

Proteomic Aging Clocks and Incident Mild Cognitive Impairment and Dementia in Older Women

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INTRODUCTION

- Chronological age is a strong predictor of chronic diseases, including mild cognitive impairment (MCI) and dementia
- Organ-specific biological age, predicted from proteomic biomarkers, links aging with molecular changes that improve our understanding of disease etiology and mechanisms
- Aim: To estimate organ-specific biological age clocks and assess their associations with incident MCI and dementia in the Women Health Initiative Memory Study (WHIMS)

METHODS

- Setting: 39 clinical sites in the United States, 1996-1999, nested case-control from a cohort of N=7479 postmenopausal women
- Participants: N= 2790 (858 with MCI or dementia)
- Measurements
  - Outcome: Time to MCI/Dementia (clinically adjudicated)
  - Exposure: AGE GAP, estimated from SomaScan 11K, is the difference between biological age and the mean biological age of those with similar chronological age<sup>1</sup>
  - Covariates: chronological age, race, education, diabetes, hypertension, smoking, eGFR
- Analysis
  - Estimate AGE GAP from Python ORGANAGE function
  - Weighted Cox’s proportional hazards model to estimate the association of organ-specific AGE GAP with MCI/dementia

RESULTS

- Distribution of AGE GAP centers around zero, with the standard deviation varying from 2 to 5 years
- Organ-specific AGE GAP estimate of brain was correlated with that of liver, organismal, and conventional clocks
- AGE GAP of organ artery, brain, heart, immune, intestine, pancreas, organismal, and conventional was associated with the incidence of MCI or dementia
- Per one standard deviation of AGE GAP, the hazard of MCI or dementia was increased by 2% (kidney) to 19% (heart)

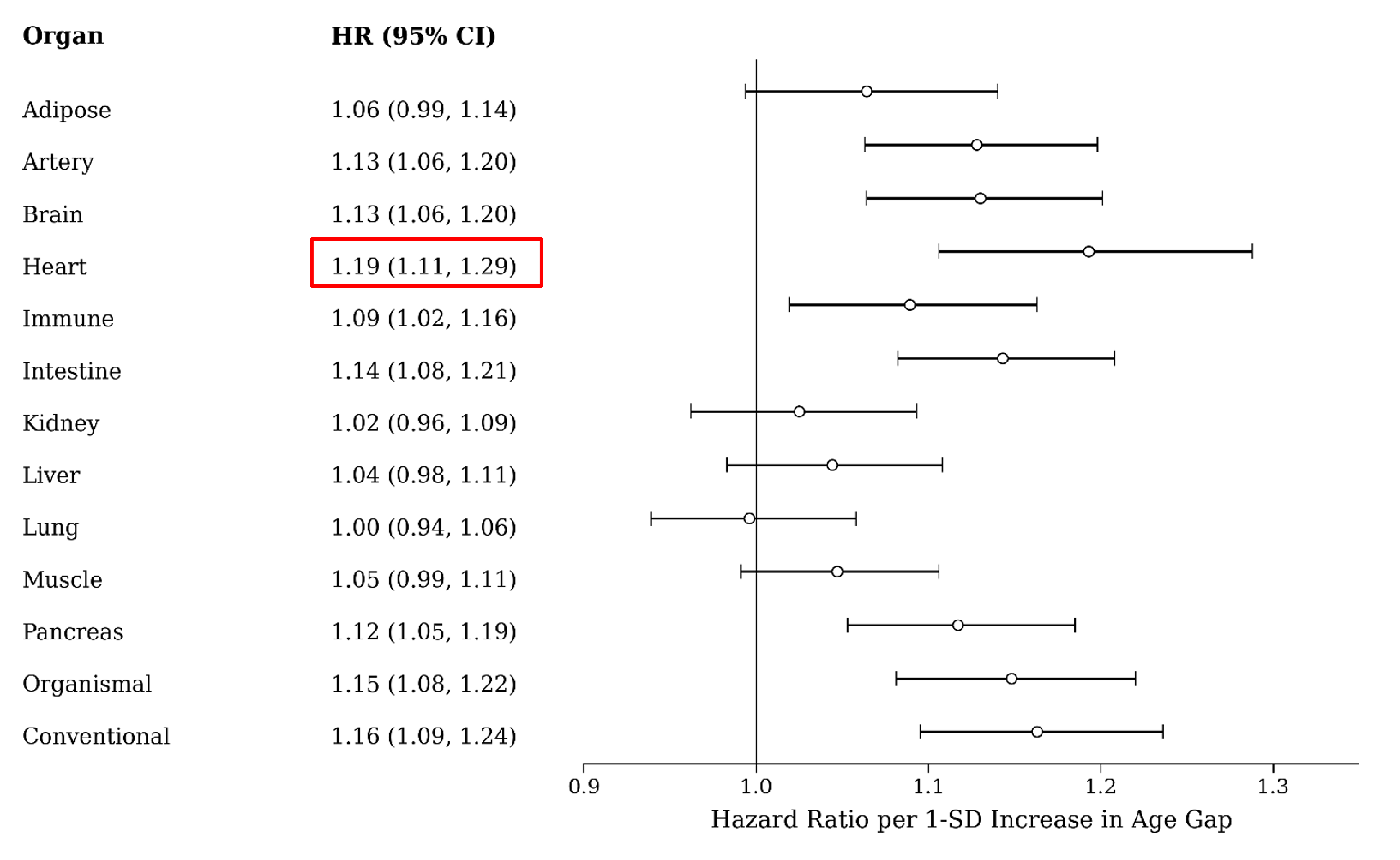
DISCUSSION

- Organ-specific aging clocks were associated with MCI or dementia, and the associations varied by organ
- The heart, brain, artery, and intestine AGE GAP showed the largest magnitudes of association with MCI or dementia

