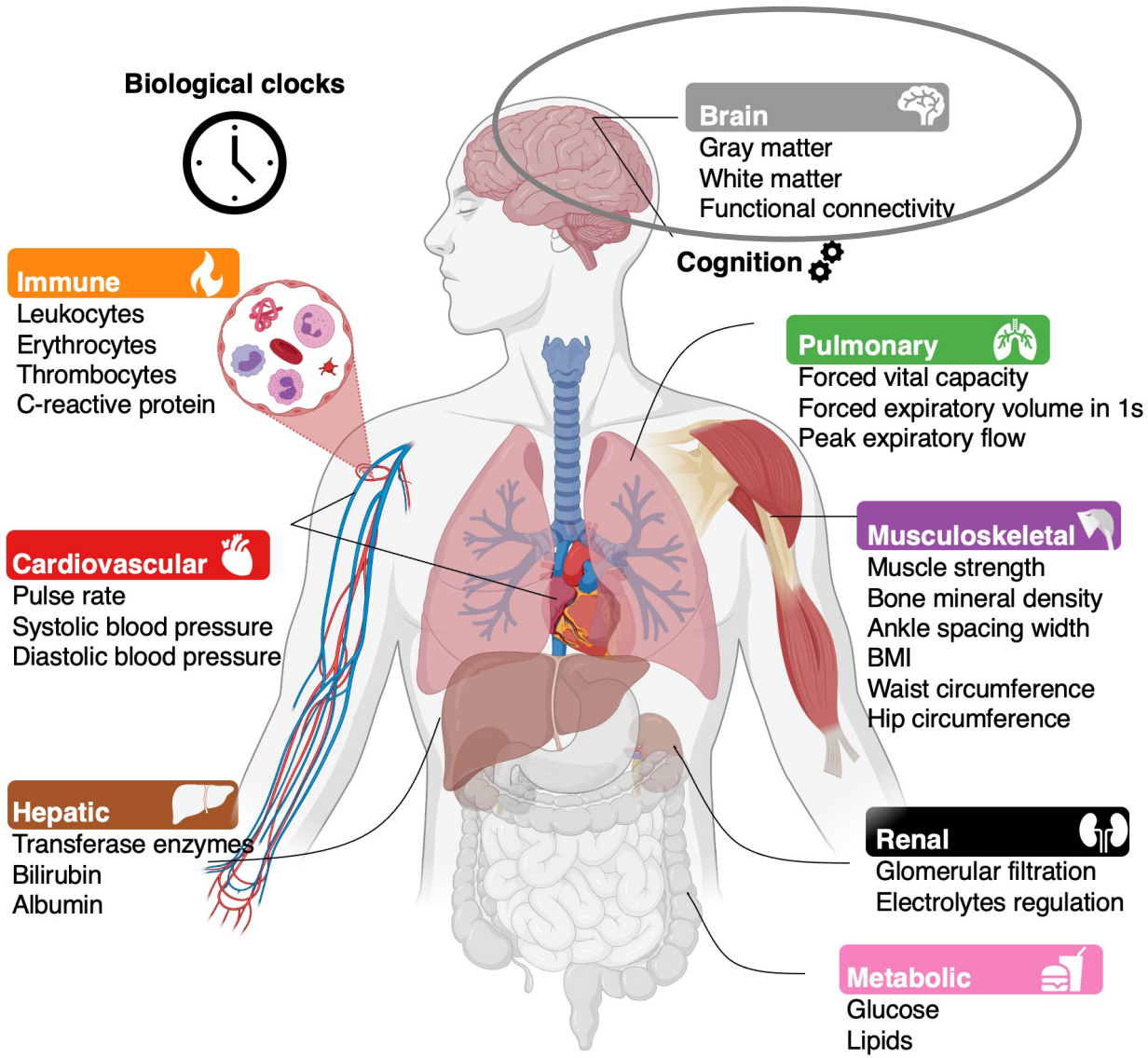


Cole et al., 2017 Trends in neuroscience

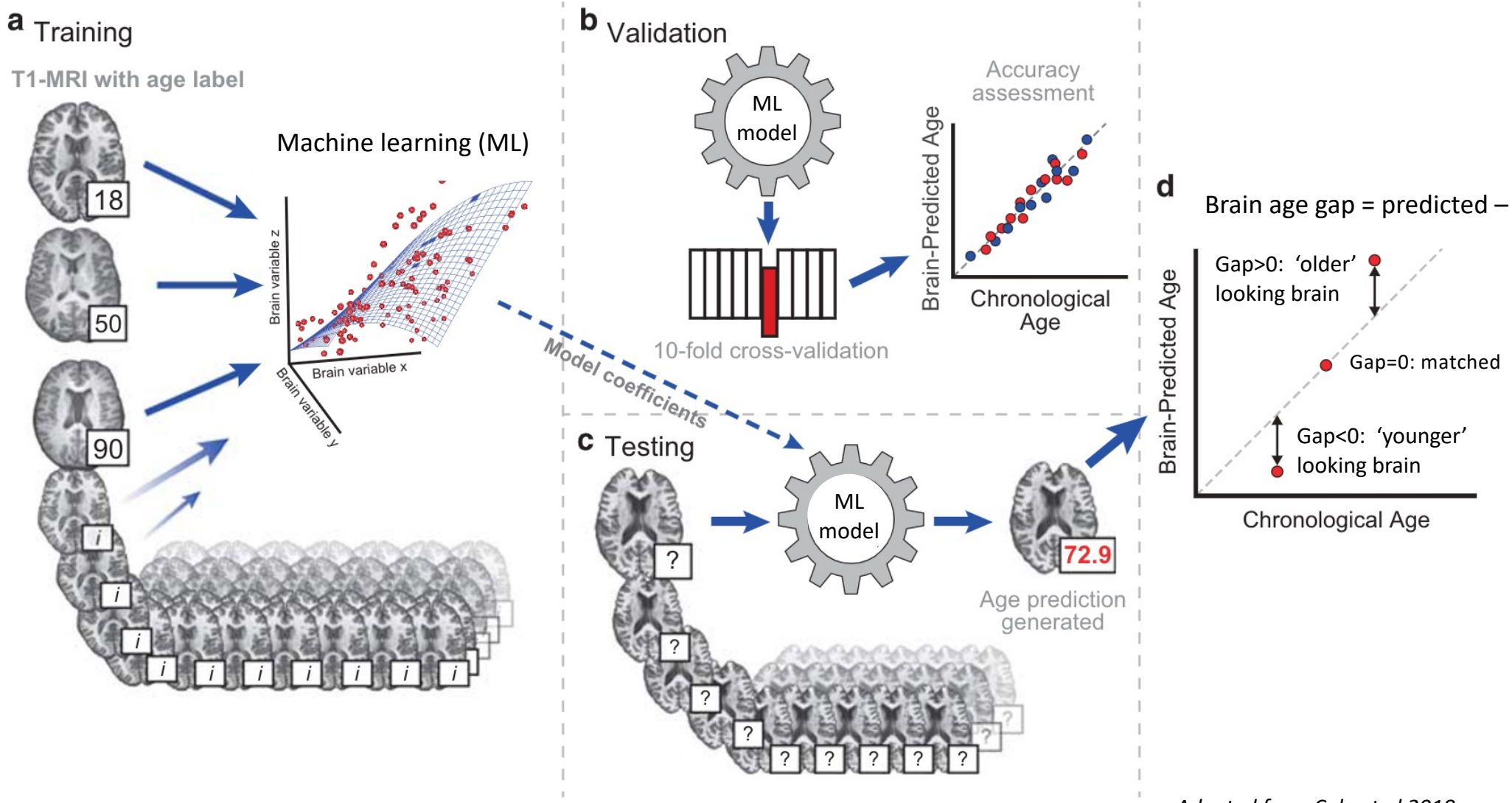
Biological age:

- The hypothetical underlying age of an organism, defined by measuring some aspect of the organism's biology.
- Biological age may differ from the organism's chronological age and may be a better indicator of residual lifespan, functional capacity, and risk of age-associated changes/diseases.

