

Accelerated PhenoAge in Midlife is Associated with Long-Term Neurodegeneration and Predicts Cognitive Decline in Middle-Aged Adults



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BACKGROUND

RESULTS

- Phenotypic Age (**PhenoAge**):
 - Is a multi-system blood-based aging measure which uses common clinical tests of glucose metabolism, inflammation, and kidney and liver function¹
 - Is calculated as risk of 10-year aging-related mortality based on 9 blood-based health markers and chronological age
 - Assesses whether a person is biologically and physiologically younger or older than expected by their chronological age
- Higher PhenoAge is associated with increased risk of disability, age-related morbidities, and all-cause mortality¹⁻⁴
- Its associations with neurodegeneration and early cognitive changes in midlife are less understood.

AIMS

The aim of this study was to determine whether accelerated PhenoAge was associated with long-term neurodegeneration and cognitive decline in middle-aged to older adults

METHODS

- N=1,496 (54% women; mean age 48years; Table 1) Beaver Dam Offspring Study-Neurocognitive Aging Study (BOSS-NCAS) participants
- BOSS-NCAS is a longitudinal sensory and cognitive aging study in previous participants of the Beaver Dam Offspring Study (BOSS)⁵
- The trail-making test B (**TMT-B**) was conducted at baseline, 5-yr and 10-yr follow-up.^{6,7} Cognitive decline was defined as being among the people of the cohort with the 10% most TMT-B decline.
- Serum neurofilament light chain (NfL) levels were measured at baseline, 5-yr and 10-yr follow-up by the Quanterix Simoa Accelerator Laboratory (Billerica, MA, USA).
- Baseline clinical blood markers were measured: albumin, creatinine, hemoglobin A1C, log c-reactive protein, lymphocyte %, mean corpuscular (cell) volume, red cell distribution width, alkaline phosphatase, and white blood cell count.

- Accelerated PhenoAge (**PhenoAgeAccel**) was the residual of:
 $PhenoAge_i = \beta_0 + \beta_1(Age_i) + \epsilon_{ij}$
- We used linear mixed-effects models (LMEM) to determine the effect of baseline PhenoAgeAccel on log-NfL levels over time (wave: baseline, 5-yr and 10-yr follow-up):

$$\text{Log}(NfL_{ij}) = \beta_0 + \beta_1(PhenoAgeAccel_{i0}) + \beta_2(Wave_{ij}) + \beta_3(PhenoAgeAccel_{i0} \times Wave_{ij}) + \gamma_i + \epsilon_{ij}$$

- We used a logistic regression model of PhenoAgeAccel on incidence of cognitive decline

$$\text{Logit}\{P(\text{Decline}_i = 1)\} = \beta_0 + \beta_1(PhenoAgeAccel_i) + \gamma_i$$



