Munich Research Institute for the Economics of Aging and SHARE Analyses (MEA-SHARE gGmbH)

DBS-based Biomarkers of Neurodegeneration predict Cognitive Decline and Dementia Seven Years Ahead in a Large Population-Based Sample

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with

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Marker	Unit	Obs.	Mean	Median	Std. Dev	Min	Max
Set 1: Seven routine blood biomarkers							
Glycosylated haemoglobin (HbA1c)	%	19,788	6.0	6.0	0.6	3.9	16.5
Total haemoglobin (THB)	g/dL	14,902	14.8	14.7	1.3	9.8	22.0
HDL-cholesterol (HDL)	mg/dL	14,902	68.5	67.9	9.2	37.9	121.9
Total cholesterol (CHO)	mg/dL	23,061	223.0	223.1	24.9	118.3	337.7
Triglycerides (TRG)	mg/dL	22,989	223.0	196.7	127.6	9.8	3,386
C-reactive protein (CRP)	mg/L	22,728	3.5	2.1	6.6	0.1	139.4
Cystatin C (CYC)	mg/L	23,061	1.0	1.0	0.1	0.5	2.5
Set 2: Pro-inflammatory cytokines and growth factors							
Interleukin 8 (IL-8)	pg/mL	15,512	3.0	2.5	7.2	0.4	515.4
Interleukin 16 (IL-16)	pg/mL	15,435	327.2	315.1	111.0	34.8	2,651
Interleukin 18 (IL-18)	pg/mL	15,515	110.3	103.9	41.6	7.1	726.6
Interleukin 12/23p40 (IL-12)	pg/mL	15,384	12.2	9.6	8.9	0.5	139.5
Monocyte chemo-attractant protein (MCP-1)	pg/mL	15,515	46.2	44.5	14.9	7.7	565.9
Brain-derived neurotrophic factor (BDNF)	pg/mL	15,214	40.9	38.2	18.0	12.2	286.7
Vascular epithelial growth factor (VEGF-A)	pg/mL	15,514	14.1	13.3	5.00	3.2	83.3
Epidermal growth factor (EGF)	pg/mL	15,231	3.2	2.9	1.7	0.1	24.5
Set 2 cont'd: Apolipoproteins							
Apolipoprotein J (Clusterin)	ng/mL	15,514	1,778	1,686	526.3	32.6	8,266
Apolipoprotein E4 (ApoE4)	ng/mL	13,108	62.8	7.2	105.7	3.7	1,192
Set 3: Neurodegenerative biomarkers							
Tau(total) Tau(total)	pg/mL	3,103	10.8	10.1	4.4	2.25	55.0
Neurofilament light chain (NfL)	pg/mL	2,488	3.7	2.7	3.9	0.15	61.3
Glial fibrillary acidic protein (GFAB)	pg/mL	3,054	1.3	1.1	1.1	0.085	33.3
Phosphorylated tau at threonine 217 (pTau217)	pg/mL	2,921	2.2	1.8	2.1	0.094	50.3

Biomarkers of neurodegenerative decline

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	ApoE4	Tau total	GFAP	NfL	pTau217
	ng/mL	pg/mL	pg/mL	pg/mL	pg/mL
male	58.03	11.27	1.19	3.34	2.14
female	55.61	10.34	1.33	2.78	2.09
age<60	62.21	10.25	1.90	4.28	2.29
age 60-74	60.44	10.72	1.04	2.40	2.06
age>=75	55.09	10.77	1.32	3.17	2.11
educ1	52.80	10.74	1.50	3.13	2.20
educ2	65.44	11.01	1.20	3.01	2.14
educ3	49.21	10.31	1.27	2.99	2.01
bmi<24	59.80	9.80	1.39	3.00	2.01
bmi 24-29	57.12	10.72	1.19	2.82	2.10
bmi 30+	50.76	12.00	1.32	3.60	2.34
Sweden	65.46	11.10	1.38	2.81	1.99
Estonia	60.44				
Denmark	73.81	10.85	1.22	2.85	2.26
Germany	64.60	10.68	1.26	3.10	2.10
Belgium	61.15				
France	57.36				
Switzerland	70.03				
Slovenia	58.70				
Italy	37.83				
Spain	52.53				
Greece	46.92				
Israel	50.09				

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Strong age, bmi and country effects for Apoe4