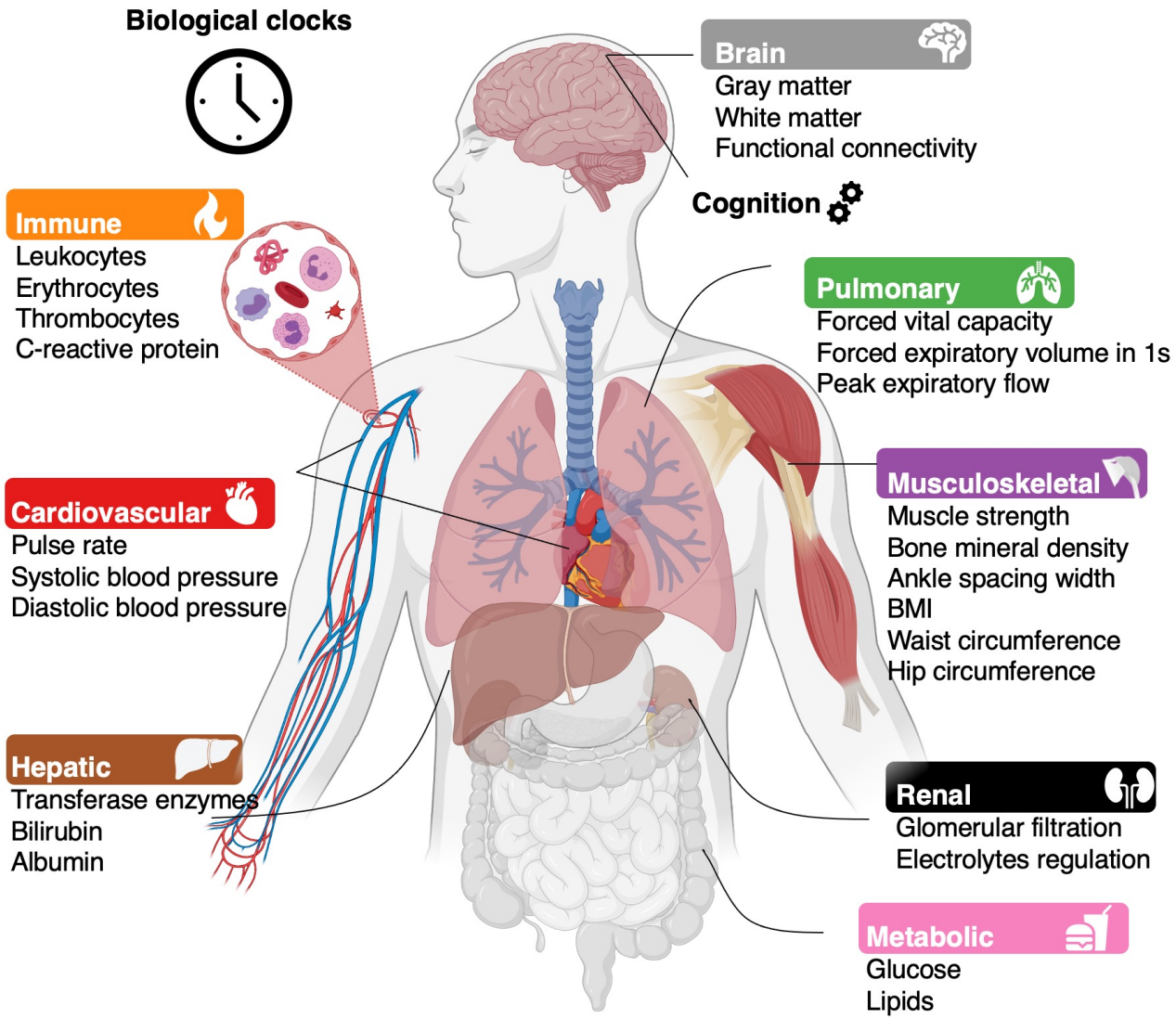
Organ-specific biological age



Brain age prediction



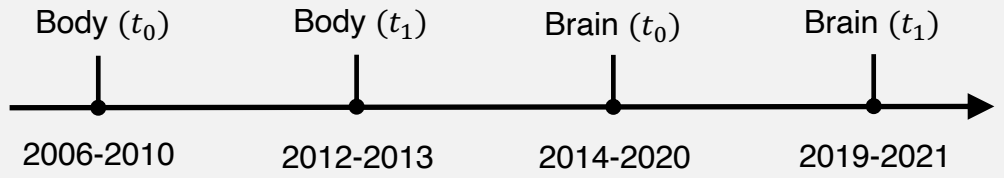
Adapted from Cole et al 2018



biobank uk

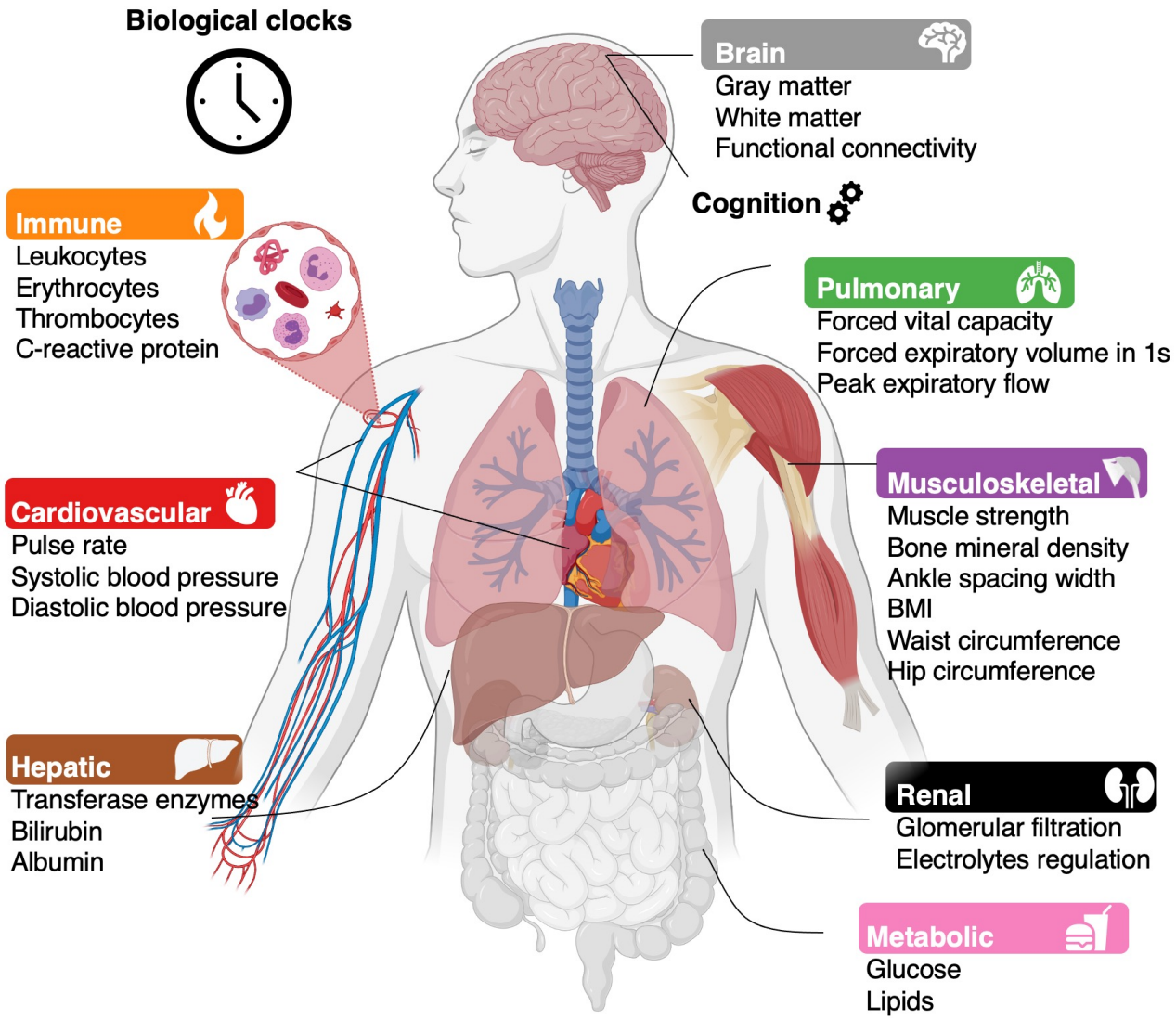
- Physical assessments
- Physiological assessments
- Blood hematology, biochemistry and urine assays
- Multi-modal brain imaging (T1w, dMRI, fMRI)

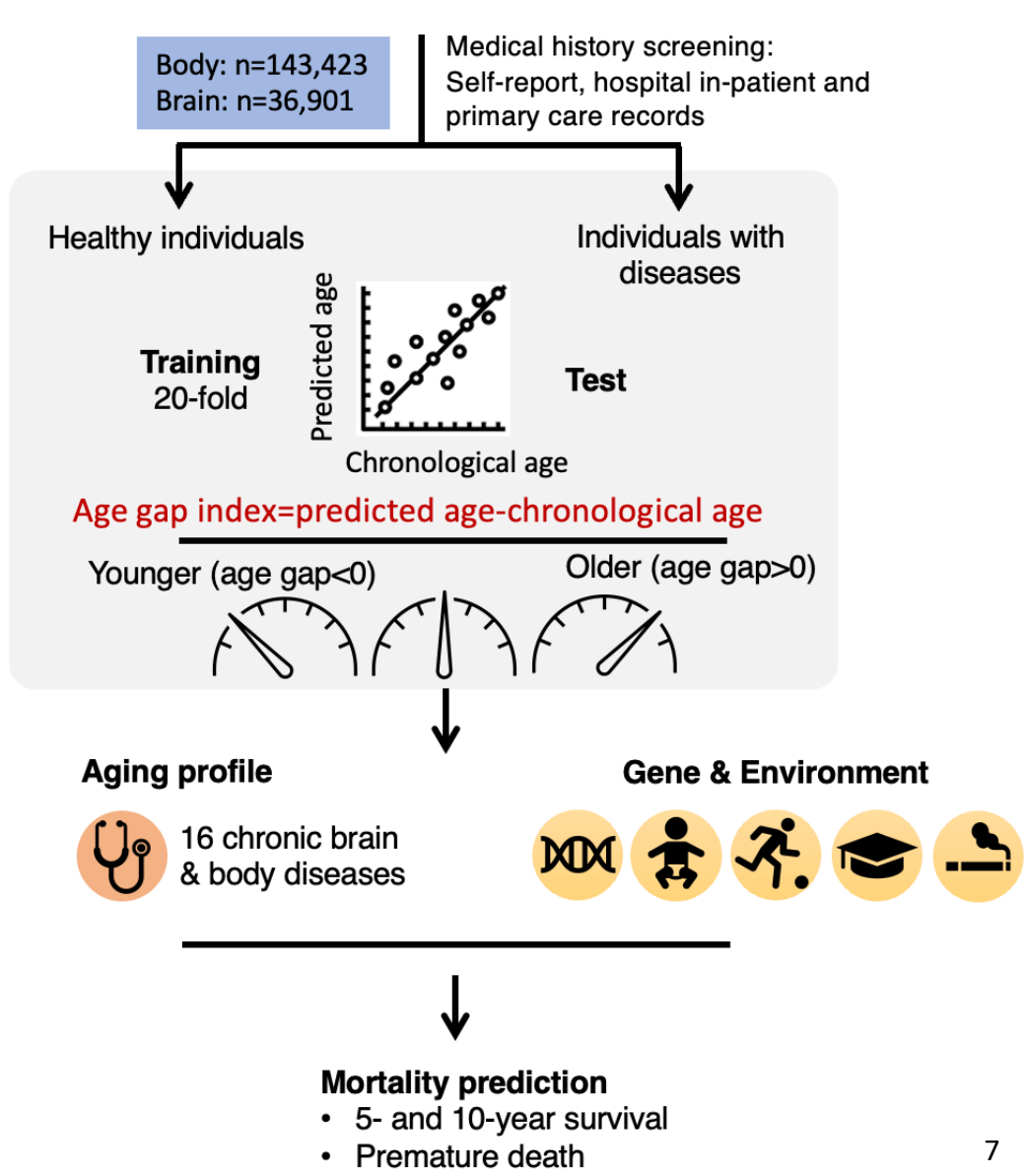
Time of assessment



N=500,000	*N*=20,000	*N*=50,000	*N*=1500

Tian, Y.E. et al., 2023 Nature Medicine





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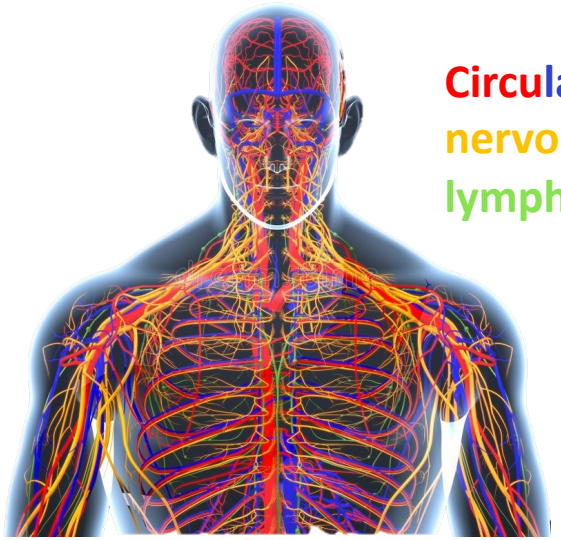
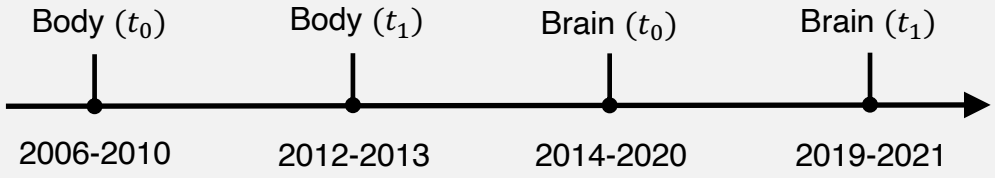
Multiorgan aging network



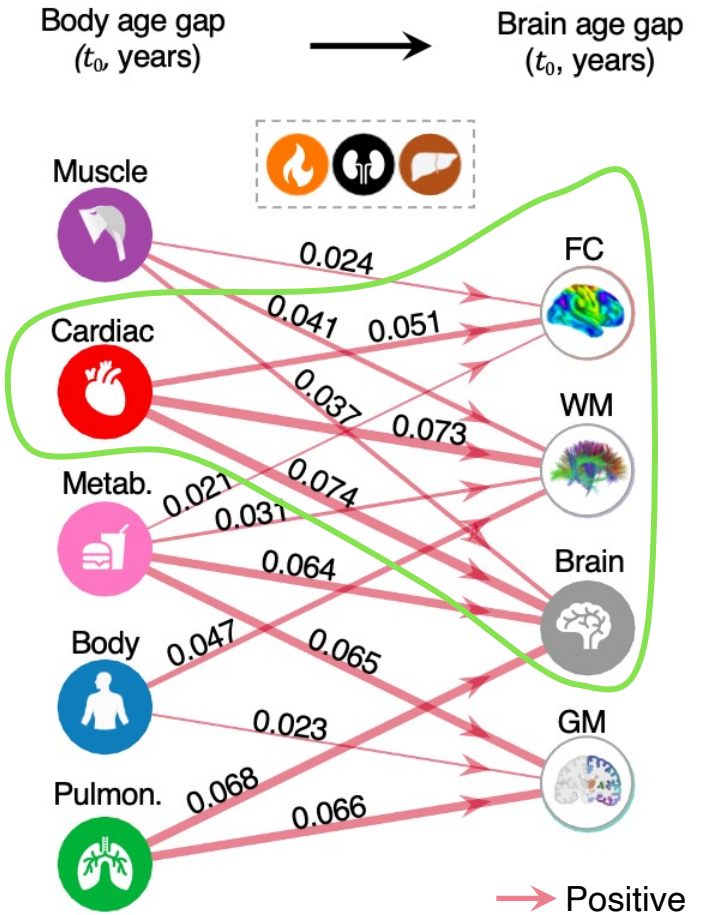
Circulatory, **nervous** and **lymphatic** networks

Hypothesis:
An organ's biological age would influence the aging of other connected organ systems

Time of assessment



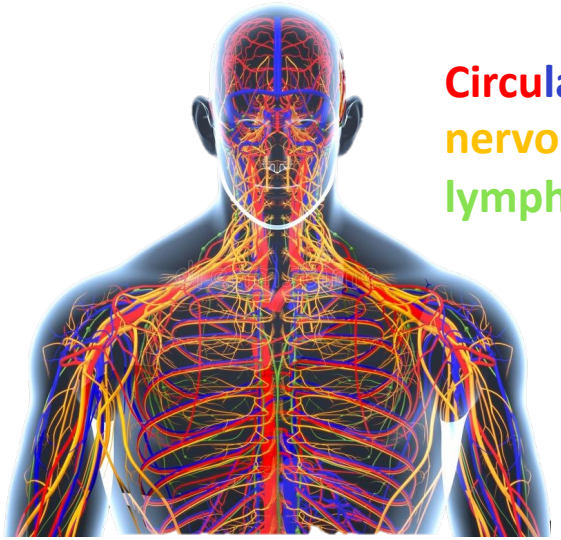
Structural Equation Modeling



Cardiovascular age shows the strongest influence on brain age, where a one-year increase in cardiovascular age explains a 0.074 year (i.e., 27 day) increase in overall brain age, and 19 and 27 day increases in FC and WM ages, respectively.

