RESEARCH ARTICLE

Midlife sensory and motor functions improve prediction of blood-based measures of neurodegeneration and Alzheimer's disease in late middle-age

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Abstract

INTRODUCTION: We assessed whether midlife sensory and motor functions added to prediction models using the Cardiovascular Risk Factors, Aging, and Incidence of Dementia Score (CAIDE) and Framingham Risk Score (FRS) improve risk predictions of 10-year changes in biomarkers of neurodegeneration and Alzheimer's disease.

METHODS: Longitudinal data of $N = 1529$ (mean age 49 years) Beaver Dam Offspring Study participants from baseline, 5-year, and 10-year follow-up were included. We tested whether including baseline sensory (hearing, vision, olfactory) impairment and motor function measures improves CAIDE or FRS risk predictions of 10-year incidence of biomarker positivity of serum-based neurofilament light chain (NfL) and amyloid beta $(A\beta)_{42}/A\beta_{40}$ using logistic regression.

RESULTS: Adding sensory and motor measures to CAIDE-only and FRS-only models significantly improved NfL and $A\beta_{42}/A\beta_{40}$ positivity predictions in adults above the age of 55.

DISCUSSION: Including midlife sensory and motor function improved long-term biomarker positivity predictions. Non-invasive sensory and motor assessments could contribute to cost-effective screening tools that identify individuals at risk for neurodegeneration early to target interventions and preventions.

Highlights

- Sensory and motor measures improve risk prediction models of neurodegenerative biomarkers
- Sensory and motor measures improve risk prediction models of AD biomarkers
- Prediction improvements were strongest in late midlife (adults >55 years of age)
- Sensory and motor assessments may help identify high-risk individuals early

1 | INTRODUCTION

Alzheimer's disease and related dementias (ADRD) are highly prevalent in older adults and a public health concern.[1,2] Alzheimer's disease (AD) has a decades-long preclinical stage: The first signs of pathologic changes, including amyloid pathology accumulation in the brain and simultaneous progression of neurodegeneration, occur as early as in midlife.[3] Early identification of people at higher risk for dementia may allow time to initiate lifestyle changes, or future early prevention or intervention methods to slow disease progression or prevent ADRD. In the search for early markers of neurodegeneration and AD, research on blood-based measures has been emerging, given their advantages in accessibility and cost-effectiveness. Ultrasensitive assays using single molecule array (SIMOA) technology have been developed that can reliably measure concentrations of biomarkers related to AD and neurodegeneration in blood, including amyloid beta ($A\beta$)$_{40}$ and $A\beta_{42}$ and neurofilament light chain (NfL).[4] Levels of these markers have been shown to be associated with neurodegenerative processes, AD brain pathology, and cognitive symptoms, and thus show promise to becoming established as useful early indicators of later brain aging.[5–8]

Various risk factors for ADRD have been studied previously. Sex differences and education effects are widely accepted risk factors for ADRD. Additionally, several cardiovascular disease risk factors such as smoking,[9–11] physical inactivity,[10–12] obesity,[10,13] diabetes,[9,11,14] hypertension,[9,14] and high cholesterol[14] have also been associated with increased risk for developing ADRD. Thus, two well-established dementia risk prediction scores are based on cardiovascular risk factors. These are the Cardiovascular Risk Factors, Aging, and Incidence of Dementia Score (CAIDE) and the Framingham Risk Score (FRS).[15] The CAIDE was developed using data from the Cardiovascular Risk Factor, Aging and Dementia Study, with the objective to predict 20-year dementia risk based on factors associated with cardiovascular disease.[15,16] The FRS was developed using data from the Framingham Heart Study and Framingham Offspring Study. The original purpose of the FRS was to assess risk of cardiovascular disease and cardiovascular disease events. More recently, the FRS has also shown to be useful for risk predictions of cognition and dementia.[17,18]

Current dementia prediction scores cannot perfectly predict ADRD onset.[15,18] Adding information to such scores using additional easy to measure predictors could improve our ability to identify high-risk individuals. Since cognitive changes and dementia symptoms occur later in the disease process,[3] blood-based biomarkers could be utilized as early proxy outcomes.[5,19] Currently, research on predictors of these outcomes is scarce. Sensory and motor declines commonly occur in aging adults and have been previously associated with the development of cognitive impairment and decline, making them potential candidates to improve risk predictions.[11,20–25] Importantly, sensory and motor assessments are easy to obtain, inexpensive, and non-invasive. However, sensory and motor assessments have not yet been established in early risk prediction algorithms.