No discernible patterns for Tau, GFAP and NfL

Age effects: ApoE4 carriers face higher mortality risk from CVD and dementia (survivor bias); metabolic behavior of ApoE4 leads to increased protein degradation and lower concentrations over time

BMI effects: Largely driven by metabolic processing, protein degradation and liver interaction

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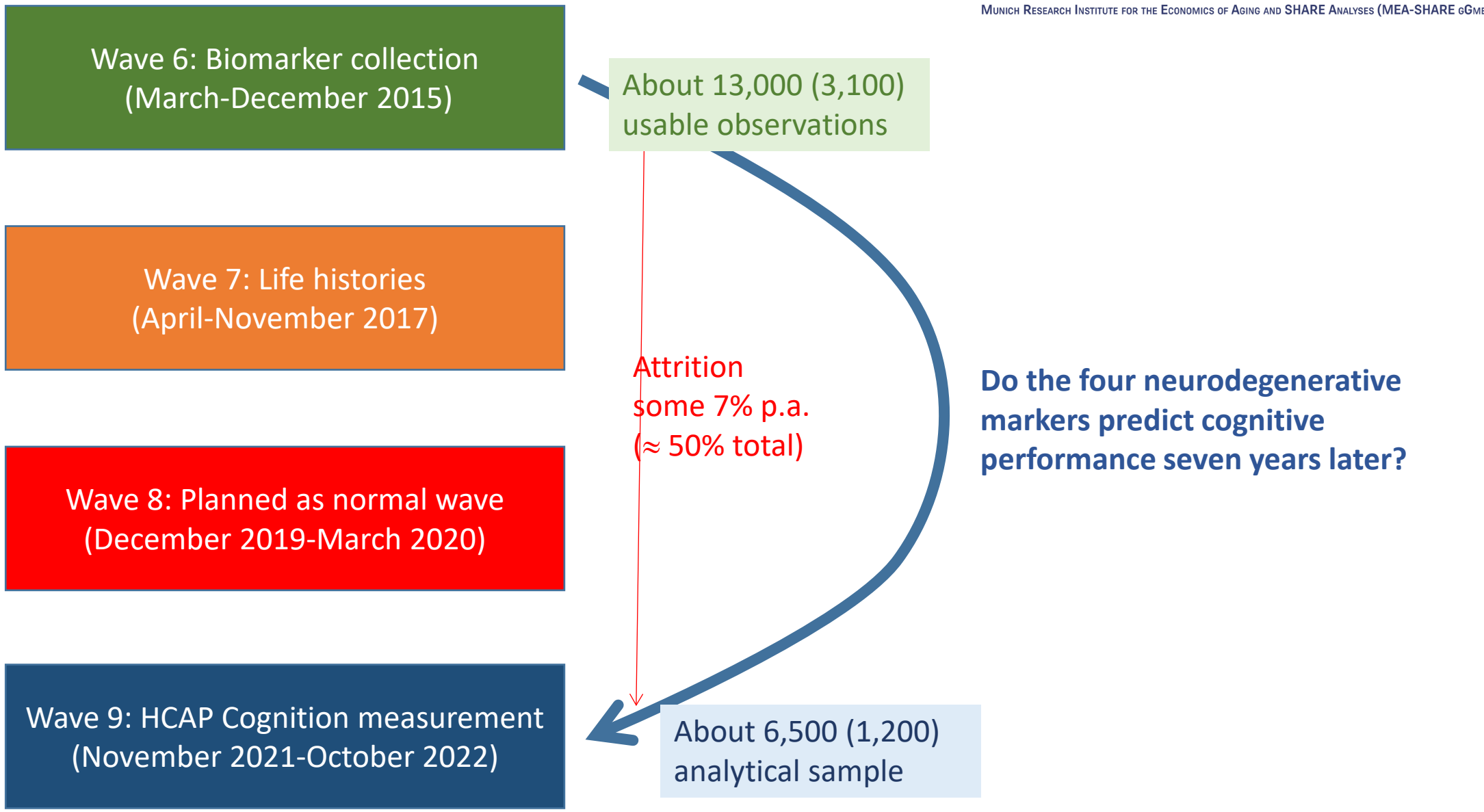

Do the four neurodegenerative markers predict cognitive performance seven years later?