Tian, Y.E. et al., 2023 Nature Medicine

Multiorgan aging network



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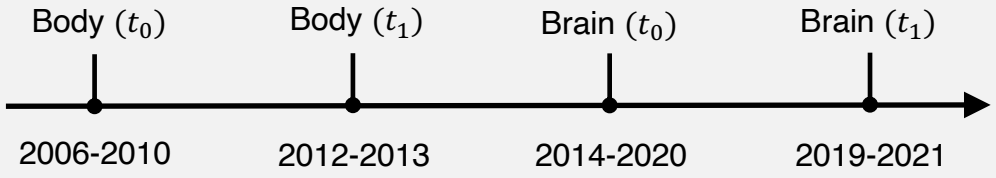
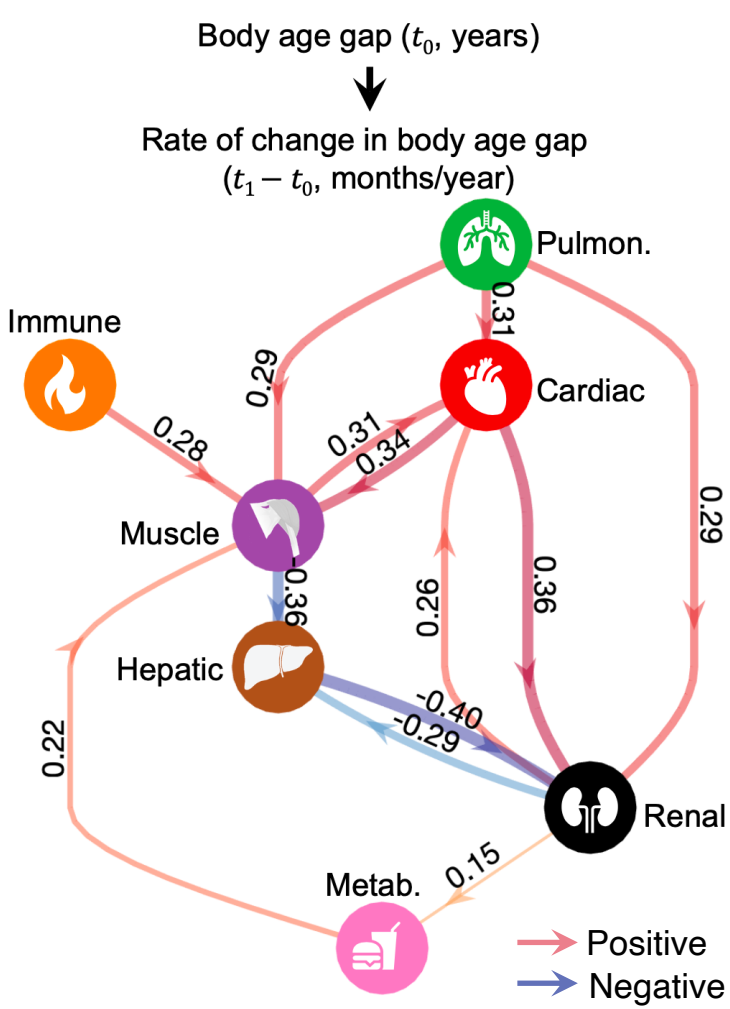
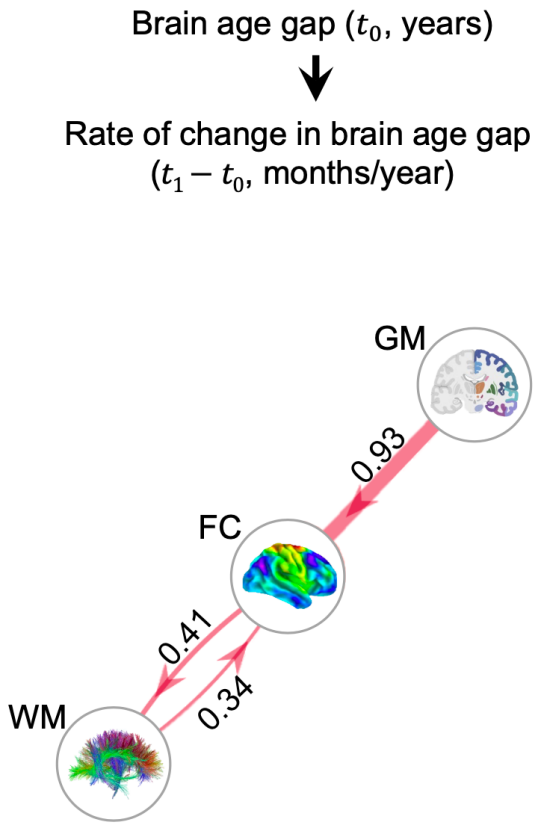


Structural Equation Modeling





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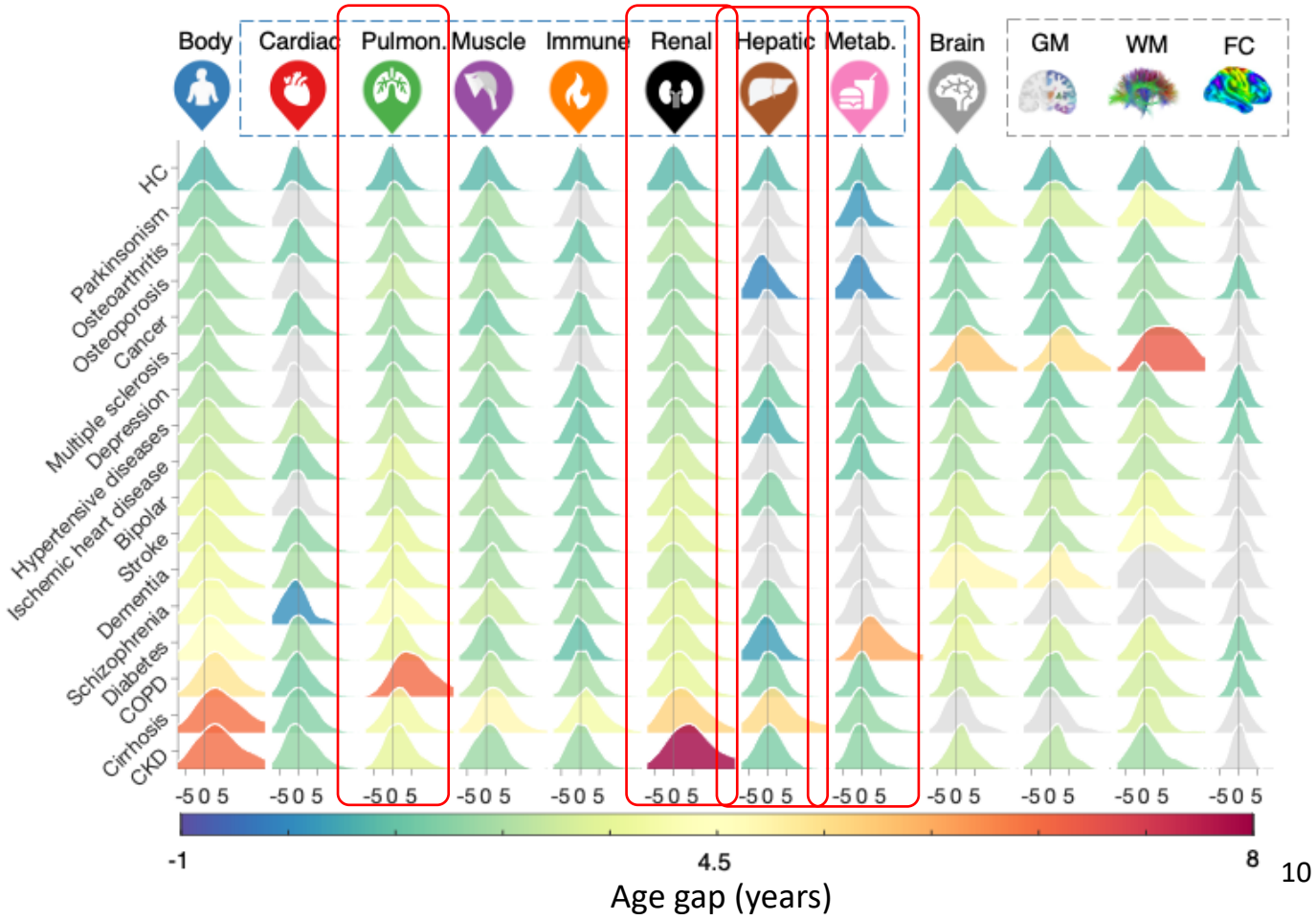
Multiorgan aging profile in chronic diseases

Lifelong contribution to brain-associated illness burden

- Depression
- Bipolar disorder
- Schizophrenia

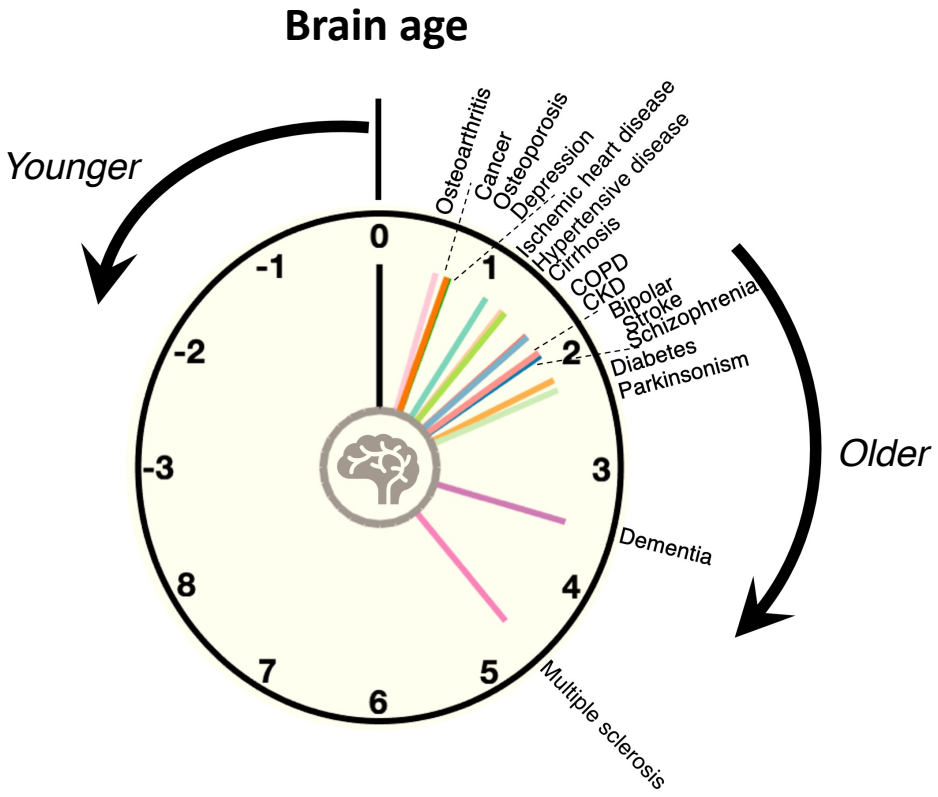
Significant health burden in older adults (e.g., disability and premature mortality)