This study aimed to assess whether midlife sensory and motor function can improve risk prediction of 10-year incidence of positivity in biomarkers of neurodegeneration and AD, when added to risk prediction models using the CAIDE or FRS.

2 | METHODS

2.1 | Study population

Data included in this study were from participants in the Beaver Dam Offspring Study (BOSS), a longitudinal study of sensory and cognitive aging in the adult offspring of the population-based Epidemiology of Hearing Loss Study.[26,27] Participants in the baseline BOSS (2005 to 2008) were 21 to 84 years of age and 55% were women.[26] Follow-up exams occurred after 5 (2010 to 2013) and 10 years (2015 to 2017). Study examinations were conducted by trained examiners following standardized protocols including measures of sensory and motor function; vascular health; a blood draw; and demographic, behavioral, and medical history questionnaires.[11,28,29] Study protocols were approved by the Health Sciences Institutional Review Board of the University of Wisconsin with written informed consent from all participants prior to each examination.

For this investigation, we included $N = 1529$ participants, who had questionnaire and examination data and serum specimen available at all three study waves, baseline (2005 to 2008), 5-year follow-up (2010 to 2013), and 10-year follow-up (2015 to 2018).[19,30] More study details were previously published.[30] The sample of this study was similar in baseline characteristics to the complete baseline BOSS cohort.[30]

2.2 | Outcomes: Measurement of $A\beta_{40}$, $A\beta_{42}$, and NfL

The blood collection, processing, and storage protocols were similar across phases and were in accordance with currently recommended protocols for measuring $A\beta_{40}$, $A\beta_{42}$, and NfL in blood.[31,32] Briefly, Quanterix Simoa Accelerator Laboratory (Billerica, MA, USA) used the Simoa Neurology 3-Plex A Advantage Kit to measure $A\beta40$ and $A\beta42$ and the Simoa NF-light Advantage Kit to measure NfL in serum samples from baseline, 5-, and 10-year follow-up examinations, stored at $-80°C$ until the time of assay.[33,34] More details and validations have been previously published.[30,35] The $A\beta_{42}/A\beta_{40}$ ratio was calculated by dividing the concentration of $A\beta_{42}$ by the concentration of $A\beta_{40}$ to normalize $A\beta_{42}$ for the total amount of $A\beta$ peptides that are present in the specimen.[36] The $A\beta_{42}/A\beta_{40}$ ratio has previously shown better performance for AD diagnostics compared to $A\beta_{42}$ alone.[36] A lower ratio represents more pathology. A natural log-transformation of NfL was used in analyses to account for the skewed distribution in this population. A higher value represents more pathology. As clinical cutpoints for serum levels of $A\beta$ ($A\beta_{42}/A\beta_{40}$) and general neurodegeneration (NfL) positivity are not yet established, we created study-specific cutpoints for analysis in the current investigation, which were in line with previous work.[37,38] The cutpoint for being $A\beta_{42}/A\beta_{40}$ positive was a ratio below 0.051. NfL blood levels vary largely by age, which has been shown previously by other groups and us.[30,38,39] Consistent with work by Hviid et al.,[38] serum positivity for NfL was thus defined by having an NfL level (pg/mL) above the age-specific cutpoint given the participants age at each examination phase: 20 to 29 years, 9.83; 30 to 39 years, 12.88; 40 to 49 years, 16.89; 50 to 59 years, 22.17; and 60+ years, 29.10. More details on the cut-off generation can be found in Appendix A.

2.3 | Sensory and motor assessments

Hearing function was measured using pure-tone audiometry, and hearing impairment was defined as a pure-tone average (PTA) of the thresholds at 0.5, 1, 2, and 4 kHz greater than 25 decibels hearing level in either ear.[40] Visual function was assessed by measuring contrast sensitivity using Pelli-Robson letter charts. Impairment was defined as contrast sensitivity of <1.55 log units in the worse eye.[29] The San Diego Odor Identification Test was used to measure olfactory function with impairment defined as identifying fewer than six out of eight odorants correctly.[41]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (eg, PubMed) sources. Previous prediction models of dementia have focused on education and cardiovascular risk factors. Several studies have linked sensory and motor changes to cognitive impairment and dementia. However, sensory and motor functions have not been established in risk prediction models for early changes in blood-based biomarkers of neurodegeneration and Alzheimer's disease (AD). Relevant citations on sensory, motor, and cognitive research, cardiovascular risk models, and blood-based biomarkers are appropriately mentioned.

