



ApoE4 protein indicates risk for cognitive impairment as measured by HCAP

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with

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Take-home messages:

- 1. ApoE4 protein detects Apoε4 allele very well**
- 2. ApoE4 protein measured in 2015
correlates strongly with 4 out of 5 measures of
contemporary cognitive status**
- 3. ApoE4 protein measured in 2015
correlates strongly with 2022 cognition measured by
HCAP in all 28 SHARE countries**
- 4. Effects of ApoE4 and education on HCAP-validated
dementia prevalence are independent from each other**

1. ApoE4 protein vs. ApoE ϵ allele

- APOE4 protein levels were identified in a multiplex immunoassay from DBS ($N = 15,974$)

- APOE genotyping for the two APOE variants, rs7412 and rs429358 was performed on a smaller subset of DBS samples ($N = 554$) using TaqMan assay.



Mesozo Research Institute for the Economics of Aging and SHARE Analysis (MEA-SHARE) (GmbH)

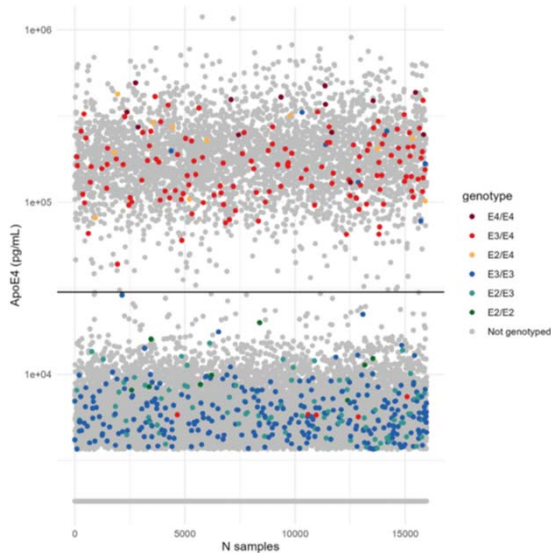


FIGURE 1 Raw data distributions of the apoE4 protein assay in SHARE DBS samples ($N = 15,974$) and genotyping of deceased SHARE respondents ($N = 549$) to define a cut-off. The y axis represents the levels of the apoE4 protein (in pg/mL) detected in the samples. Number of samples are depicted in the x axis. The anticipated apoE4 true specifics are in the upper part of the graph and the anticipated apoE4-negative samples are those in the bottom part of the graph. Each dot represents an apoE4 protein measurement with those genotyped shown in color and those not genotyped shown in gray. Carriers of one or two $\epsilon 4$ alleles (yellow, red, brown) were identified in the higher distribution, while carriers of other APOE alleles ($\epsilon 2$ and $\epsilon 3$) are found in the lower distribution of protein measurements (in green and blue). The line shows the cut-off at 30,000 pg/mL. APOE, apolipoprotein E; DBS, dried blood spots; SHARE, Survey of Health, Ageing and Retirement in Europe

- Large subset ($N = 15,974$) of the available DBS samples
- 10-plex immunoassay using preprinted Meso Scale plates (Meso Scale Diagnostics [MSD]) coated with antibodies specific for apoE4 and nine other biomarkers reported elsewhere.
- Intra-assay variations (apoE4: 6.96%) were based on 24 replicate measurements of an internal control. Inter-assay variations (apoE4: 17.9%) were calculated from controls analyzed in duplicate on each plate during the sample analysis

TABLE 1 Association between fieldwork conditions and apoE4 protein levels in SHARE

Predictor (unit)	Outcome: apoE4 (log)		
	Mean (SD), range	β coefficient	95% CI
Shipment time (days)	4.96 (3.71), 1-30	-0.02	-0.02, -0.01*
Drying time (min)	22.8 (14.19), 1-83	0.00	-0.00, 0.00 ns
Outside temperature ($^{\circ}$ C)	13.90 (7.78), 0-35	-0.01	-0.01, -0.00*
Open/close bag (Y/N = 0/1)	0.09 (0.28)	-0.10	-0.21, 0.00 ns
Mean spot size (cm^2)	0.71 (0.41), 0.10-2.0	0.15	0.06, 0.24*

Note: Observations were controlled for sex, age, and country, and weighted by the inverse of its probability of being sampled. Abbreviations: apoE, apolipoprotein E; CI, confidence interval; ns, not significant; R^2 , adjusted R-squared; SD, standard deviation; SHARE, Survey of Health, Ageing and Retirement in Europe.
* $P < 0.001$, $N = 3837$.