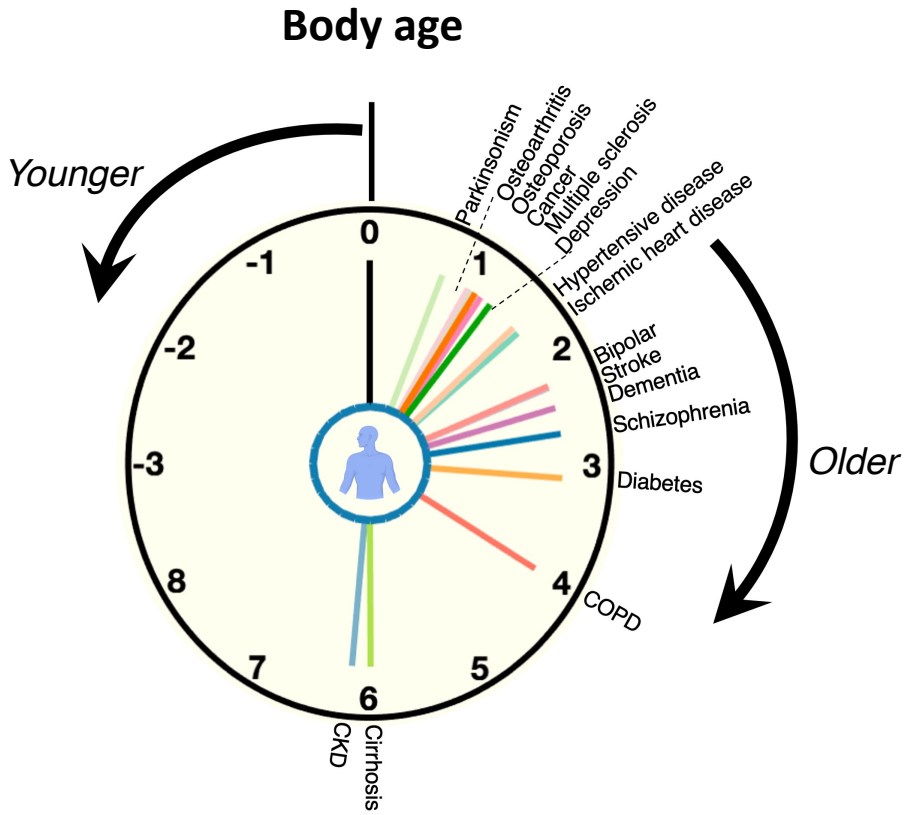
- Parkinsonism
- Multiple sclerosis
- Stroke
- Dementia
- Ischemic heart disease
- Hypertensive diseases
- Chronic obstructive pulmonary disease (COPD)
- Chronic kidney disease (CKD)
- Diabetes
- Cirrhosis
- Osteoarthritis
- Osteoporosis
- Cancer



Tian, Y.E. et al., 2023 Nature Medicine

Multiorgan aging profile in chronic diseases





- Chronic diseases are characterized by unique organ aging profiles
- Across 16 common, chronic diseases, advanced biological aging extends from the organ of primary disease pathology to multiple organ systems

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Advanced pulmonary, immune, renal and hepatic age increases mortality risk

Cox proportional hazard regression

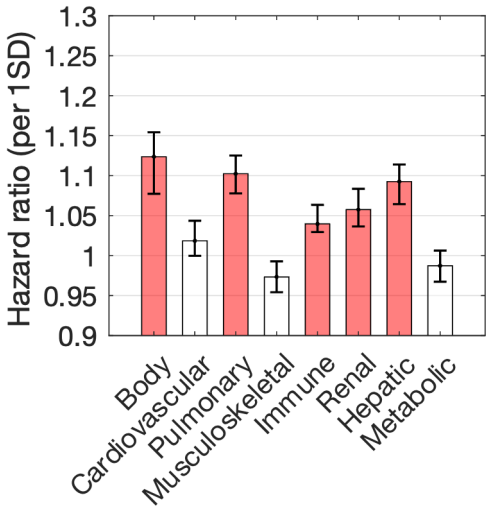
Body function assessment: 2006-2010

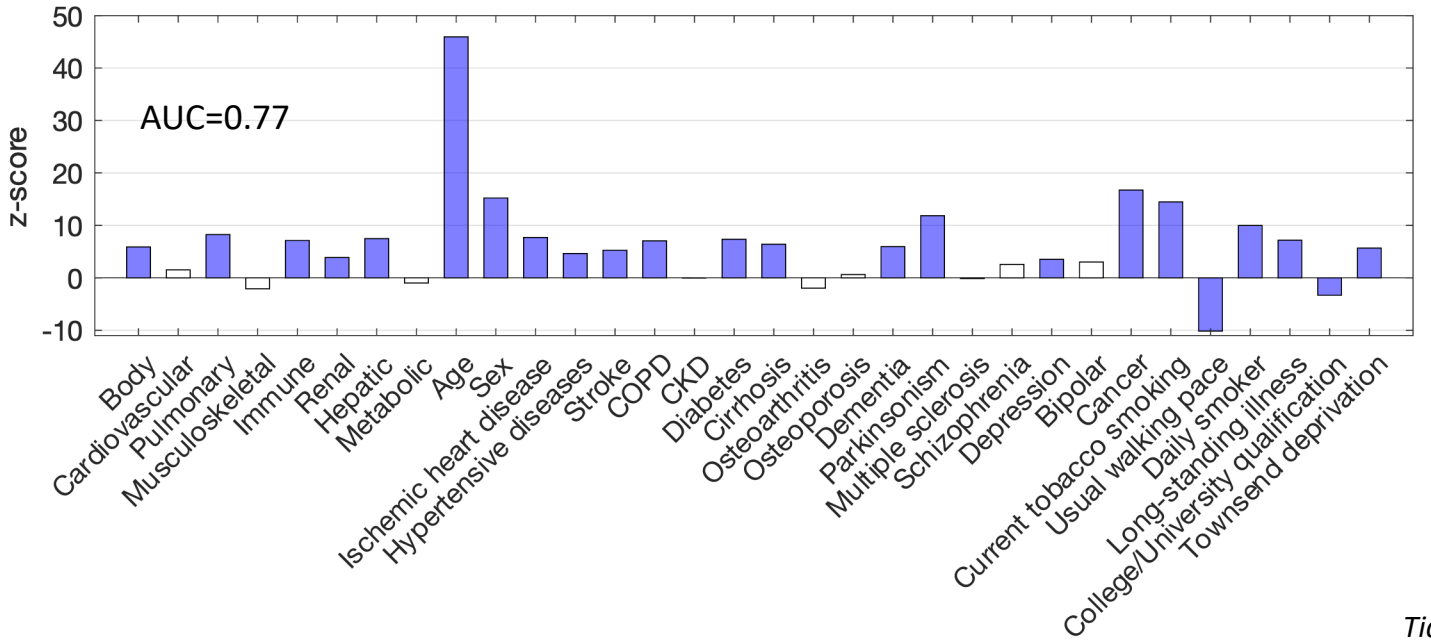
Survival: up to 13.41 years

Mortality data (4 March 2021)

Deceased: n=8,190

Non-deceased: n=135,314





Tian, Y.E. et al., 2023 Nature Medicine

Advanced brain age “dose not” increase mortality risk

Cox proportional hazard regression

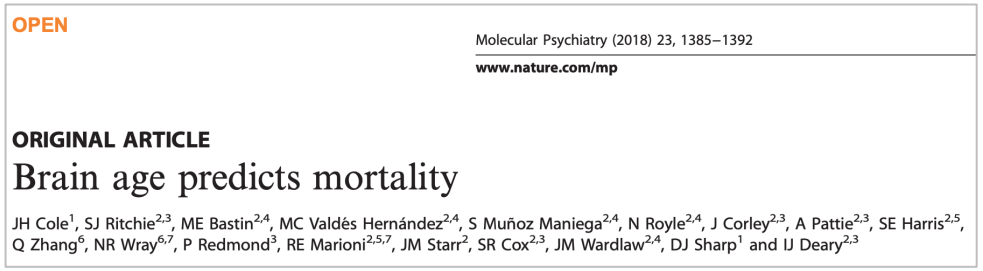
Brain imaging: 2014-2020

Survival: up to 6.07 years

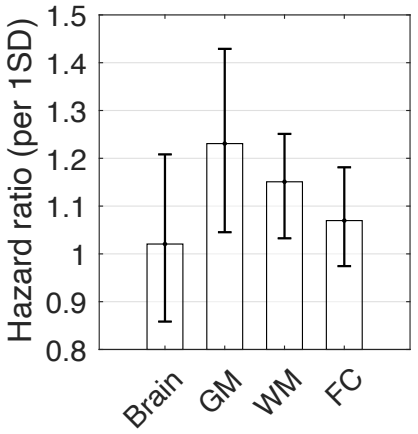
Mortality data (4 March 2021)

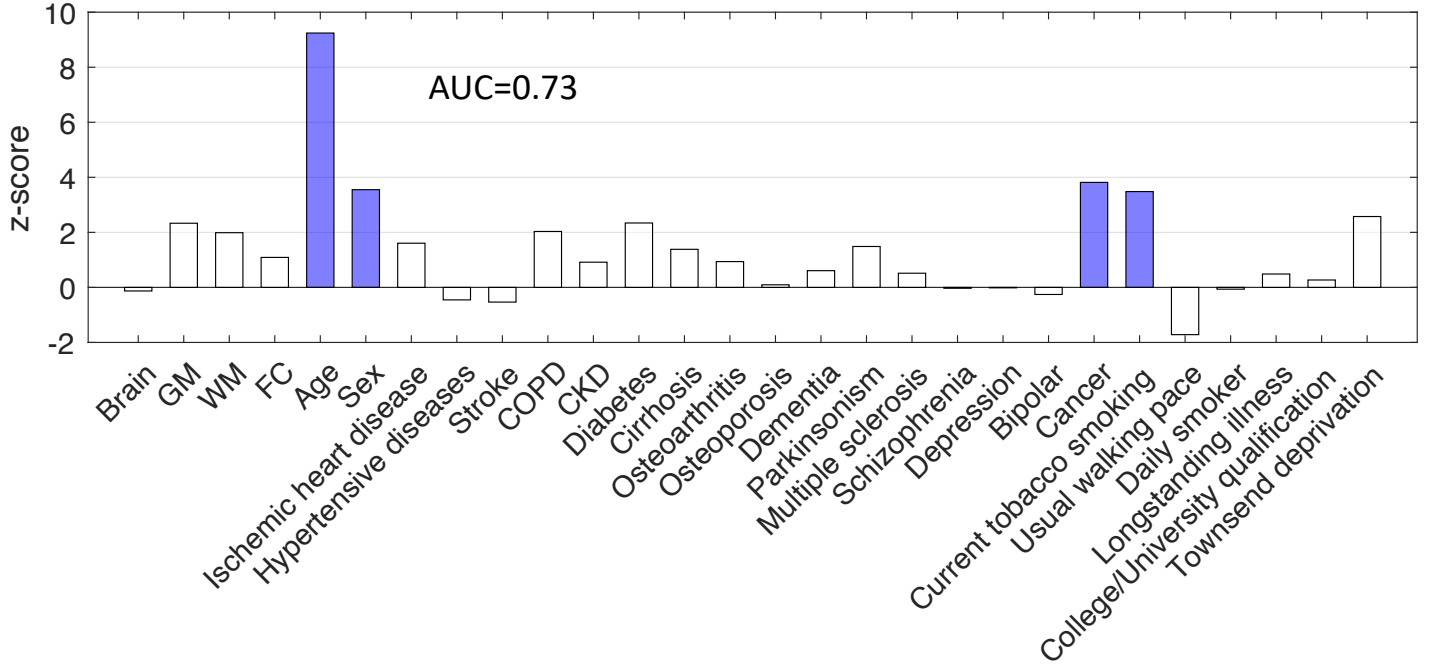
Deceased: n=330

Non-deceased: n=36,571



- Low mortality rate (UKB: 0.009 vs Lothian Birth Cohort: 0.11)
- Continued follow-up





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Multiorgan age predicts mortality

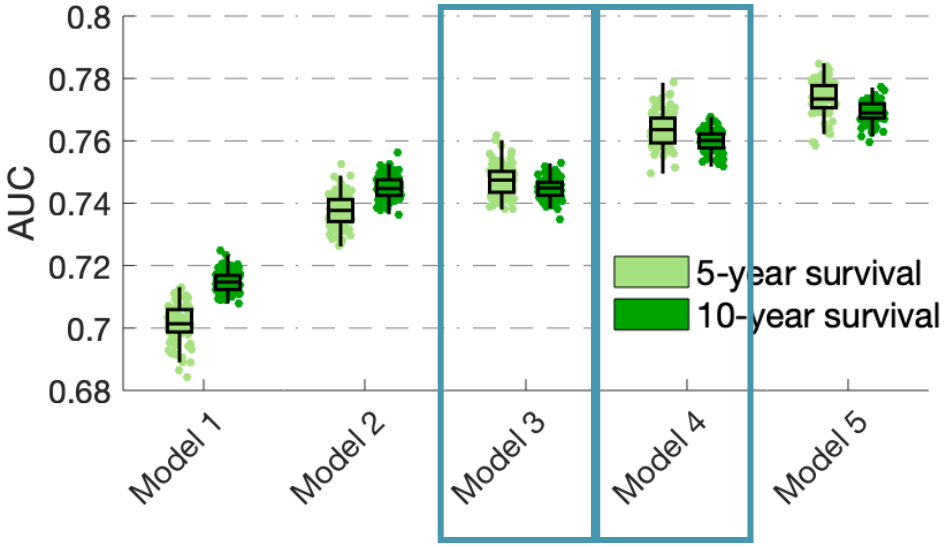
Survival time
5-year survival
10-year survival

