Do cardiovascular, metabolic, or inflammatory risk factors relate to brain age in late life?

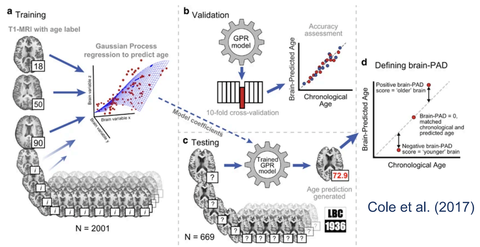
Thomas E. Kraynak[1,2], Helmet T. Karim[2], Carmen Andreescu[2], Caterina Rosano[1]

Departments of [1]Epidemiology and [2]Psychiatry, University of Pittsburgh

Background

- 'Brain age' can be estimated using patterns of brain morphology measured with structural MRI and used in cross-validated models to predict chronological age (Fig 1a-c).
- Having a brain age 'older' than chronological age relates to risk for cognitive decline and Alzheimer's Disease (Fig 1d).

Fig 1



Cole et al. (2017)

- Having elevated cardiovascular, metabolic, and inflammatory risk factors is associated with 'greater' brain age in midlife.
- **Open question:** the importance of these factors on predictions of brain aging in late life are not well understood.
- **Current study:** test cross-sectional and longitudinal associations of cardiovascular, metabolic, and inflammatory risk factors (blood pressure, dyslipidemia, adiposity, insulin resistance, systemic inflammation) with predictions of MRI-derived 'brain age' in a cohort of community-dwelling older adults.

Participants

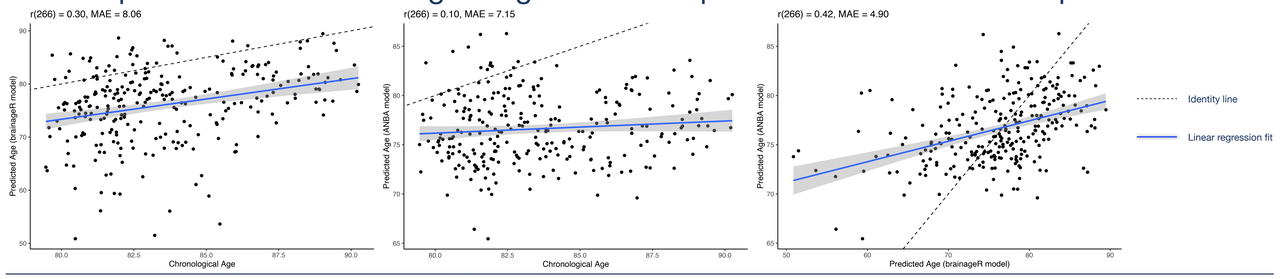
- Cohort: Pittsburgh Healthy Brain Project, a sub-study of the Health Aging and Body Composition (HealthABC) study, originally recruited at age 70-79 in 2 sites, followed annually
- N = 315 Health ABC participants underwent MRI in year 10, 11, or 12
- Inclusion criteria: no assistive devices for walking, eligible for MR scanning, had a mobility measure on the previous visit, no history of neurological or psychological illnesses
- Analytic N = 268: age 78-90; 156 women and 112 men; 160 whites and 108 blacks
- Follow-up MRIs in 245 participants M(SD) = 3.28(0.47), range 2.32 to 4.98 years later

Procedure

- MRI Preprocessing: tissue segmentation, normalization to MNI space (SPM12)
- Apply 2 validated models of brain age:
  - brainageR (Cole et al. 2017): trained on N = 3377, age range 18-92
  - Amyloid Negative Brain Age (ANBA) (Ly et al . 2020): trained on N = 1256, age range 28-85, with and without amyloid pathology
- Examine prediction accuracy and consistency
- Test for sex and race differences in brain age predictions
- Test associations of brain age predictions with cardiovascular, metabolic, inflammatory risk factors

Results

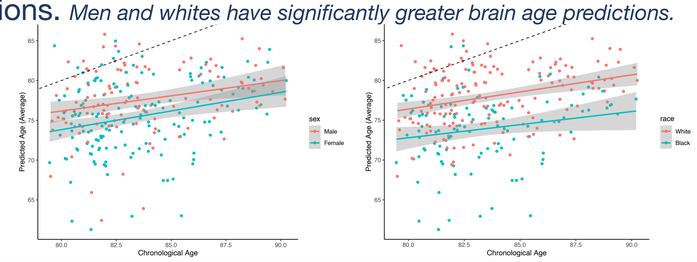
Model predictions of chronological age and correspondence between model predictions



Sex and race differences in model predictions. *Men and whites have significantly greater brain age predictions.*

Standardized beta (β) and p-values from multivariable regressions

	brainageR	ANBA	Average
Age	**0.23 (.001)**	0.04 (.571)	**0.19 (.004)**
Sex	**-0.32 (.005)**	-0.23 (.068)	**-0.33 (.003)**
Race	**-0.80 (<.001)**	**-0.53 (<.001)**	**-0.82 (<.001)**