TABLE 1: Predictive power of ApoE4 protein seven years later

Dependent variable	Explanatory variable is ApoE4_detected				
	Coeff	StdErr	p-value	R-squared	Nobs
immword	-0.143	0.042	0.001	0.303	6495
delword	-0.235	0.052	0.000	0.279	6505
orientt	-0.101	0.021	0.000	0.320	6660
Hscore	-0.069	0.018	0.000	0.579	6470
Gscore	-0.089	0.021	0.000	0.419	5942
Lscore	-0.094	0.022	0.000	0.391	6521

Three cognition tests
Three summary measures

Strong effects

Notes: The dependent variables are the six cognition measures in the first column. Besides the detection of ApoE4, the regressions include the following covariates: **Demographic** variables include age categories and sex. **Education** variables include ISCED-1997 education categories. **Comorbidity** variables include BMI, EURO-D depression scale, ADL and IADL scores, CVR score, and indicators for affective symptoms, cholesterol and hypertension. Also included are country indicators and the number of waves participated.

TABLE 2: Robustness with respect to included covariates

	Coeff	StdErr	p-value	Coeff	StdErr	p-value	Coeff	StdErr	p-value	Coeff	StdErr	p-value
Hscore	-0.068	0.026	0.009	-0.076	0.026	0.003	-0.061	0.019	0.001	-0.069	0.018	0.000
Gscore	-0.062	0.025	0.015	-0.081	0.023	0.001	-0.073	0.022	0.001	-0.089	0.021	0.000
Lscore	-0.074	0.025	0.003	-0.091	0.024	0.000	-0.081	0.022	0.000	-0.094	0.022	0.000
Demographics		included			included			included			included	
Education					included			included			included	
Comorbidities								included			included	
Countries											included	

Notes: The dependent variables are the three summary cognition measures in the first column. Besides the detection of ApoE4, the regressions include the following covariates: **Demographics** includes age categories and sex. **Education** includes ISCED-1997 education categories. **Comorbidities** includes BMI, EURO-D depression scale, ADL and IADL scores, CVR score, and indicators for affective symptoms, cholesterol and hypertension. **Countries** includes indicators for each country.

Effects get stronger with more covariates

TABLE 3: Predictive power of pTau217, GFAP and NfL seven years later

Dependent variable	Coeff	StdErr	p-value	R-squared	Nobs
	Explanatory variable pTau217				
immword	-0.057	0.027	0.037	0.242	1205
delword	0.000	0.000	0.011	0.239	1204
orientt	0.001	0.022	0.959	0.272	1225
Hscore	-0.032	0.016	0.040	0.402	1203
Gscore	-0.039	0.025	0.116	0.321	1214
Lscore	-0.060	0.025	0.014	0.292	1204
	Explanatory variable GFAP				
	Coeff	StdErr	p-value	R-squared	Nobs
Immword	-0.028	0.030	0.340	0.238	1262
Delword	-0.060	0.032	0.062	0.229	1261
Orientt	-0.066	0.023	0.004	0.267	1282
Hscore	-0.030	0.018	0.099	0.390	1259
Gscore	-0.059	0.027	0.028	0.313	1271
Lscore	-0.046	0.027	0.086	0.282	1261
	Explanatory variable NfL				
	Coeff	StdErr	p-value	R-squared	Nobs
immword	-0.038	0.027	0.167	0.239	1262
delword	-0.054	0.030	0.071	0.229	1261
orientt	-0.032	0.021	0.135	0.263	1282
Hscore	-0.006	0.017	0.740	0.389	1259
Gscore	-0.045	0.025	0.068	0.312	1271
Lscore	-0.049	0.025	0.047	0.283	1261

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Correct direction, weak significance (small sample size)

Notes: The dependent variables are the six cognition measures in the first column. Besides pTau217, GFAP or NfL, the regressions include the following covariates: **Demographic** variables include age categories and sex. **Education** variables include ISCED-1997 education categories. **Comorbidity** variables include BMI, EURO-D depression scale, ADL and IADL scores, CVR score, and indicators for affective symptoms, cholesterol and hypertension. Also included are country indicators and the number of waves participated.