Premature death
70 years old
75 years old

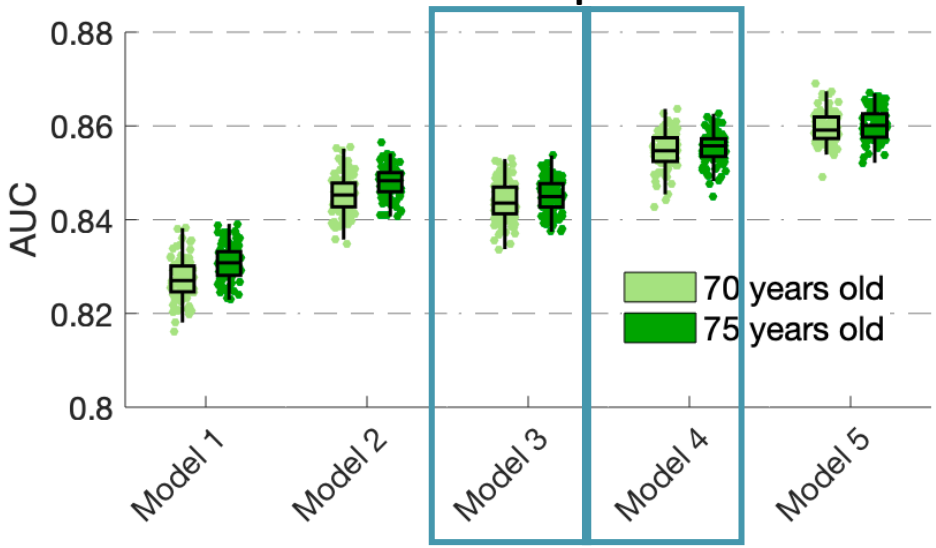
Logistic regression and 10-fold cross-validation

Model 1: Age + Sex
Model 2: Age + Sex + Body age gap
Model 3: Age + Sex + Existing diagnoses
Model 4: Age + Sex + Body age gap + Existing diagnoses
Model 5: Age + Sex + Body age gap + Existing diagnoses + Lifestyle

Survival time prediction



Premature death prediction



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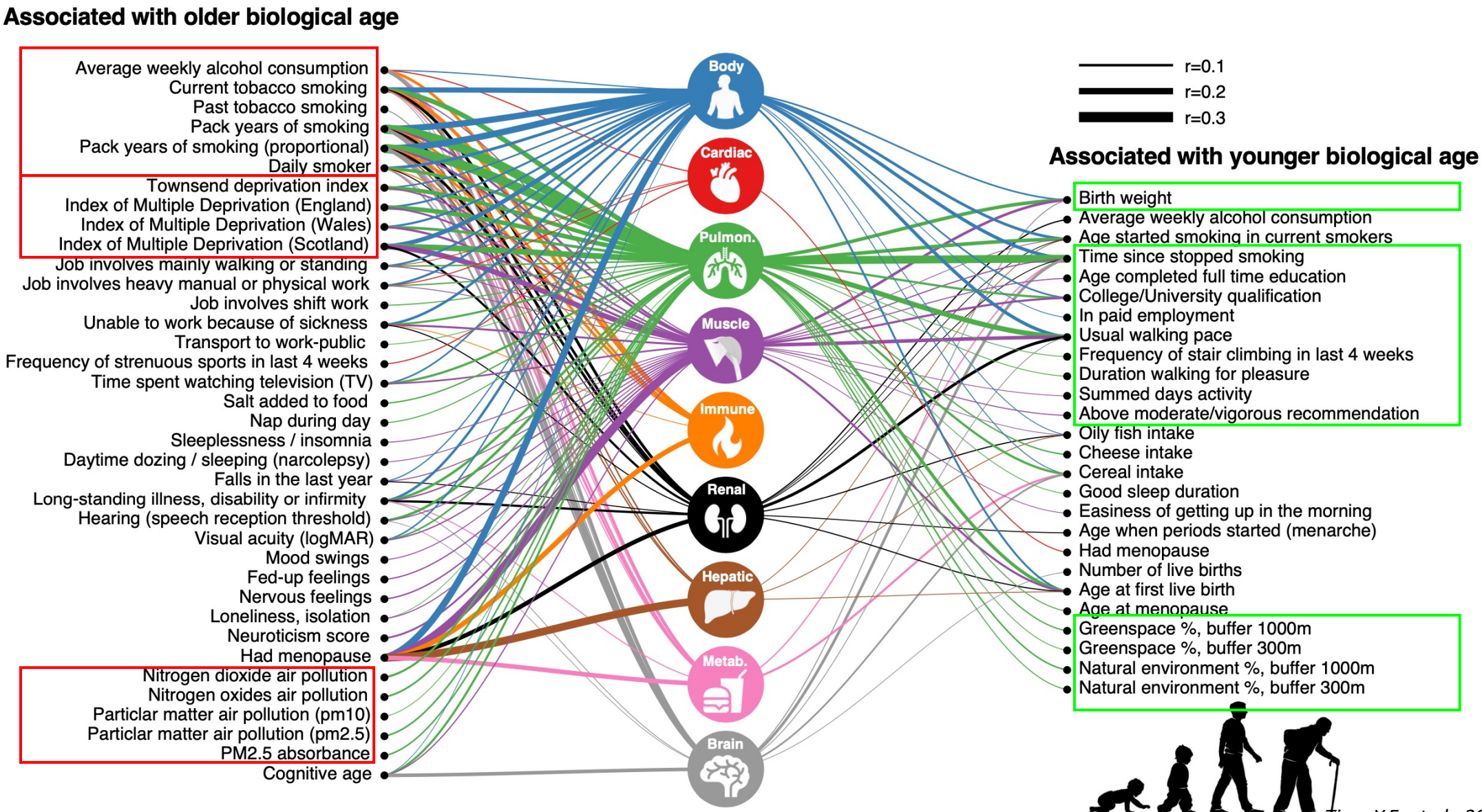
Environmental and lifestyle factors associate with brain and body age



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Summary

nature medicine

Article

https://doi.org/10.1038/s41591-023-02296-6

Heterogeneous aging across multiple organ systems and prediction of chronic disease and mortality

Received: 26 September 2022

Accepted: 9 March 2023

Published online: 06 April 2023

Check for updates

Ye Ella Tian[1], Vanessa Cropley[1], Andrea B. Maier[2,3,4], Nicola T. Lautenschlager[5,6], Michael Breakspear[7,8] & Andrew Zalesky[1,9]

Biological aging of human organ systems reflects the interplay of age, chronic disease, lifestyle and genetic risk. Using longitudinal brain imaging and physiological phenotypes from the UK Biobank, we establish normative

- We establish normative models of biological age for three brain and seven body systems.
- Multiorgan aging network
- An organ's biological age selectively and characteristically influences the aging of other organ systems. Brain age is most strongly influenced by the biological age of the cardiovascular, pulmonary and metabolic systems, whereas the musculoskeletal system is an in-degree hub of the aging network.

- Multiorgan aging profile in chronic disease, where advanced biological aging extends from the organ of primary disease pathology to multiple organ systems
- Advanced biological age predicts mortality

Part 2: Brain-body health in psychiatry

The *Lancet Psychiatry* Commission: a blueprint for protecting physical health in people with mental illness

Joseph Firth, Najma Siddiqi, Ai Koyanagi*, Dan Siskind*, Simon Rosenba… Rebekah Carney, Andre F Carvalho, Mary Lou Chatterton, Christoph U Co… Sarah E Jackson, Steve Kisely, Karina Lovell, Mario Maj, Patrick D McGorry… Jerome Sarris, Felipe B Schuch, David Shiers, Lee Smith, Marco Solmi, Shui… John Torous, Tim Usherwood, Davy Vancampfort, Nicola Veronese, Philip…*

EDITORIAL

Physical health care … in persons with severe mental illness: a public hea… th and ethical priority

President, World Psychiatric Association

WPA EDUCATIONAL MODULE

Physical illness in patients … I. Prevalence, impact of me… in health care

Marc De Hert[1], Christoph U. Correll[2], Julio Bobes[3] … Itsuo Asai[6], Johan Detraux[1], Shiv Gautam[7], Hans-Ju… John W. Newcomer[10], Richard Uwakwe[11], Stefan Le…

- ~2-3 folds increased risk of chronic physical illness, e.g., heart disease, stroke, diabetes
- Reduced life expectancy of 10-25 years
- The majority (~80%) of years of life lost in people with mental illness relates to poor physical health

Open Access

Research

… in physical comorbidity: … al comparative cohort study … ith severe mental illness

Siobhan Reilly,[1] Ivan Ol… r,[2] Claire Planner,[3] Tim Doran,[4] David Reeves,[5] Darren M Ashcroft,[6] Lin… a Gask,[3] Evangelos Kontopantelis[3,7]

Original Investigation

Association of Mental Disorders Wi… Subsequent Chronic Physical Conditions

World Mental Health Surveys From 17 Countries

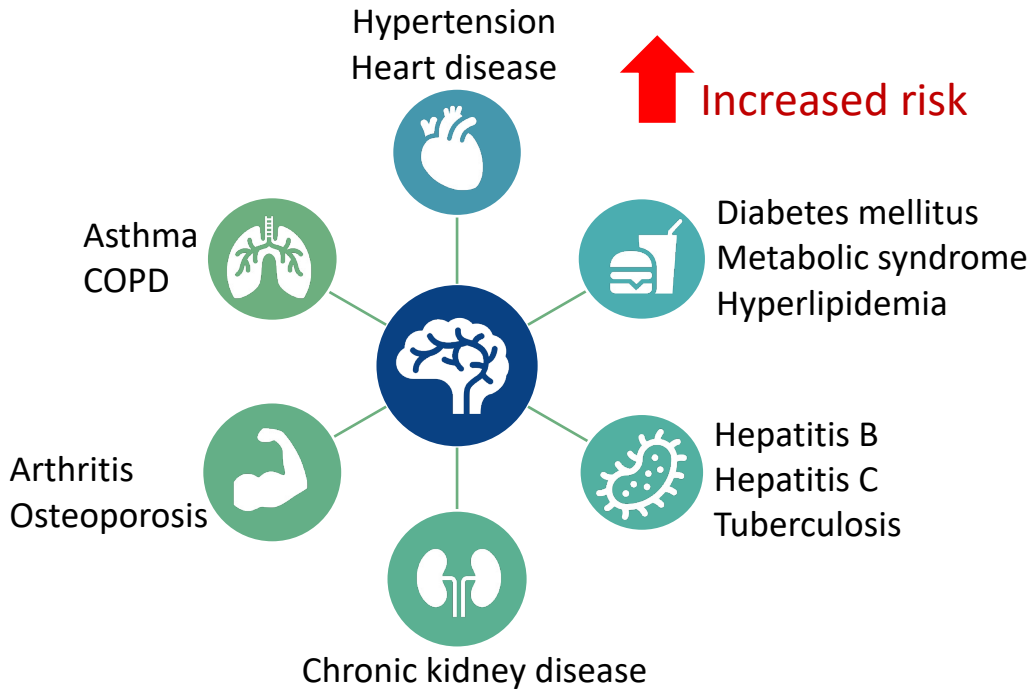
Kate M. Scott, MA(ClinPsych), PhD; Carmen Lim, MSc; Ali Al-Hamzawi, MD; Jordi Alonso, MD, DrPH; Ronny Bruffaerts, PhD; José Miguel Caldas-de-Almeida, MD, PhD; Silvia Florescu, MD, PhD; Giovanni de Girolamo, MD; Chiyi Hu, PhD; Peter de Jonge, PhD; Norito Kawakami, MD, DMSc; Maria Elena Medina-Mora, PhD; Jacek Moskalewicz, PhD; Fernando Navarro-Mateu, MD, PhD; Siobhan O'Neill, MPsychSc, PhD; Marina Piazza, ScD, MPH; José Posada-Villa, MD; Yolanda Torres, MPH, DraHC; Ronald C. Kessler, PhD

The temporal relationship between severe mental illness diagnosis and chronic physical comorbidity: a UK primary care cohort study of disease burden over 10 years

Naomi Launders, Leiah Kirsh, David P J Osborn, Joseph F Hayes

Epidemiological links vs Biological origins

Epidemiological links



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Morbidity, Disability, Mortality