Table 1. Baseline Characteristics of the Study Sample

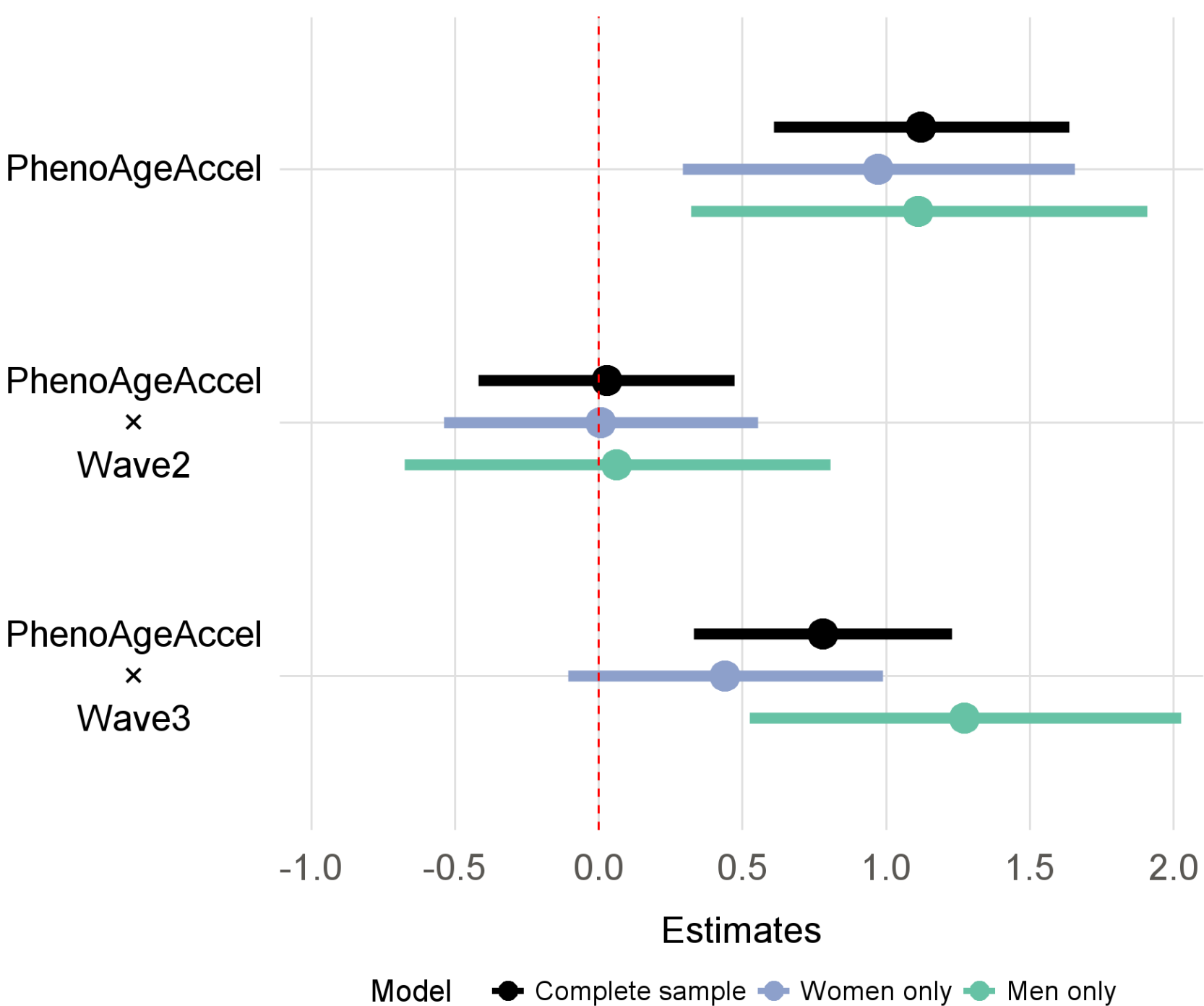
	Total; N=1,496 Mean(SD) or N(%)	Women; N=806 Mean(SD) or N(%)	Men; N=690 Mean(SD) or N(%)	Sex Difference
Age (years)	49.2 (9.4)	48.9 (9.5)	49.5 (9.2)	$p=.22$
Education	456 (30.5%)	244 (30.3%)	212 (30.7%)	$p=.88$
0-12 years	519 (34.7%)	284 (35.2%)	235 (34.1%)	
13-15 years	511 (34.2%)	272 (33.8%)	239 (34.6%)	
16+ years				
Body Mass Index (BMI)	30.3 (6.5)	30.0 (7.1)	30.7 (5.7)	$p=.03$
History of kidney disease	13 (0.9%)	6 (0.7%)	7 (1.0%)	$p=.57$
PhenoAge (years)	44.8 (10.0)	44.5 (10.0)	45.2 (10.0)	$p=.16$
PhenoAgeAccel (years)	-0.2 (4.0)	-0.2 (4.2)	-0.2 (3.8)	$p=.50$
Serum NfL level (pg/mL)	11.1 (7.6)	11.0 (5.7)	11.2 (9.4)	$p=.64$
Trail-Making Test B time (s)	65.5 (27.6)	62.3 (26.5)	69.1 (28.5)	$p<.0001$