FINANCIAL DISCLOSURE

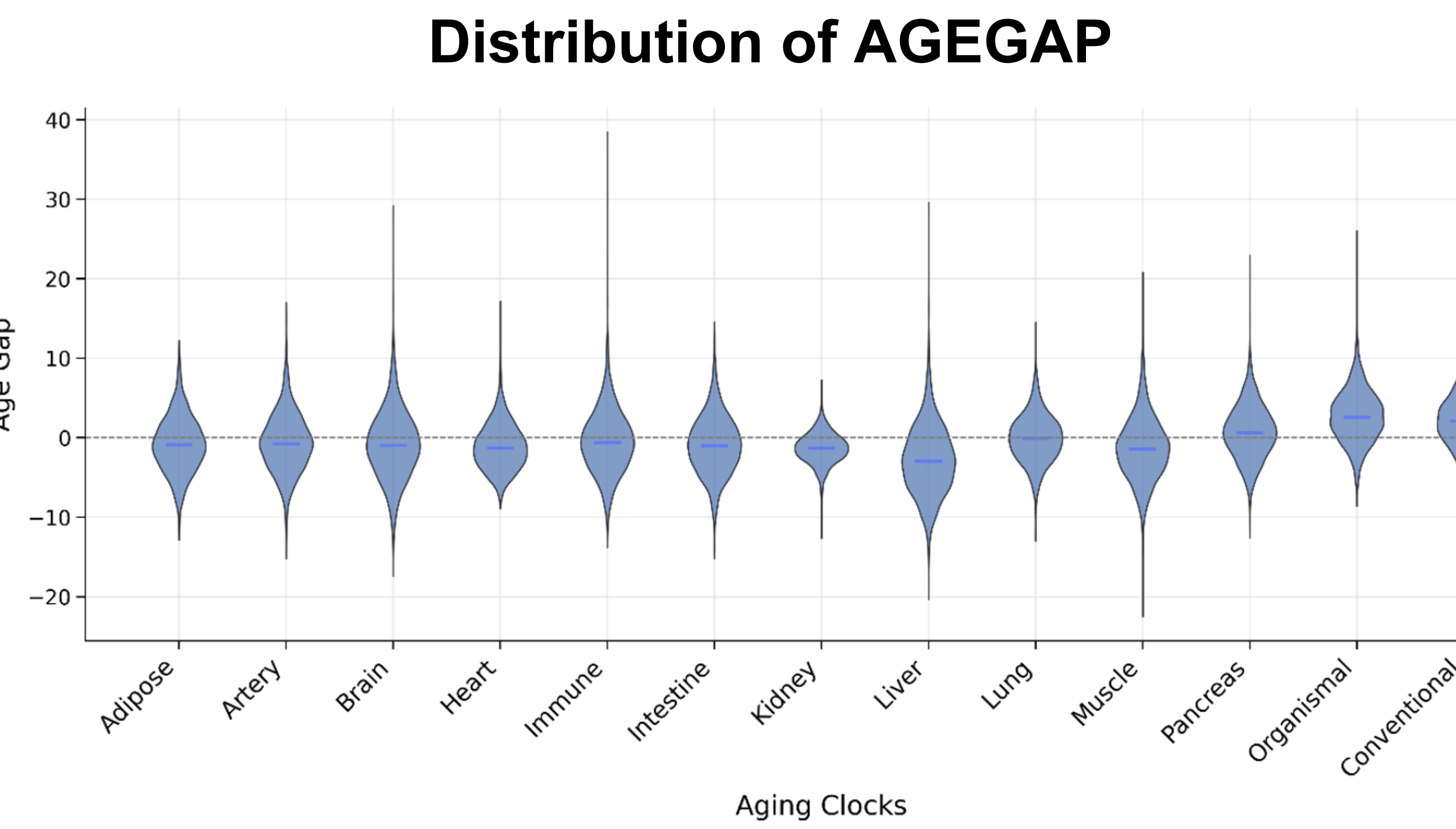
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Eight out of 13 organ-specific proteomic clocks were associated with incident MCI or dementia, increasing disease risk by up to 19% per 3 years of AGE GAP



Clinical Implications

Accelerated biological aging across multiple body organs, including the artery, heart, brain, and intestine, was associated with incident MCI/dementia among older women. These findings suggest that multisystem biological aging, especially in the cardiovascular system, may increase the risk of cognitive impairment.



Patient Characteristics

| Characteristic        | Mean (SD) or N(%) |
|-----------------------|-------------------|
| Age                   | 69.9 (3.8)        |
| White                 | 2026 (74%)        |
| BMI                   | 28.6 (5.6)        |
| Current Smoker        | 148 (5.4%)        |
| College Graduate      | 870 (31%)         |
| Diabetes              | 191 (7%)          |
| Hypertension          | 1960 (71%)        |
| eGFR (ml/min/1.73 m²) | 83.7 (13.5)       |
| APOE ε4 carrier       | 488 (27%)         |

<sup>1</sup>Oh et al.. Organ aging signatures in the plasma proteome track health and disease. Nature. 2023 Dec 7;624(7990):164-72.