2. **Interpretation**: Our findings add to the existing research, showing that sensory and motor functions may add relevant information to risk prediction models of biologically determined early changes along the AD and neurodegenerative spectrum.

3. **Future directions**: Importantly, sensory and motor functions can be assessed reliably, are cost-effective and non-invasive, and could thus serve as a practical addition for future prediction models to identify high-risk individuals early to target future intervention and prevention strategies.

A hand dynamometer (model 78010, Lafayette Instruments, Lafayette, IN, USA) was used to measure the grip strength (kilograms) of the dominant hand. Participants performed the measure twice, while standing. The average of the two measures was used in analyses.[30] The Grooved Pegboard Test is considered to measure fine motor and psychomotor function. The test was performed with the dominant hand, and the time in seconds to correctly place 25 slotted pegs was used as the score (Lafayette Instruments, Lafayette, IN, USA).[30] The Medical Outcomes Study Short Form Health Survey (SF-36) was administered as a questionnaire. The SF-36 physical function scale is considered to assess mobility, locomotion, and endurance.[30]

2.4 | Other variables

Years of education, smoking history, blood pressure medication use, and frequency of exercise (long enough to work up a sweat) were obtained by questionnaire. Height and weight were measured. Body mass index (BMI) was calculated as kg/m^2. Blood pressure was measured three times using a Dinamap Procare 100 (GE Medical Systems, Milwaukee, WI) with a 1-minute rest interval between measures. The average of the second and third readings was used as the blood pressure.[28] Total and high-density lipoprotein (HDL) cholesterol were

measured in serum, and hemoglobin A1C (HbA1C) was measured in whole blood.[26] Participants were classified as having diabetes if they had an HbA1C of $\geq$6.5%, a physician diagnosis of diabetes, or suspected diabetes with current treatment.[28]

2.5 | Statistical analyses

We calculated the baseline CAIDE score: a summary score based on age, education, sex, systolic blood pressure, BMI, total cholesterol, and physical activity for each participant.[15] The original CAIDE scoring algorithm assigned a score of 3 for 0 to 6 years, 2 for 7 to 9 years, and 0 for $\geq$10 years of education.[15] To account for the fact that our cohort had a higher average level of education and to capture the variation in our cohort appropriately, we assigned a score of 3 for less than 12 years, a score of 2 for 12 years, and a score of 0 for more than 12 years of education, in the CAIDE calculation.

The FRS total percent risk estimate (FRS%) was developed by D'Agostino et al. and is based on sex-specific Cox proportional hazards regression models. It represents a subject-specific first cardiovascular disease event risk but has been used recently to assess risk of AD and dementia.[17,18] We calculated the baseline FRS% for each participant based on the published sex-specific weights for age, systolic blood pressure, blood pressure medication use, total and HDL cholesterol levels, smoking, and diabetes status.[17]

2.5.1 | Logistic regression models

All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). We tested whether including baseline sensory (hearing, vision, olfactory) impairment and motor function (grip strength, Grooved Pegboard, SF-36 physical function scale) improved CAIDE or FRS% risk prediction models of 10-year incidence of Aβ (Aβ_{42}/Aβ_{40}) and NfL positivity. Individuals with baseline biomarker positivity were excluded from the respective incidence models. For both biomarker outcomes, logistic regression models were used to determine the area under the receiver operating characteristic curve (AUC) for models including (1) only the CAIDE, (2) the CAIDE plus the sensory-motor function variables (sensory-motor), (3) only the FRS, and (4) FRS plus sensory-motor. All variables for sensory and motor function were added simultaneously as individual variables to the "plus sensory-motor" model: Sensory impairments (hearing, vision, olfaction) were included in models as binary variables. Given the lack of established clinical cut-offs, motor function test scores were included continuously. Because of known sex differences in performance on motor measures (grip strength, Grooved Pegboard, SF-36 physical function scale) and observed differences in motor function between men and women in this cohort, we used sex-specific scales for motor function and calculated z-scores standardized by sex.[30] These z-scores were used in regression models. We tested for significance in improvement in the AUCs between risk prediction models with and without sensory-motor variables using chi-square tests. Receiver operating

characteristic (ROC) curves are included in the Appendix B (Figures S2–S5).