Note: Beaver Dam Offspring Study (BOSS) participants with baseline PhenoAge, and with neurofilament light chain (NfL) levels and Trail-Making Test B at baseline and 10-year follow-up were included in this study (N=1,496). Sex differences were calculated and p-values generated using two-sample t-tests for age, BMI, PhenoAge and PhenoAgeAccel, Wilcoxon rank-sum tests for serum NfL level and Trail-Making Test B time, and Pearson chi-squared tests for education and history of kidney disease.

Missingness was <1% for any variable.

SD, standard deviation; PhenoAge, 10-year aging-related mortality risk score including weighted measures of albumin, creatinine, hemoglobin A1C, log c-reactive protein, lymphocyte %, mean corpuscular (cell) volume, red cell distribution width, alkaline phosphatase, white blood cell count and chronological age; PhenoAgeAccel, Accelerated PhenoAge, defined as the residual of a linear model with chronological age as the predictor and PhenoAge as the outcome.

Fig 1. Accelerated PhenoAge and NfL over 10 years



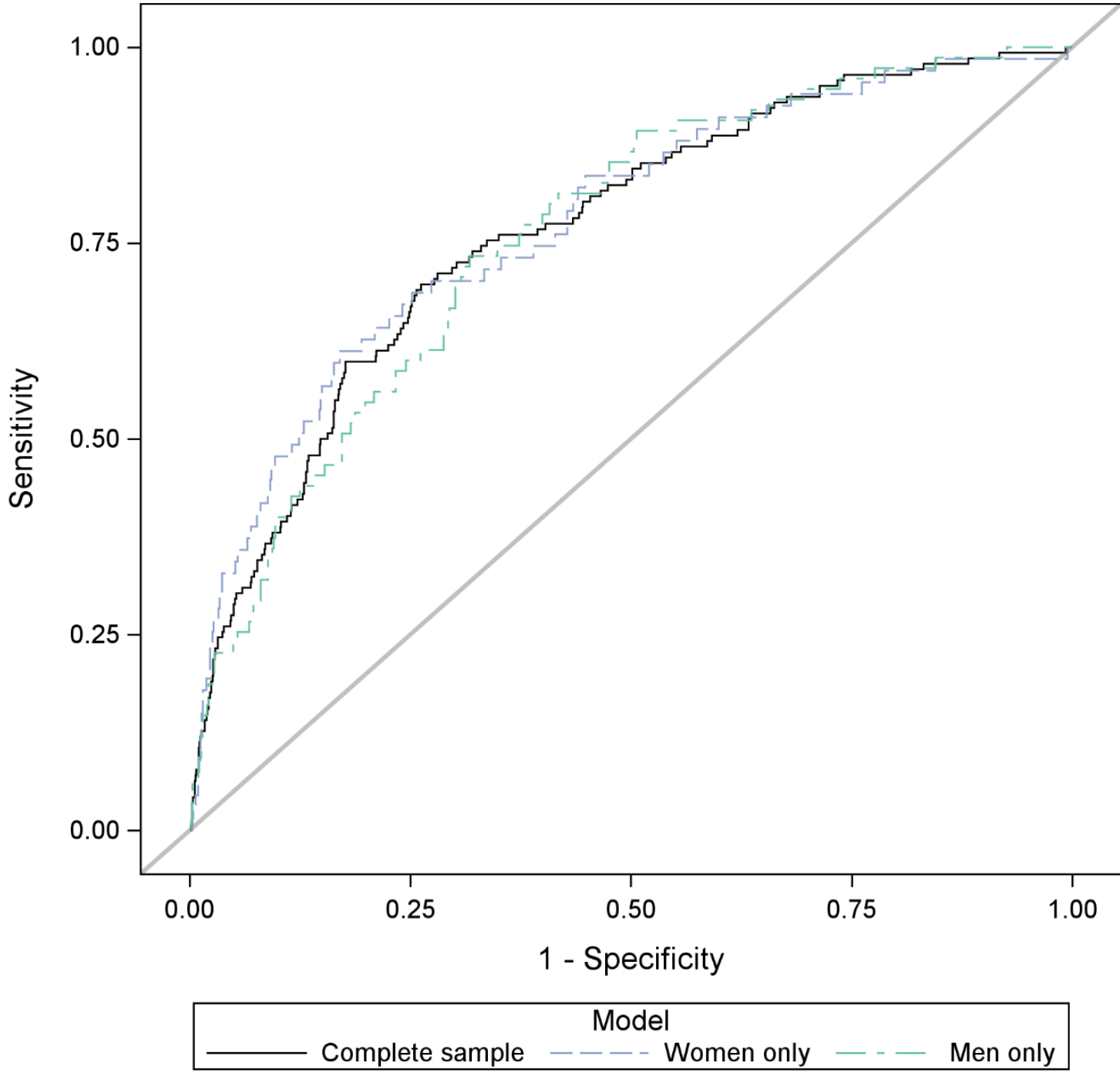
Forest plot of coefficient estimates for main and interaction effects from linear mixed-effects models (LMEM) using baseline accelerated PhenoAge (PhenoAgeAccel) and the interaction of baseline PhenoAgeAccel with exam wave (baseline, 5-yr follow-up, 10-yr follow-up) as determinants and log-transformed serum neurofilament light chain (NfL) levels as outcomes. The effect estimates represent % changes in NfL per 1-year increase in PhenoAgeAccel.