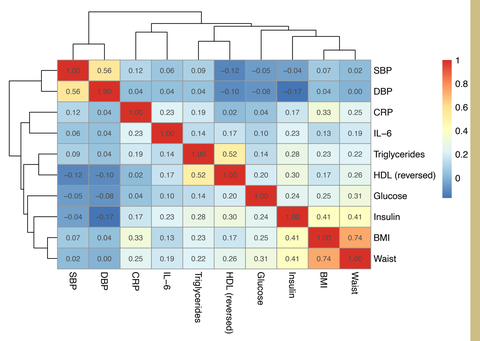
Associations of brain age predictions with cardiovascular, metabolic, inflammatory risk

*Standardized betas (**β**) and p-values from multivariable regressions accounting for chronological age, sex, race, education, medication use, smoking status, image quality*

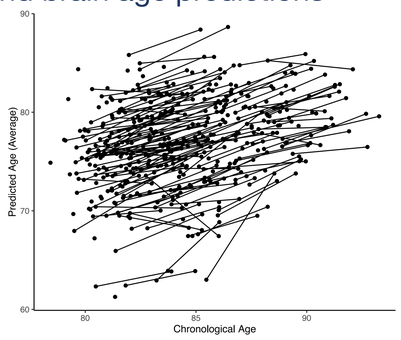
		Descriptive Statistics M(SD)	Association with brain age β (p-value)		
			brainageR	ANBA	Average
Blood pressure	Systolic blood pressure (mmHg)	135.0 (19.0)	.04 (.459)	.05 (.380)	.05 (.341)
	Diastolic blood pressure (mmHg)	70.3 (10.4)	.03 (.534)	.04 (.540)	.04 (.456)
Dyslipidemia	Triglycerides (mg/dL)	117 (53.7)	-.04 (.432)	**.12 (.048)**	.01 (.823)
	High-density lipoprotein (mg/dL)	56.5 (16.4)	-.02 (.754)	**-.22 (.001)**	-.10 (.104)
Insulin resistance	Glucose (mg/dL)	97.8 (22.0)	.07 (.215)	.10 (.122)	.09 (.100)
	Insulin (mg/dL)	10.3 (8.9)	-.03 (.652)	.03 (.631)	-.01 (.885)
Adiposity	Body mass index (kg/m^2)	27.2 (4.4)	-.07 (.214)	-.00 (.998)	-.05 (.336)
	Waist circumference (cm)	99.3 (12.2)	-.01 (.784)	-.02 (.796)	-.02 (.749)
Inflammation	Interleukin-6 (pg/mL)	3.4 (2.4)	**.11 (.042)**	**.12 (.049)**	**.14 (.016)**
	C-reactive protein (ng/mL)	4.0 (6.1)	-.02 (.769)	-.05 (.425)	-.03 (.567)

Covariance structure of risk factor indicators

Hierarchical clustering analysis



Longitudinal changes in chronological age and brain age predictions



Associations of baseline risk factors and longitudinal brain age predictions

Standardized beta (β) and p-values from mixed effect models (time x risk factor, fixed intercept, fixed slope)

Blood pressure	SBP (mmHg)	.01 (.409)
	DBP (mmHg)	-.01 (.620)
Dyslipidemia	Triglycerides (mg/dL)	.02 (.231)
	HDL (mg/dL)	.01 (.570)
Insulin resistance	Glucose (mg/dL)	-.00 (.931)
	Insulin (mg/dL)	**.14 (.050)**
Adiposity	BMI (kg/m^2)	-.02 (.214)
	Waist circumference (cm)	.01 (.702)
Inflammation	IL-6 (pg/mL)	.00 (.769)
	CRP (ng/mL)	**-.04 (.014)**

Summary & Discussion

- Applied validated & published models of 'brain age' to individual structural MRI to predict age.
- Model predictions were modest in effect size; most participants (>88%) showed 'younger' brains.
- Significant sex and race differences: men showed greater brain age than women (consistent with literature) yet blacks showed lower brain age than whites (inconsistent with literature).
- Interleukin-6 (marker of systemic inflammation) related to greater brain age in both models.
- Greater triglycerides and lower HDL related to greater brain age in ANDA model.
- Blood pressure, insulin resistance, and adiposity not significantly related to brain age predictions, in contrast to midlife literature.
- Risk factor indicators showed acceptable covariance structure, with exception of blood pressure.
- Greater insulin concentration and lower C-reactive protein associated with greater longitudinal changes in brain age predictions.

Future Directions

- Examine associations of brain age with preceding (i.e., before year-10 visit) risk factors.
- Identify other factors (e.g., psychosocial) related to 'resilient' brain aging in this cohort.
- Explore relationships between brain aging, body composition, and mobility in this cohort.

References

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Contact

tekraynak@pitt.edu