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated via the classification table in Proc Logistic in SAS. (Appendix C)

To determine if there were differences in the performance of the prediction models by age or by sex, analyses were repeated stratified by age group (<55 years and 55 years and older) and by sex. Penalized logistic regression (PLR) by the Firth method was used to address any quasi-complete separation in the stratified models.[42]

3 | RESULTS

Participant baseline characteristics are shown in Table 1. Participants had a mean age of 49 years (standard deviation [SD] = 9.4) and 54% were women. Mean CAIDE was 5.2 (SD = 3.0) and mean FRS% was 9.6 (SD = 9.6). In the full cohort, there were $N = 105$ participants who were Aβ_{42}/Aβ_{40} positive and $N = 69$ who were NfL positive at baseline who were excluded from respective analyses. Over the 10-year follow-up, there were $N = 71$ (5.0%) incident cases of Aβ_{42}/Aβ_{40} and $N = 115$ (7.9%) incident cases of NfL positivity.

3.1 | Ten-year incidence of Aβ_{42}/Aβ_{40} positivity

The AUC for prediction of incident Aβ_{42}/Aβ_{40} positivity using the CAIDE score and FRS% were 0.52 and 0.55, respectively. Adding sensory and motor function to the prediction models improved the AUC of both the CAIDE and FRS% prediction models to 0.60, which was a statistically significant improvement for the CAIDE (Table 2; Appendix B Figures S2 and S3).

In stratified models, in those aged 55 years or older, the AUC of the CAIDE and FRS% prediction models improved by adding sensory and motor function, from 0.54 to 0.71 and from 0.53 to 0.69 (on a trend-level), respectively (Table 2). The AUC did not statistically significantly improve for either the CAIDE or FRS% when adding sensory and motor function to the prediction models of participants below the age of 55 years (Table 2).

In sex-stratified models, the magnitude of change in AUC for men and women was only statistically significant among men for the CAIDE model and showed a trend for improvements for the FRS% model (Table 2).

3.2 | Ten-year incidence of NfL positivity

The AUC for prediction of incident NfL positivity using the CAIDE score and FRS% were 0.68 and 0.69, respectively. Adding sensory and motor function to the prediction models improved the AUC of both the CAIDE and FRS% prediction models to 0.72, which was a statistically significant improvement for the CAIDE (Table 3; Appendix B Figures S4 and S5).

TABLE 1 Baseline participant characteristics.

Baseline Characteristic	N (%)
Age	
<47 years	615 (40.2)
47 to 53 years	437 (28.6)
>53 years	477 (31.2)
Women	828 (54.2)
Education	
<12 years	31 (2.0)
12 years	433 (28.5)
>12 years	1055 (69.5)
Systolic blood pressure > 140 mmHg	279 (18.3)
Taking blood pressure medication	340 (22.3)
Total cholesterol > 251 mg/dL	165 (10.8)
HDL cholesterol	
<35 mg/dL	187 (12.3)
35 to 44 mg/dL	448 (29.6)
45 to 49 mg/dL	222 (14.7)
50 to 59 mg/dL	348 (23.0)
≥60 mg/dL	310 (20.5)
Exercise <2 times per week	768 (50.3)
Current smoker	225 (14.7)
BMI > 30 kg/m^2	673 (44.4)
Diabetes	75 (4.9)
Hearing Impairment (PTA > 25 dB HL)	217 (14.2)
Vision impairment (CS log triplets < 1.55)	250 (16.4)
Olfactory impairment (SDOIT < 6)	54 (3.5)
	Mean (SD, Range)
Grooved Pegboard, time, seconds	71.7 (15.6, 45 to 243)
Grip Strength, kg	38.5 (12.4, 5.0 to 77.5)
SF-36 PFS	88.4 (16.0, 0 to 100)
CAIDE score	5.2 (3.0, 0 to 13)
FRS%	9.6 (9.6, 0.3 to 76.5)

Note: Baseline characteristics of $N = 1529$ Beaver Dam Offspring Study participants. Categories chosen reflect usage of categories in CAIDE and/or FRS. For the education variable, categories were adapted to capture the variation in our cohort appropriately. Sample sizes vary slightly due to missing data, which was less than 1% for any individual variable.
Abbreviations: BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia; CS, contrast sensitivity; dB HL, decibel hearing level; FRS, Framingham Risk Score; HDL, high-density lipoprotein; SDOIT, San Diego Odor Identification Test; SF-36 PFS, Short Form Health Survey 36 physical function score; PTA, pure-tone average.

