DNA Methylation and Epigenetic Age Acceleration are Associated with Frailty in Postmenopausal Women

Shivam Chadha[1,2] (chadhas1@myumanitoba.ca), Benjamin Bydak [2,3], James Ducas [4], Todd A. Duhamel [3,4], Ayesha Saleem [2,3], Meaghan J Jones [1,2]

Abstract

Purpose

- Frailty and healthy aging are understudied in postmenopausal women.
- DNA methylation (DNAm) can predict epigenetic age (DNAmAge), linked to physiological dysregulation preceding disease and mortality.

Results

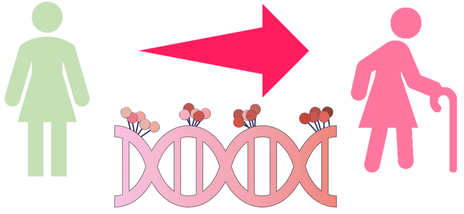
- We found significant (FDR < 0.05, logFC > 0.01) changes in DNAm at 7 loci associated with 4 genes.
  - Blood lipids, body composition, and self-care contributed to frailty-related DNAm most .
- DNAmAge was highly correlated (r = 0.712, $p < 0.00001$) with chronological age.
  - Frail participants aged marginally faster ($p = 0.0807$, $d = 0.476$) than robust participants.
  - Faster agers were 43% more frail than slow agers ($p = 0.0332$, $d = 0.585$).

Conclusions

- **DNAmAge is associated with frailty through a decrease in psychosocial wellness and changes in metabolism.**
- Although underlying mechanism is still not fully understood, **physical activity and mental wellness for faster agers can continue to be targeted to reduce frailty in later life.**

Background

Previous research shows DNA methylation (DNAm) changes widely with age, **however…**



few studies link DNAm changes with frailty **specifically in women**. Additionally, **frailty index components have not been studied in association with frailty related DNAm.**

Study population

- 1000+ postmenopausal women recruited from Winnipeg, MB between 2018-2020 as part of WARMHearts
- This study uses a 56 participant sample selected during recruitment, approved by UofM Bannatyne REB (HS22576)

Figure 1. Study population (N=56) characteristics. The participants were selected using propensity matching to balance for common confounders in DNA methylation studies, including tobacco, age, and income.

Methods

Whole blood DNAm

- Illumina EPIC array, preprocessing/normalization using *minfi* and *wateRmelon*
- Batch correction using *ComBat*, unaccounted variance with *sva*
- *FlowSortedBloodEPIC* used to estimate cell type proportions

Epigenetic Age

- DNAmPhenoAge clock by Levine et al. 2018
- Age acceleration calculated as the residual of DNAmPhenoAge regressed on chronological age

Frailty

- WARMHearts frailty index (FI) capturing 42 deficiencies associated with aging
- Robust: FI < 0.1; Frail: FI > 0.2

Statistical analysis

- Linear regression to assess frailty-DNAm relationship
- 2 sided independent samples t-test for comparing cell types and epigenetic age acceleration
- Step-back multivariable regression with Akaike Information Criterion to identify frailty deficiencies driving DNAm and epigenetic age

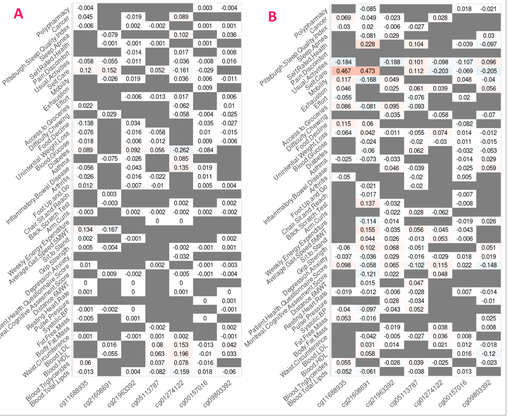
Results

Frailty is associated with 7 DNAm loci across 4 genes

Table 1. EWAS identified differentially methylated probes including location and gene association. Some probes have not been linked with genes while other probes do not necessarily predict the gene expression outcome. That said, probes located in CpG islands of promoter regions (including shelves) tend to have inverse relationships with expression.