TABLE 4: Cognitive performance as function of all four neurodegenerative biomarkers

Explanatory	Dependent variable: immword			Dependent variable: delword			Dependent variable: orientt		
variable	Coeff	StdErr	p-value	Coeff	StdErr	p-value	Coeff	StdErr	p-value
GFAP_std	-0.0096	0.036	0.792	-0.0460	0.039	0.243	-0.0650	0.028	0.022
NFL_std	-0.0438	0.034	0.197	-0.0387	0.037	0.293	-0.0029	0.026	0.914
pTau217_std	-0.0587	0.027	0.032	-0.0791	0.030	0.007	-0.0035	0.021	0.869
ApoE4_det	-0.0444	0.051	0.384	-0.0539	0.055	0.329	-0.1295	0.040	0.001
	R-squared	Nobs	**p-value**	R-squared	Nobs	**p-value**	R-squared	Nobs	**p-value**
	0.245	1204	**0.092**	0.244	1203	**0.012**	0.283	1224	**0.001**

Explanatory	Dependent variable: Hscore			Dependent variable: Gscore			Dependent variable: Lscore		
variable	Coeff	StdErr	p-value	Coeff	StdErr	p-value	Coeff	StdErr	p-value
GFAP_std	-0.0393	0.022	0.077	-0.0445	0.033	0.176	-0.0235	0.033	0.474
NFL_std	-0.0119	0.021	0.565	-0.0293	0.031	0.340	-0.0471	0.031	0.124
pTau217_std	-0.0344	0.017	0.039	-0.0426	0.025	0.084	-0.0633	0.025	0.010
ApoE4_det	-0.0727	0.031	0.020	-0.0709	0.046	0.123	-0.0440	0.046	0.339
	R-squared	Nobs	**p-value**	R-squared	Nobs	**p-value**	R-squared	Nobs	**p-value**
	0.407	1202	**0.014**	0.326	1213	**0.03**	0.297	1203	**0.013**

Notes: The dependent variable are the six cognition measures in the first row of each panel. Besides GFAP, NfL, pTau217 (each of them standardized) and ApoE4 detected, the regressions include the following covariates: **Demographic** variables include age categories and sex. **Education** variables include ISCED-1997 education categories. **Comorbidity** variables include BMI, EURO-D depression scale, ADL and IADL scores, CVR score, and indicators for affective symptoms, cholesterol and hypertension. Also included are country indicators and the number of waves participated.

All directions correct,
Some significance
(but small sample size….)

TABLE 5: Test for attrition bias

Dependent variable: HCI, binary probit				Dependent variable: HCI, three-way probit with attrition model					
	Probability of severe impairment			Probability of severe impairment			Probability of attrition		
Explanatory Variable	**Coeff**	**StdErr**	**p-value**	**Coeff**	**StdErr**	**p-value**	**Coeff**	**StdErr**	**p-value**
ApoE4_det	0.247	0.071	0.000	0.204	0.058	0.000	0.183	0.040	0.000
Nobs:	6470			10985					
	Probability of severe impairment			Probability of severe impairment			Probability of attrition		
Explanatory Variable	**Coeff**	**StdErr**	**p-value**	**Coeff**	**StdErr**	**p-value**	**Coeff**	**StdErr**	**p-value**
ApoE4_det	0.408	0.175	0.020	0.308	0.144	0.033	0.091	0.087	0.300
GFAP	0.093	0.102	0.361	0.063	0.084	0.455	0.091	0.055	0.098
NFL	0.002	0.027	0.927	0.008	0.021	0.704	0.025	0.014	0.070
pTau217	0.039	0.038	0.299	0.037	0.030	0.222	0.041	0.020	0.039
Nobs:	1202			2078					

Notes: The dependent variable is the probability to be cognitively impaired. The probit regressions include the following covariates: **Demographic** variables include age categories and sex. **Education** variables include ISCED-1997 education categories. **Comorbidity** variables include BMI, EURO-D depression scale, ADL and IADL scores, CVR score, and indicators for affective symptoms, cholesterol and hypertension. Also included are country indicators and the number of waves participated.

Only small attenuation if attrition modelled (identification by functional form)

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Conclusions and take-home messages:

1. ApoE4 protein predicts all six cognition measures very well seven years ahead

2. This association gets stronger if more covariates are included

3. Much lower signal for GFAP, NfL and pTau217 (small sample size!)

4. Strongest pTau217 with Hscore

5. No discernible attrition bias

Thank you

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Data availability: https://www.share-eric.eu/data/data-set-details/share-dbs
Release reports: https://www.mea-share.eu/publications/mea-discussion-series
Cohort Profile Update: International Journal of Epidemiology, in press