In models stratified by age, in those aged 55 years or older, both the AUC of the CAIDE and FRS% prediction models were significantly improved by adding sensory and motor function, from 0.61 to 0.69 and from 0.63 to 0.70, respectively (Table 3). The AUC did not statistically significantly improve for either the CAIDE or FRS% when adding sen-

sory and motor function to the prediction models for NfL positivity in those aged below 55 years.

Stratified by sex, the AUCs improved in both women and men for the CAIDE models when adding sensory and motor function (slightly better performance among women). The AUCs from the sex-stratified models with the FRS% and the improvements when adding sensory and motor function were similar in size compared to the AUCs of models in the complete cohort but were not significant in sex strata (Table 3).

3.3 | Additional metrics of risk prediction models for biomarker positivity outcomes

Sensitivity and specificity values of the risk prediction models varied; positive predictive values were low (Appendix C). However, the negative predictive values were excellent (> 94% for all models).

4 | DISCUSSION

In the current study, adding sensory and motor function to established dementia risk scores improved the risk prediction of 10-year incidence of biomarker positivity in Aβ and NfL in individuals above the age of 55 years at baseline. This adds to existing research using cardiovascular assessments to predict dementia, by showing that sensory and motor functions may add relevant information to risk prediction models of biologically determined early changes along the AD and neurodegeneration spectrum. Importantly, sensory and motor functions can be assessed reliably and non-invasively and are cost-effective. They could thus serve as a practical addition for future prediction models to identify individuals at high risk for developing ADRD.

Since the accumulation of amyloid proteinopathies is one of the hallmark pathological changes in AD,[3] blood-based levels of Aβ_{42}/Aβ_{40} have been widely studied and been found to be associated with changes in cognitive function and the development of AD and dementia and with brain amyloidosis.[5,6,39,43] We found that adding sensory and motor variables to the CAIDE and FRS% models for Aβ_{42}/Aβ_{40} positivity improved the AUCs of the models to 0.60, which was a significant improvement for the CAIDE model and a trend of an effect for FRS%. Notably, the AUCs of these models were still fairly low in the full cohort. However, in individuals above the age of 55 years, risk predictions improved considerably with the addition of sensory and motor functions from 0.54 to 0.71 for CAIDE models and 0.53 to 0.70 in FRS%, bringing the predictive performances up to a level similar to previous models for prediction of dementia (AUC values of ≥0.70) even in this relatively young community-based and non-AD specific cohort.[15,16,18] More research will be needed to determine whether these age group differences may be due to the limited change in the blood-based biomarkers over time[30] and the small number of incidence cases in the "younger" middle-aged adults, our rather to a conservative definition of amyloid positivity,[37] or whether sensory and motor changes may have a particular prognostic value for amyloid pathology in late middle age.

TABLE 2 Risk prediction for 10-year incidence of amyloid beta positivity for the CAIDE and FRS% individually and after adding sensory and motor functions.

| | Amyloid beta positivity[a] | | | | | | | | | |
| | All[b] | | <55 years[c] | | ≥55 years[c] | | Women[d] | | Men[d] | |
	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p
CAIDE	0.52 (0.46, 0.59)	0.03	0.52 (0.44, 0.60)	0.27	0.54 (0.42, 0.67)	0.04	0.53 (0.44, 0.63)[e]	0.13	0.51 (0.42, 0.60)[e]	0.02
CAIDE + Sens-Motor	0.60 (0.53, 0.67)		0.57 (0.49, 0.65)		0.71 (0.60, 0.82)		0.61 (0.52, 0.70)[e]		0.65 (0.55, 0.74)[e]	
FRS%	0.55 (0.48, 0.62)	0.10	0.56 (0.47, 0.65)[e]	0.16	0.53 (0.40, 0.66)[e]	0.09	0.58 (0.50, 0.67)[e]	0.43	0.56 (0.45, 0.67)[e]	0.05
FRS% + Sens-Motor	0.60 (0.54, 0.67)[e]		0.60 (0.52, 0.68)[e]		0.69 (0.57, 0.81)[e]		0.61 (0.52, 0.71)[e]		0.66 (0.57, 0.76)[e]	

Abbreviations: AUC, area under the receiver operating characteristic curve; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia score; CI, confidence interval; FRS, Framingham Risk Score; Sens-Motor, sensory and motor assessments.