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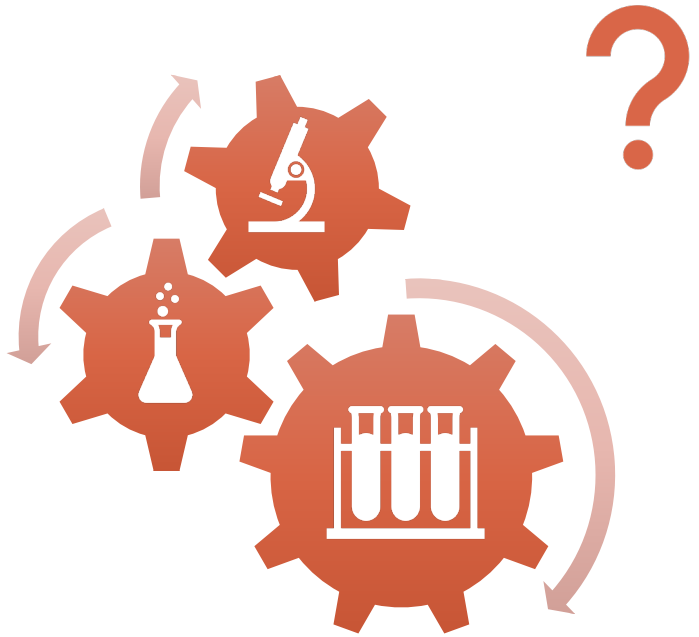
Global health and economic burden

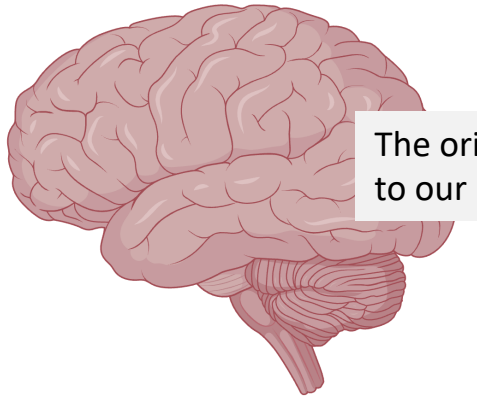
Biological origins & sequela



Disparities in health care for people with mental illness:

- Lack of access to adequate primary care
- Diagnostic overshadowing
- Difficulties with acknowledging and reporting medical problems

…

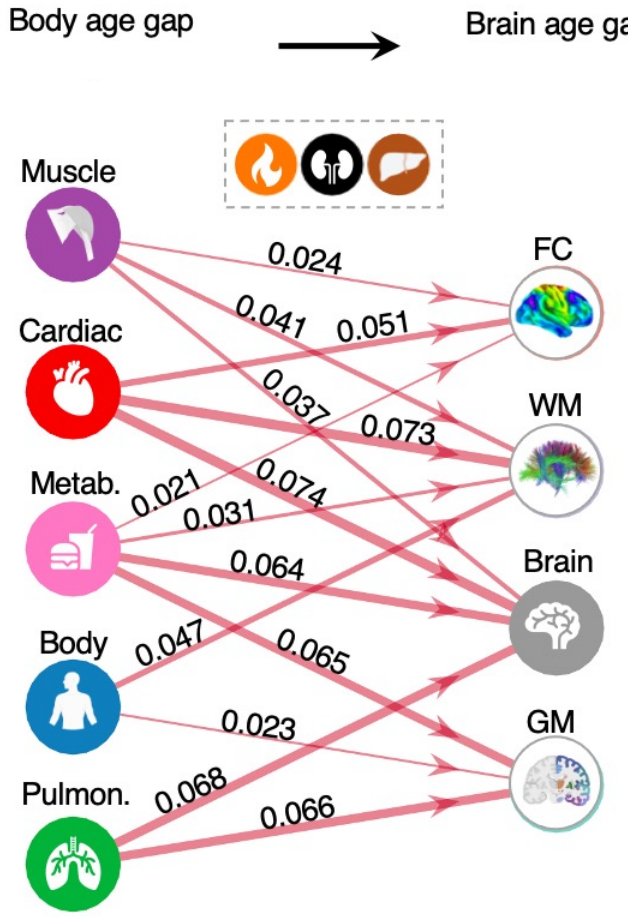


The origin of mental illness to our knowledge to date

Multiorgan aging network

Circulatory, nervous, lymphatic networks

Structure equation modeling



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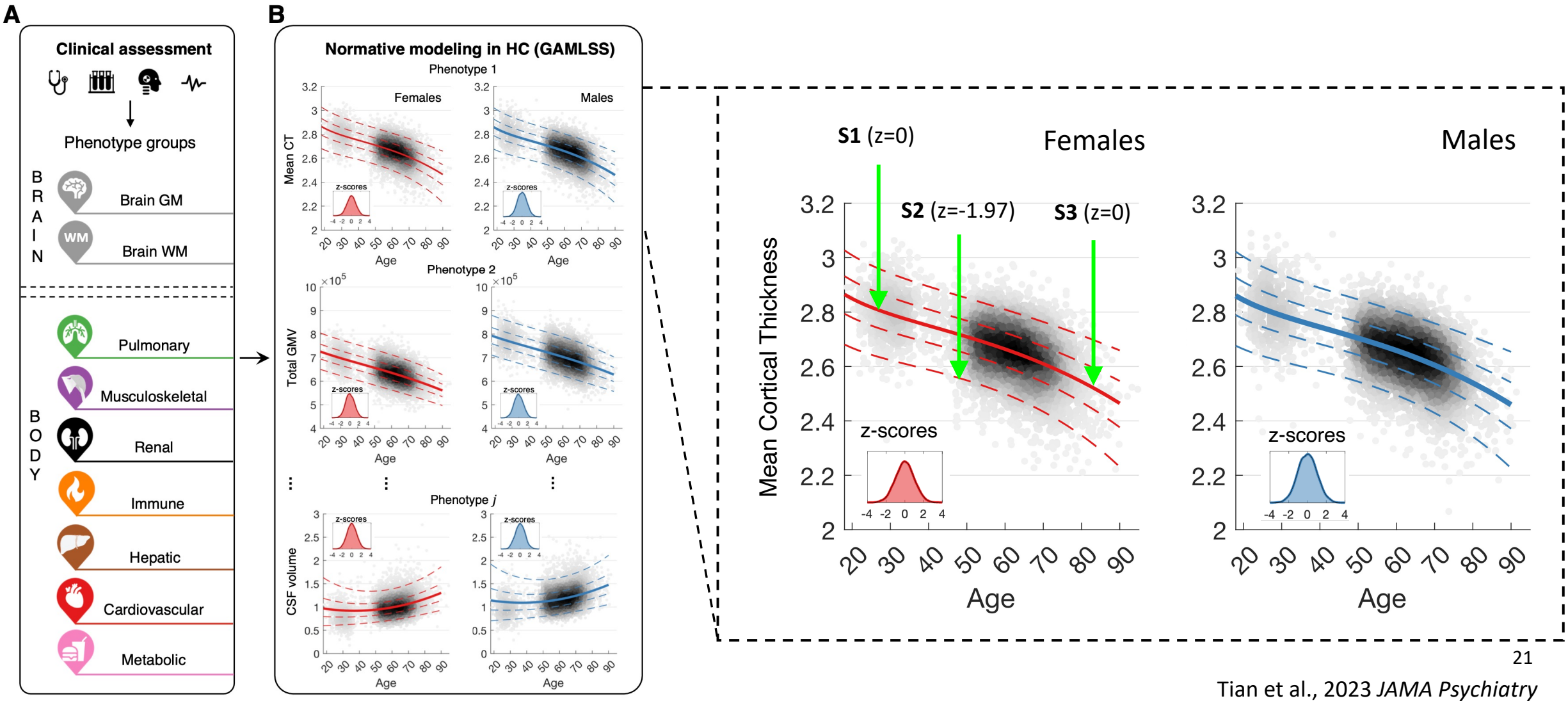
Neuropsychiatric disorders

- Schizophrenia
- Bipolar disorder
- Depression
- Generalized anxiety disorder
- Dementia

- UK Biobank
- Australian Schizophrenia Research Bank (ASRB)
- Australian Imaging, Biomarkers and Lifestyle flagship study of ageing (AIBL)
- Alzheimer's Disease NeuroImaging Initiative (ADNI)
- Prospective Imaging Study of Ageing (PISA)
- Human Connectome Project Young Adult (HCP-YA)
- Human Connectome Project Aging (HCP-A)

***N* > 100,000 adults (age range: 18-90 years)**

Normative modeling



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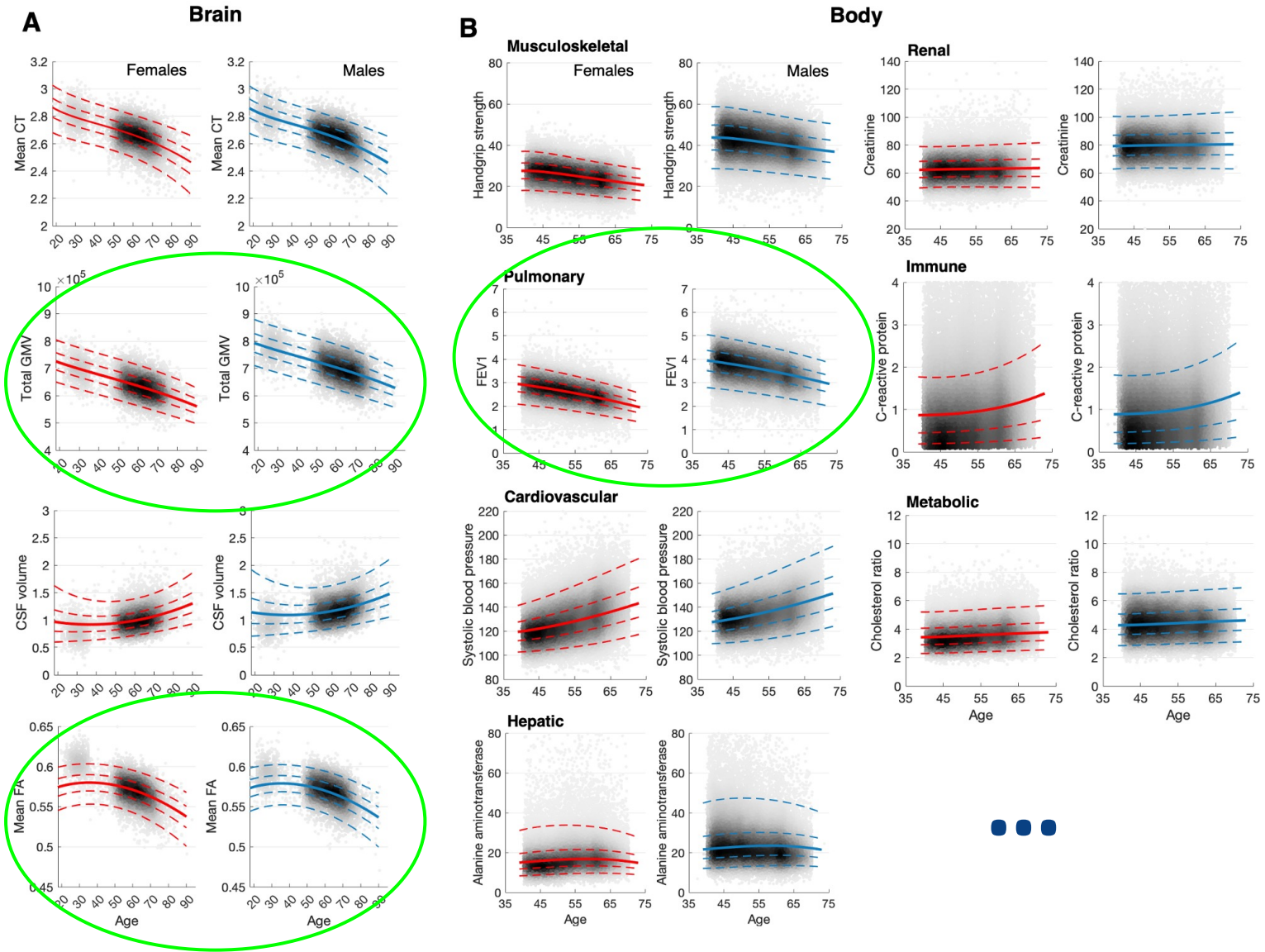
Normative modeling