	P-value	FDR	Δβ	Chromosome	Location	Gene Name
cg01274122	3.86E-07	0.000773	0.065739	Chr8	Island	MFHAS1
cg21963392	5.24E-07	0.001155	-0.03101	chrX	Open Sea	
cg00157016	1.42E-06	0.003295	0.012969	Chr2	North Shore	PFN4
cg21608691	1.78E-06	0.004723	-0.08621	Chr7	South Shore	PTPRN2
cg05113787	1.70E-06	0.004723	-0.04015	chr20	Open Sea	
cg09803392	3.52E-06	0.013539	-0.03468	chr11	Open Sea	
cg11688935	6.59E-06	0.034487	-0.05522	chr10	Open Sea	LRRC20

Figure 2. Self Care and Activities of Daily Living like chewing have the largest effect on frailty-related DNAm, along with blood lipids and body composition. While **A** shows the absolute effect of each frailty index category on the CpG, **B** uses the deficiency score (ranging from 0-1) in each domain to give a scaled representation.



DNAmAge is a better predictor of frailty than frailty is of DNAmAge

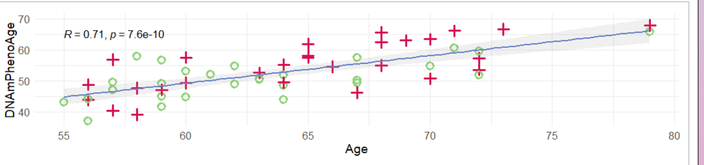
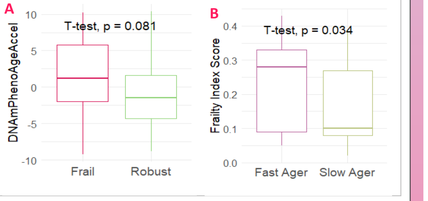


Figure 3. DNAmPhenoAge is strongly correlated with chronological age. + and O indicate frail and robust participants, respectively. Participants below the trend line are considered Slow Agers, while those above are considered Fast Agers.

Figure 4. Age acceleration is a better predictor of frailty than vice versa. In **A** we only see a marginal effect comparing Age acceleration between Frail and Robust. However, comparing frailty scores in **B** shows a 43% increase for those above the trend line in Figure 2.



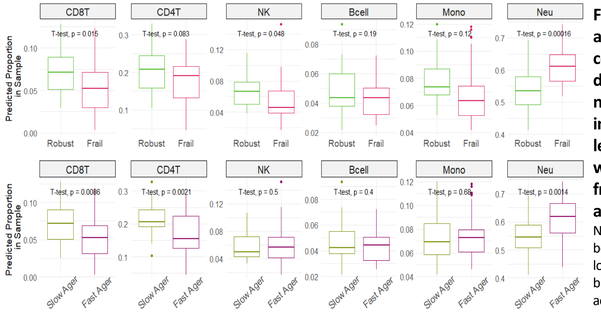


Figure 5. CD8 and CD4 T-cells decrease and neutrophils increase in % leukocyte with frailty/age acceleration. NK cells seem to be significantly lower with frailty, but not with age acceleration.

Conclusions

- Frailty is associated with 7 DNAm loci in an income and age matched sample, most strongly associated with declines in metabolic and psychosocial well being.
- Epigenetic age acceleration can predict frailty more accurately than the other way around.
- Blood distribution decreases in CD4 and CD8 T-cells, and increases in neutrophils are indicative of immuno-senescence with age acceleration and frailty.

Affiliations

1. Department of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, MB, Canada
2. Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada
3. Faculty of Kinesiology and Recreation Management, University of Manitoba, Winnipeg, MB, Canada
4. Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

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