[1] LMEM in the complete sample of N=1,469 participants. The model was adjusted for random intercept, age, sex, education, body mass index and history of kidney disease.

[2] LMEM in women only (N=794). The model was adjusted for random intercept, age, education, body mass index and history of kidney disease.

[3] LMEM in men only (N=675). The model was adjusted for random intercept, age, education, body mass index and history of kidney disease.

Fig 2. Cognitive Decline Incidence ROC



Receiver operating characteristic (ROC) curves of logistic regression models on 10-yr incidence of cognitive decline with accelerated PhenoAge (PhenoAgeAccel) as determinant and adjustment for age, sex and education

[1] Complete sample: AUC=0.77[95% confidence interval 0.73,0.81].

[2] Women: AUC=0.78[0.71,0.84].

[3] Men: AUC=0.76[0.71,0.82].

With **each additional year that PhenoAge exceeded chronological age** at baseline **participants had higher baseline NfL** (complete sample: 1.14% higher, 95% Confidence Interval [0.63%,1.65%]; women:1.00%[0.33%,1.67%]; men:1.12%[0.33%,1.92%];Figure 1) and **had faster NfL increases over 10 years** (main effect+wave interaction in complete sample: 1.89% faster [1.38%,2.40%]; women:1.41%[0.73%,2.08%]; men:2.37%[1.59%,3.16%]).

The logistic model with PhenoAgeAccel, age, sex and education **predicted cognitive decline over 10 years** with an area under the curve AUC=0.77[0.73,0.81] in the complete sample (Figure 2).

CONCLUSIONS

Accelerated PhenoAge in midlife was associated with 10-year increases in NfL, overall and in men, and predicted cognitive decline over 10 years with good AUCs

- Longer follow-up will be needed to investigate sex differences further and to determine whether PhenoAge might be predictive of the onset of cognitive impairment later in life
- If confirmed, PhenoAge could become a cost-effective marker of cognitive decline and dementia and might help identify at-risk individuals early. This could inform targeted prevention and treatment methods to promote healthy brain aging

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