N=203

Imaging
Blood
Urine
Physiological

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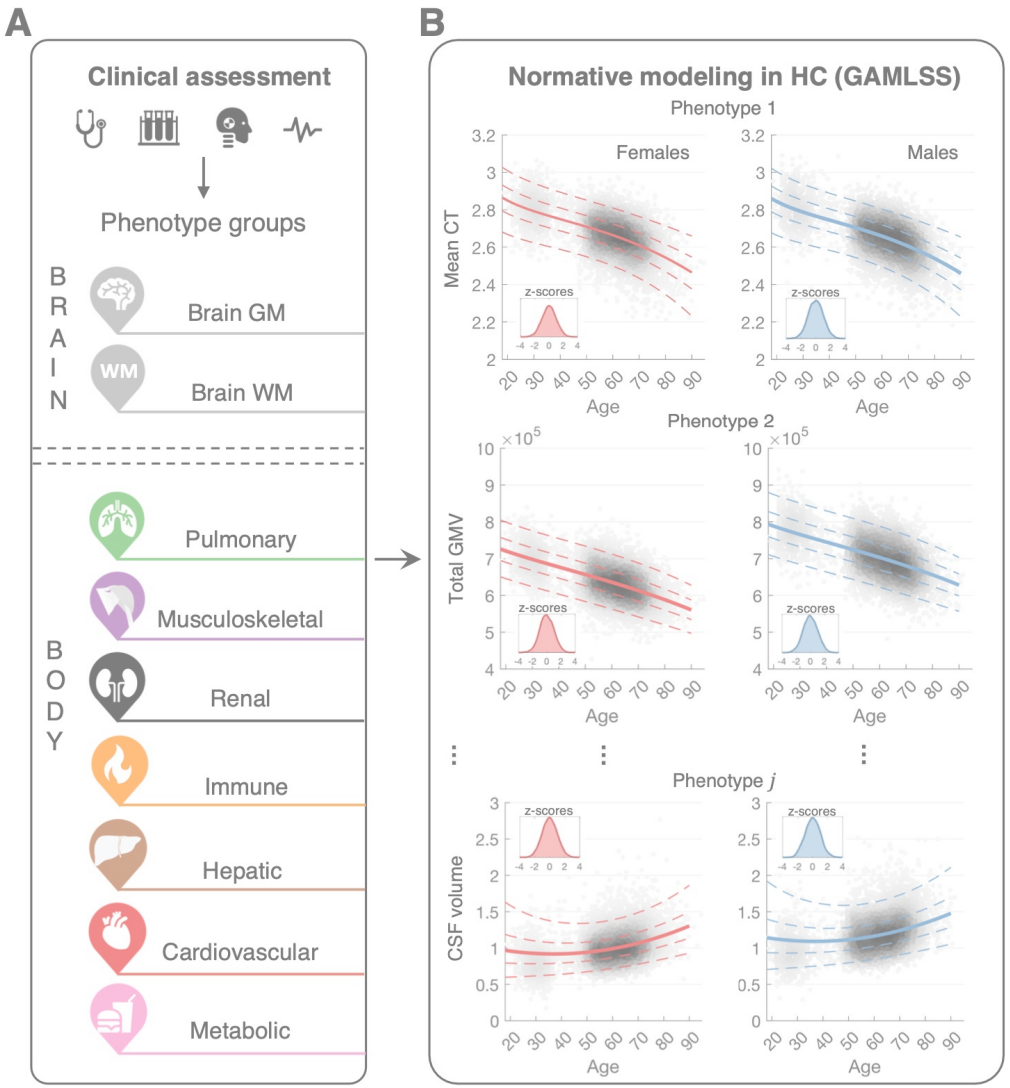
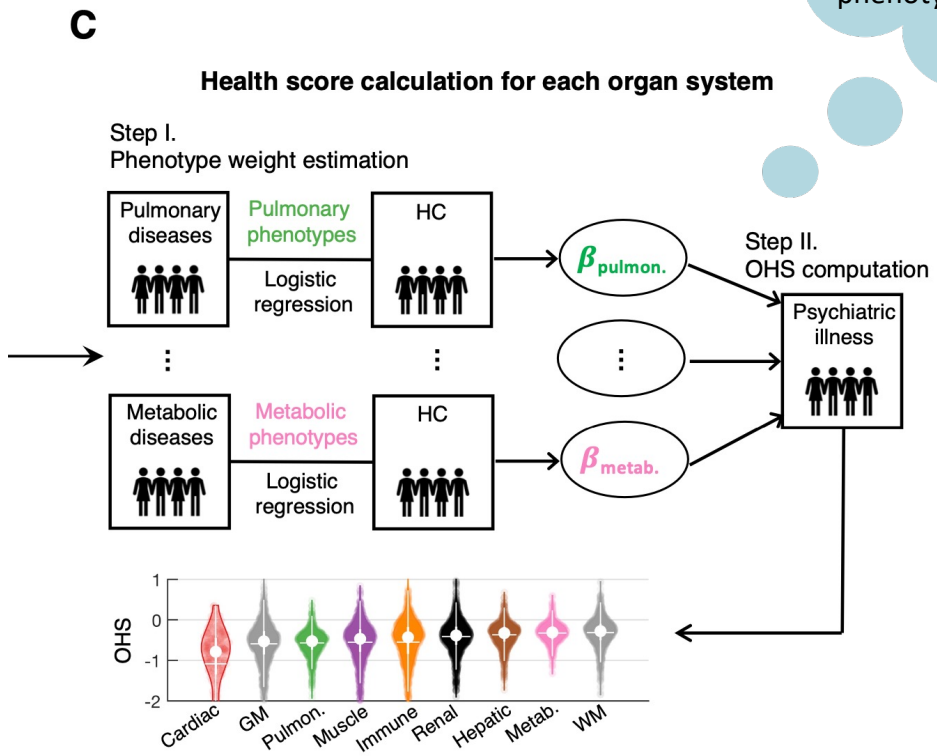
Organ health score

OHS: Weighted sum of deviation scores (z-scores) across organ-specific phenotypes.





0 Normal

Poorer

$$OHS(n,k) = -\left(w_0^k + \sum_{j=1}^{J} w_j^k x_j(n)\right)$$

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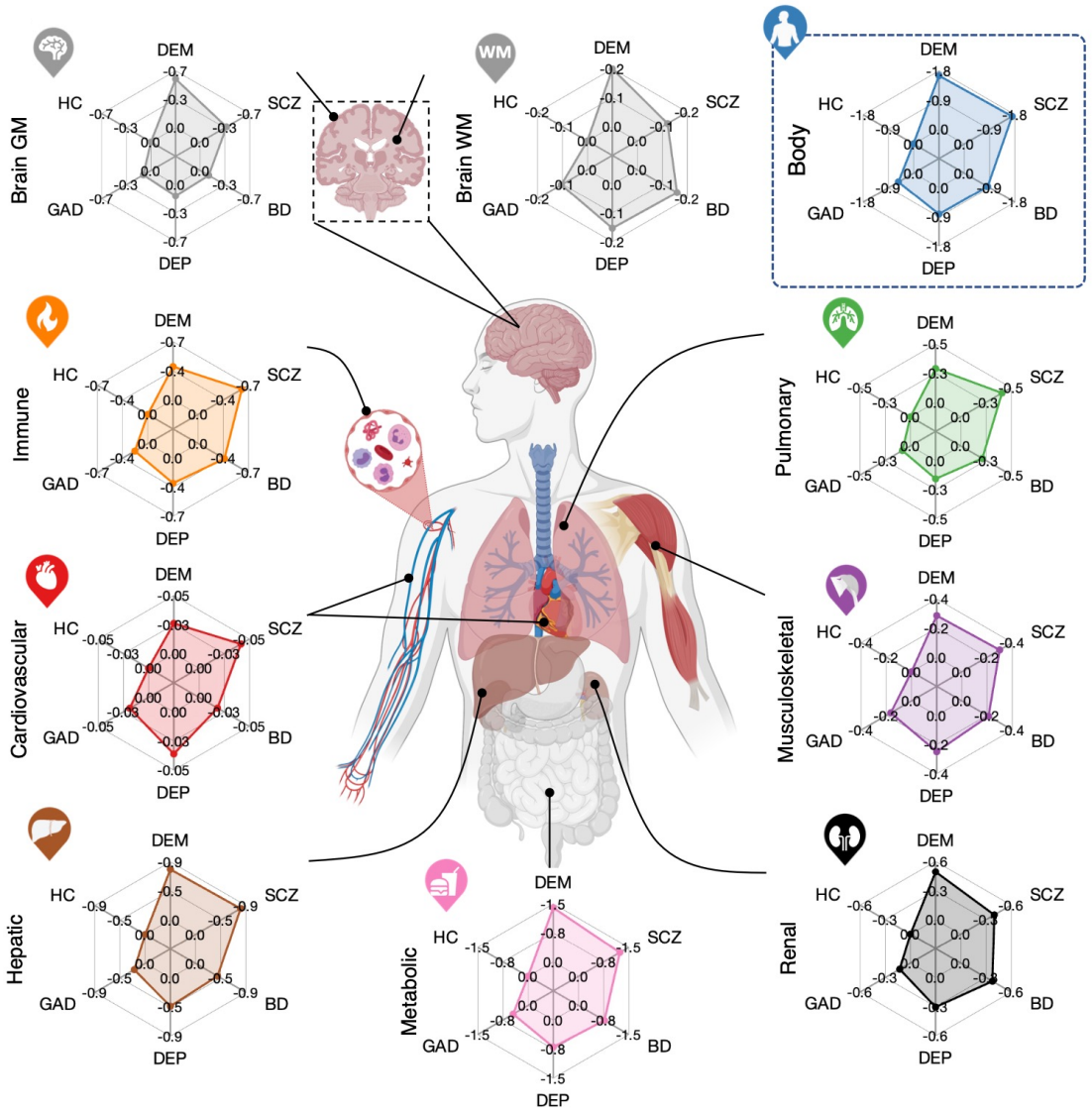
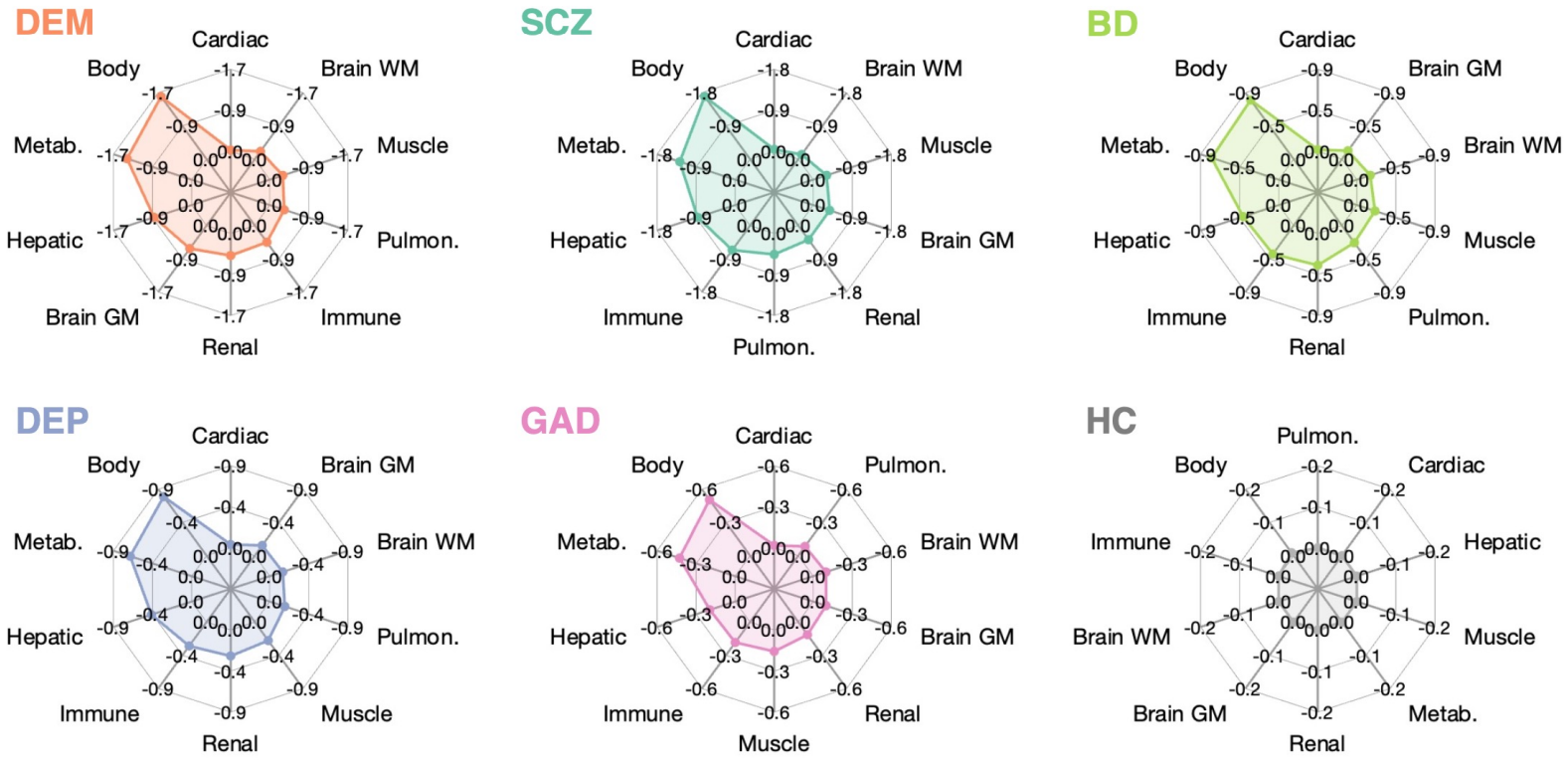
Multisystem health profile in neuropsychiatric disorders