[a] Results of logistic regression models on 10-year incidence of amyloid beta positivity ($A\beta_{42}/A\beta_{40}$). p-Value is the result of a chi-square test to determine statistically significant differences between AUCs of models including the standard risk score only and models including the standard risk score and additionally sensory and motor measures (hearing impairment, vision impairment, olfactory impairment, grip strength, grooved pegboard test, and Short Form Health Survey 36 physical function score).

[b] Sample N = 1381 with 68 cases.

[c] Model stratified by age group. In individuals aged <55 years, sample N = 1006 with N = 45 cases; in individuals aged ≥55 years, sample N = 375 with N = 23 cases.

[d] Model stratified by sex. For women, sample N = 748 with N = 39 cases; for men, sample N = 633 with N = 29 cases.

[e] Penalized logistic regression by the Firth method was used to address quasi-complete separation in this stratified model.

TABLE 3 Risk prediction for 10-year incidence of NfL positivity for the CAIDE and FRS% individually and after adding sensory and motor functions.

| | 10-year Incidence of NfL Positivity[a] | | | | | | | | | |
| | All[b] | | <55 years[c] | | ≥55 years[c] | | Women[d] | | Men[d] | |
	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p
CAIDE	0.68 (0.62, 0.73)	0.002	0.57 (0.48, 0.66)	0.11	0.61 (0.53, 0.69)	0.005	0.73 (0.65, 0.80)	0.02	0.62 (0.53, 0.70)	0.01
CAIDE + Sens-Motor	0.72 (0.66, 0.77)		0.61 (0.52, 0.70)		0.69 (0.62, 0.76)		0.76 (0.68, 0.83)		0.68 (0.60, 0.76)	
FRS%	0.69 (0.64, 0.75)	0.10	0.60 (0.51, 0.68)	0.38	0.63 (0.56, 0.71)	0.045	0.72 (0.65, 0.79)	0.47	0.70 (0.62, 0.78)	0.26
FRS% + Sens-Motor	0.72 (0.67, 0.78)		0.63 (0.54, 0.71)		0.70 (0.64, 0.76)		0.74 (0.67, 0.81)		0.72 (0.65, 0.80)	

Abbreviations: AUC, area under the receiver operating characteristic curve; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia score; CI, confidence interval; FRS, Framingham Risk Score; NfL, neurofilament light chain protein; Sens-Motor, sensory and motor assessments.

[a] Results of logistic regression models on 10-year incidence of NfL positivity. p-Value is the result of a chi-square test to determine statistically significant differences between AUCs of models including the standard risk score only and models including the standard risk score and additionally sensory and motor measures (hearing impairment, vision impairment, olfactory impairment, grip strength, grooved pegboard test and Short Form Health Survey 36 physical function score).

[b] Sample N = 1417 with 111 cases.

[c] Model stratified by age group. In individuals aged <55 years, sample N = 1026 with 46 cases; in individuals aged ≥55 years, sample N = 391 with 65 cases.

[d] Model stratified by sex. For women, sample N = 765 with 55 cases; for men, sample N = 652 with 56 cases.

Sex differences in dementia have been widely acknowledged.[1,44] Women have a higher likelihood for developing AD and dementia than men, particularly at older ages.[1] Selective survival among men and/or biological sex differences have been discussed as potential reasons.[44] We found sex differences in our risk prediction models, that is, sensory and motor function improved risk prediction of $A\beta_{42}/A\beta_{40}$ positivity slightly more in men. However, these results should be treated with a caveat given the small number of cases in both groups. More research is warranted to determine if these differences are due to sex-specific pathological mechanisms of AD between men and women.

NfL is an axonal protein, which is released into the brain interstitial fluid after neuronal or axonal injury. Importantly, NfL levels are also elevated in the blood of individuals with mild cognitive impairment, dementia, AD, and other neurodegenerative diseases.[5,39,45] In our study, adding sensory and motor variables to the CAIDE and FRS% models for NfL positivity improved the AUCs of the models to 0.72 (this increase was only statistically significant for CAIDE). These AUCs met the prediction performances of previous studies on the development of dementia later in life.[15,16,18] Similar to the $A\beta_{42}/A\beta_{40}$ prediction models, improvements in the AUC when adding sensory and motor function to NfL prediction models were larger in individuals >55 years of age. This could be due to increased variation in NfL levels in the older group[30] and increased power.