- Organ-specific health scores are on average significantly lower in individuals with neuropsychiatric disorders compared to age- and sex-matched healthy peers.
- Body health scores are markedly lower for dementia, schizophrenia, bipolar disorder, depression and generalized anxiety disorder, compared to healthy individuals

Tian et al., 2023 *JAMA Psychiatry*

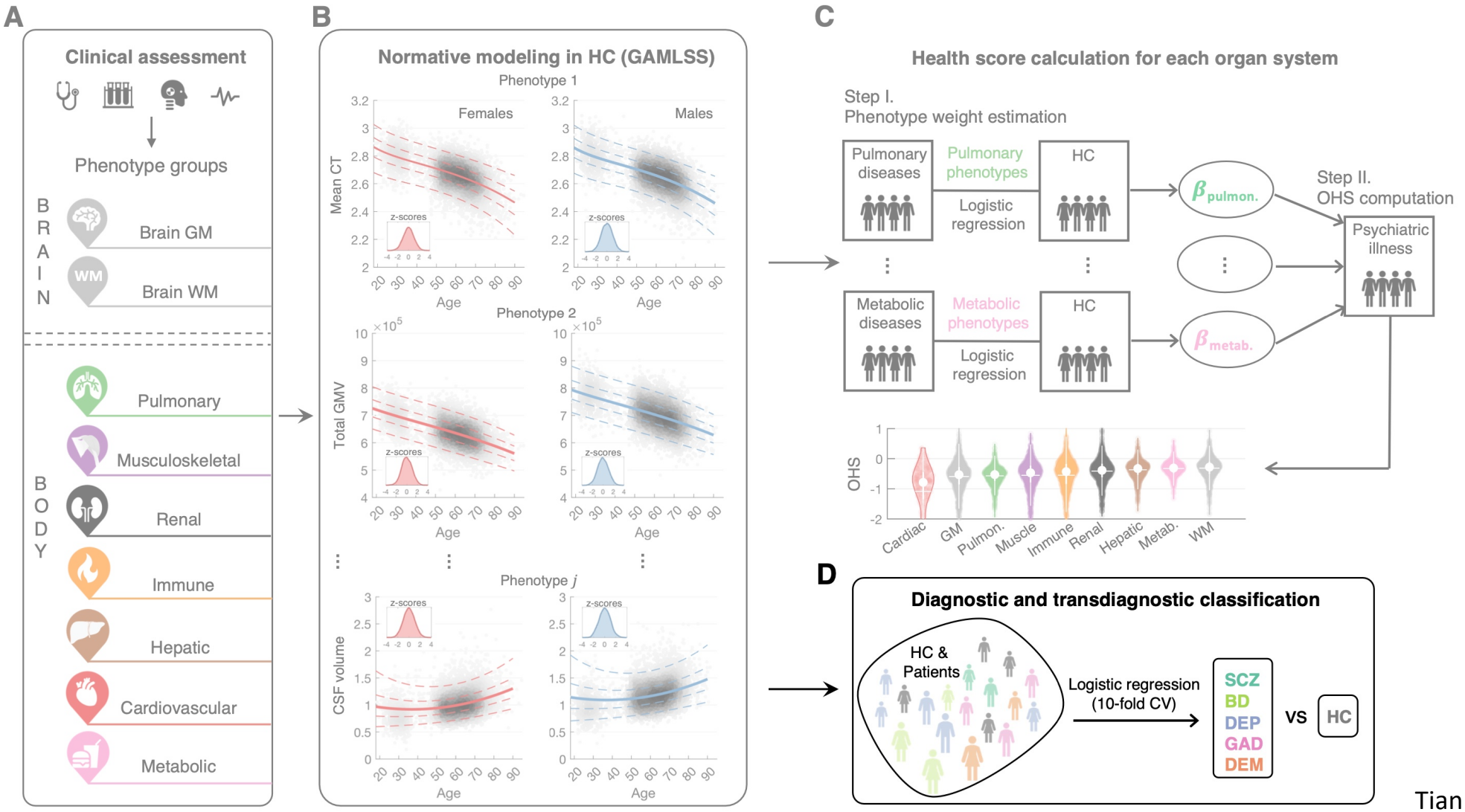
Multisystem health profile in neuropsychiatric disorders



- Poor body health is a more pronounced manifestation of neuropsychiatric illness than brain changes for the disorders studied. Particularly for BD, DEP and GAD.
- Consistent across the 5 disorders, poor organ health is most evident for **metabolic**, **hepatic**, **immune** and **renal** systems.

Tian et al., 2023 *JAMA Psychiatry*

Diagnostic vs transdiagnostic classification



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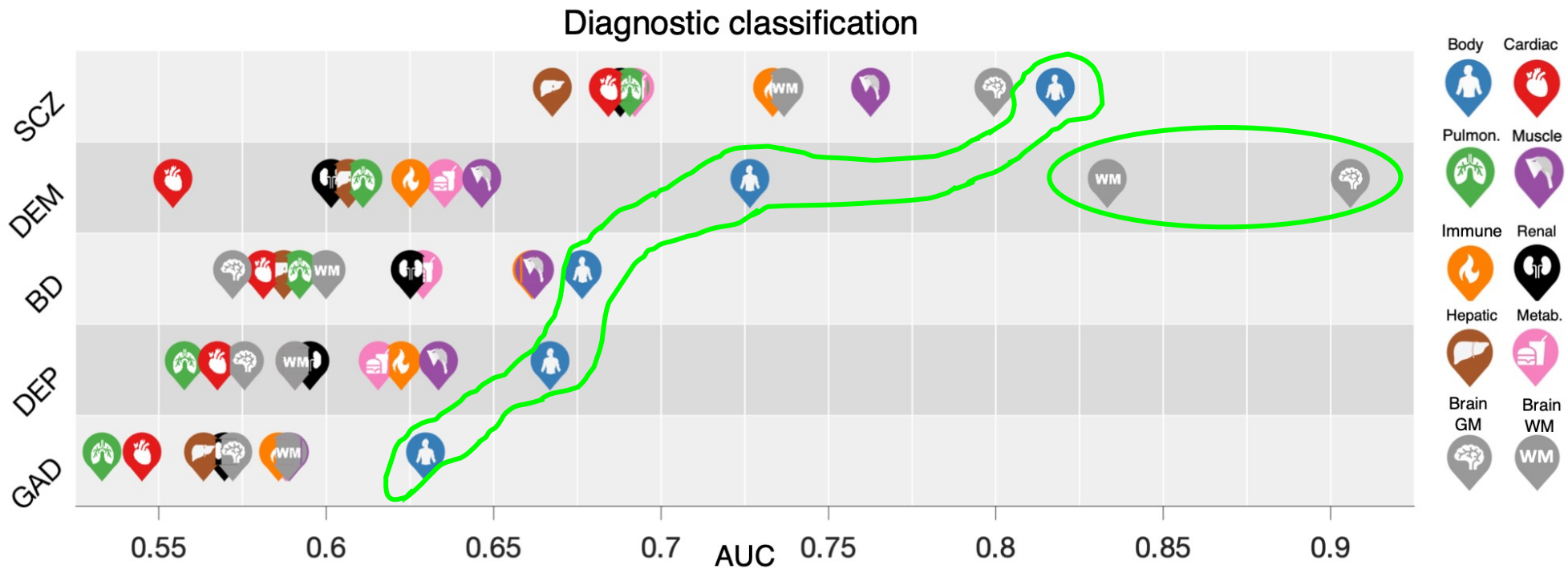
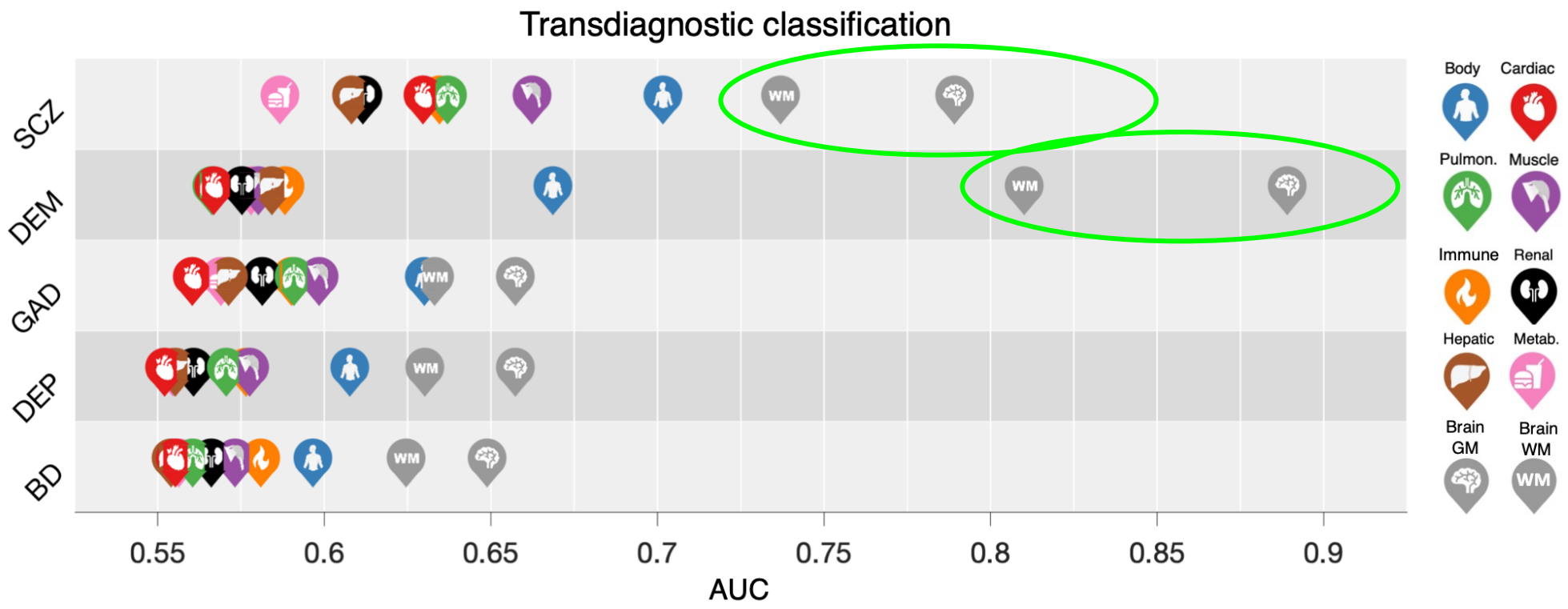
Diagnostic vs transdiagnostic classification



- Body phenotype deviation scores alone allow differentiation of individuals with neuropsychiatric disorders from healthy individuals.

Tian et al., 2023 *JAMA Psychiatry*

Diagnostic vs transdiagnostic classification



- Brain phenotype deviation scores enable more accurate differentiation between distinct neuropsychiatric diagnoses.

Tian et al., 2023 *JAMA Psychiatry*

Summary

Research

JAMA Psychiatry | Original Investigation

Evaluation of Brain-Body Health in Individuals With Common Neuropsychiatric Disorders

Ye Ella Tian, MBBS, PhD; Maria A. Di Biase, PhD; Philip E. Mosley, MD, PhD; Michelle K. Lupton, PhD; Ying Xia, PhD; Jurgen Fripp, PhD; Michael Breakspear, MD, PhD; Vanessa Cropley, PhD; Andrew Zalesky, PhD

- Different neuropsychiatric disorders possess distinct fingerprints of poor brain and body health profile.
- Individuals diagnosed with neuropsychiatric disorders (SCZ, BD, DEP, GAD, DEM) are not only characterized by deviations from normative references ranges for brain phenotypes, but also present considerably poorer physical health across multiple body systems compared to their healthy peers.
- Poor physical health was a more pronounced manifestation of neuropsychiatric illness than brain health.
- Brain phenotypes enabled more accurate differentiation between pairs of neuropsychiatric diagnoses.

Acknowledgment

Characterizing brain-body relationships using normative modeling

Ye Ella Tian, PhD

NHMRC Research Fellow
Department of Psychiatry
The University of Melbourne

ye.tian2@unimelb.edu.au
@yetianmed

Collaborators
Andrew Zalesky
Vanessa Cropley
Michael Breakspear
Anrea Maier
Nicola Lautenschlager
Maria Di Biase
Philip Mosley
Michelle Lupton
Ying Xia
Jurgen Fripp

Australian Government
National Health and Medical Research Council