While other metrics of the prediction models were rather low, the negative predictive values were good to excellent in this study. This finding is expected given the nature of the BOSS, recruiting from the general population without a specific risk profile or family history of ADRD. For usage in a population with a low prevalence of disease, screening tools are not intended as a diagnostic tool but should rather serve as a screener to identify individuals that should undergo further confirmatory diagnostic procedures. Thus, the primary goal is to attain a high negative predictive value,[46] which was the case in our study.

This study focused on whether adding sensory and motor function to previous risk prediction scores could improve the prediction of early biomarker changes related to neurodegeneration and AD. Different pathways, including a shared cardiovascular pathway, were discussed in previous research that investigated sensory and motor changes as risk factors for neurodegeneration and AD.[30,47,48] In our study, when added to models using the CAIDE or FRS, risk predictions improved, although the magnitude of improvement was rather small in the full cohort. However, it is important to note that sensory and motor functions added to the predictive performance and explained variance of the development of neurodegeneration and AD biomarker positivity beyond the already explained variance by education, sex, and cardiovascular risk factors. Future studies will be needed to assess possible mechanistic pathways and to determine whether and how sensory and motor declines might contribute to accumulation of neurodegenerative and AD pathologies in the blood.

The CAIDE and FRS% have been established in predicting dementia onset. Our study outcome was biomarker positivity only and not based on cognitive test performance, CSF, imaging, or diagnosis of AD or dementia. Biomarker positivity may occur earlier than symptomology or a definitive decline in cognitive test performance.[3] Recent work by us and others has shown associations between a number of cardiovascular and health-related factors with levels of $A\beta$ and NfL and their change over time.[19,49] However, it remained unclear whether cardiovascular risk scores, which have been developed to predict clinical/symptomatic changes of dementia, could also predict onset of biomarker positivity and whether sensory and motor functions would improve such prediction models; this is the knowledge that the current study contributes to the field.

The sensory and motor assessments used in this study are validated and standardized measures that are widely used clinically and in research. They are easy to administer and could thus be particularly feasible additions to future clinical screening tools for brain aging. More research is needed and should focus on determining the best predictor variables to be used in parsimonious models. Prediction model studies of early changes in the course of the disease,[3] such as changes in (blood-based) biomarkers will enhance the field to be better qualified to identify individuals at risk for ADRD. Additionally, future research will be needed to understand how sensory and motor functions could contribute to the long-term prediction of behavioral and/or clinical changes in cognitive function and onset of cognitive impairment.

4.1 | Limitations and strengths

This study is based on a subsample of the BOSS, but the sample was not different from the complete baseline sample.[30] Our study cohort is predominantly non-Hispanic White, which may limit our ability to generalize the findings to other populations. While we aimed to assess predictors of early changes, the changes in biomarker levels and incidence rates of positivity might not have been sufficient to develop strong prediction models, and longer follow-up might be needed. Only an odor identification test was available in this study and the prevalence of odor identification impairment was low in this younger cohort. An odor detection threshold test might have had increased sensitivity to detect more variability in olfactory function. Apolipoprotein E (*APOE*) ε4-carrier status, a risk factor for and predictor of AD and dementia, was not available in this study cohort. However, *APOE* genotype did not improve CAIDE-based risk prediction models in previous work.[15]

There are multiple strengths of our study. We utilized a large, well-characterized general population cohort that has standardized objective assessments of cardiovascular risk factors, sensory systems (hearing, vision, and olfaction), and motor functions. We had repeated measures of blood biomarker levels with follow-up over 10 years, which is novel.

5 | CONCLUSION

Including sensory-motor function variables in models with standard risk scores based on cardiovascular risk factors may improve risk

prediction of biological indicators of neurodegeneration and AD. Sensory and motor changes are easy to assess and may be especially useful for risk predictions of biomarker changes that may occur early in the disease, where intervention and prevention methods might be more effective.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report. Author disclosures are available in the supporting information S1,S2.

CONSENT STATEMENT

All human subjects provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.