2. ApoE4 protein measured in 2015 correlates with 2015 cognition



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RESEARCH ARTICLE

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Circulating apoE4 protein levels from dried blood spots predict cognitive function in a large population-based survey setting

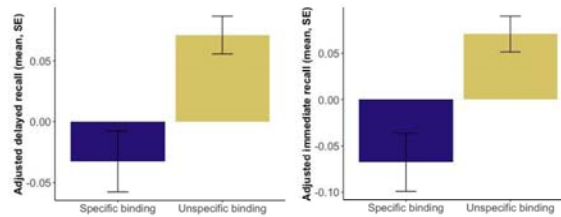
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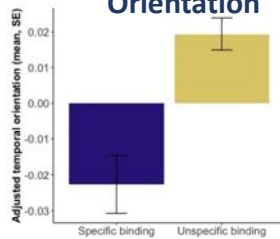
ApoE4 protein measured in 2015 correlates with 2015 cognitive status



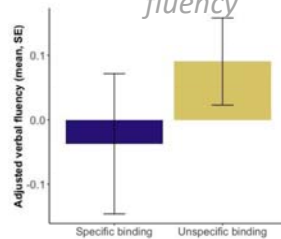
Delayed and immediate word recall



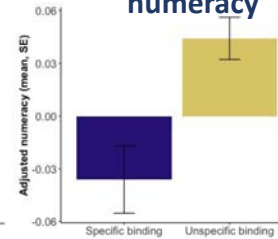
Orientation



fluency



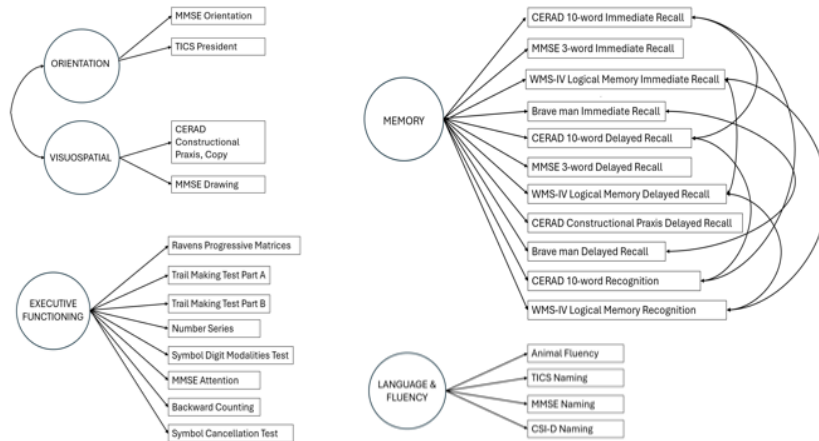
numeracy



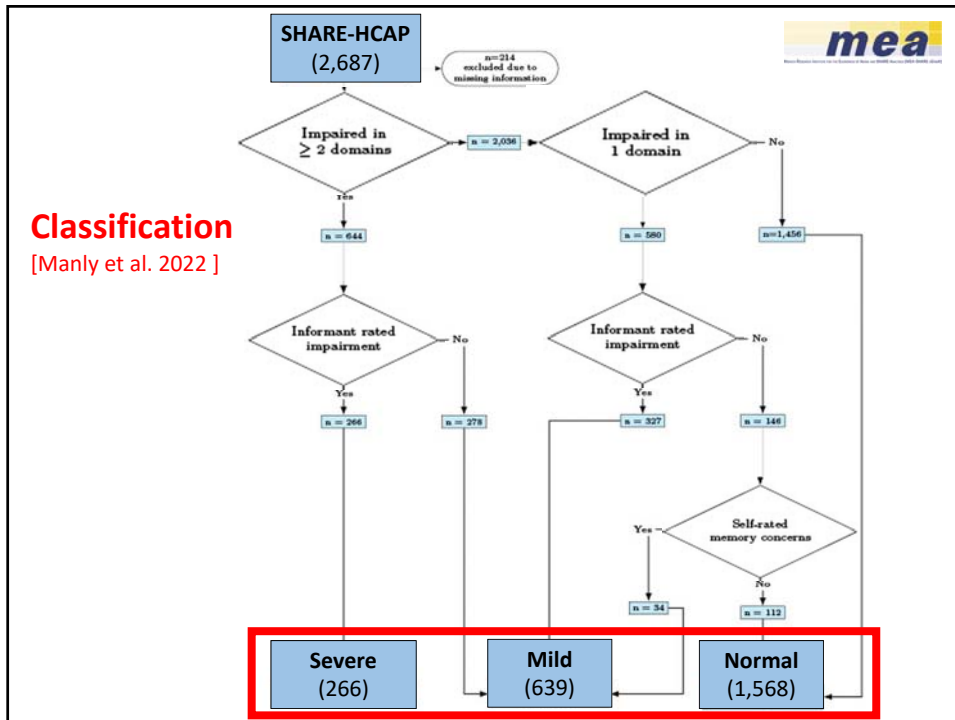
3. ApoE4 protein measured in 2015 correlates with 2022 cognition measured by HCAP

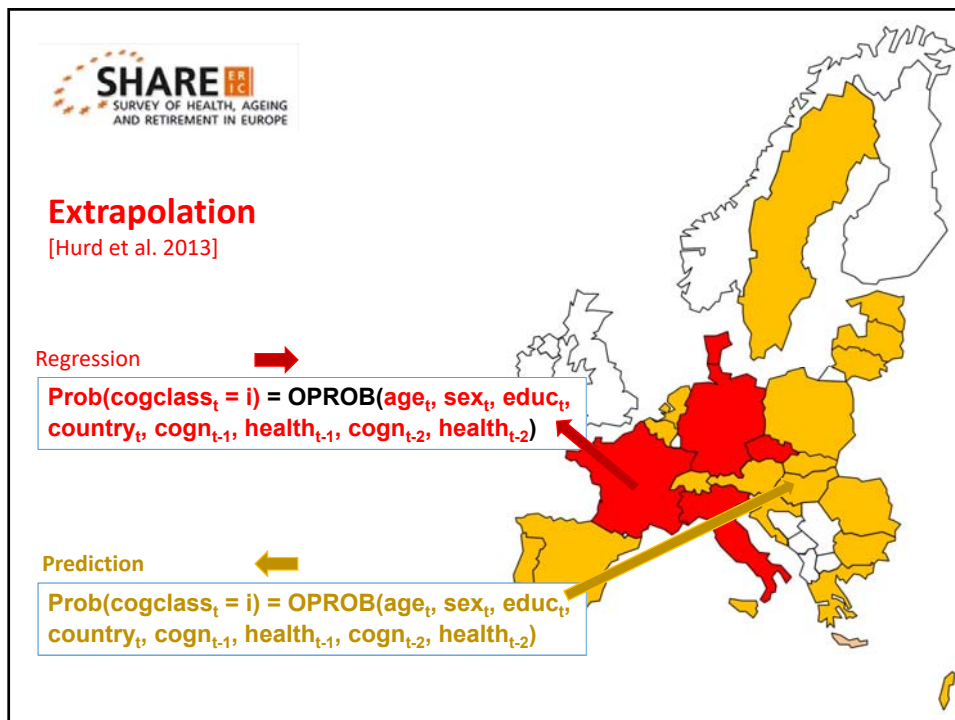
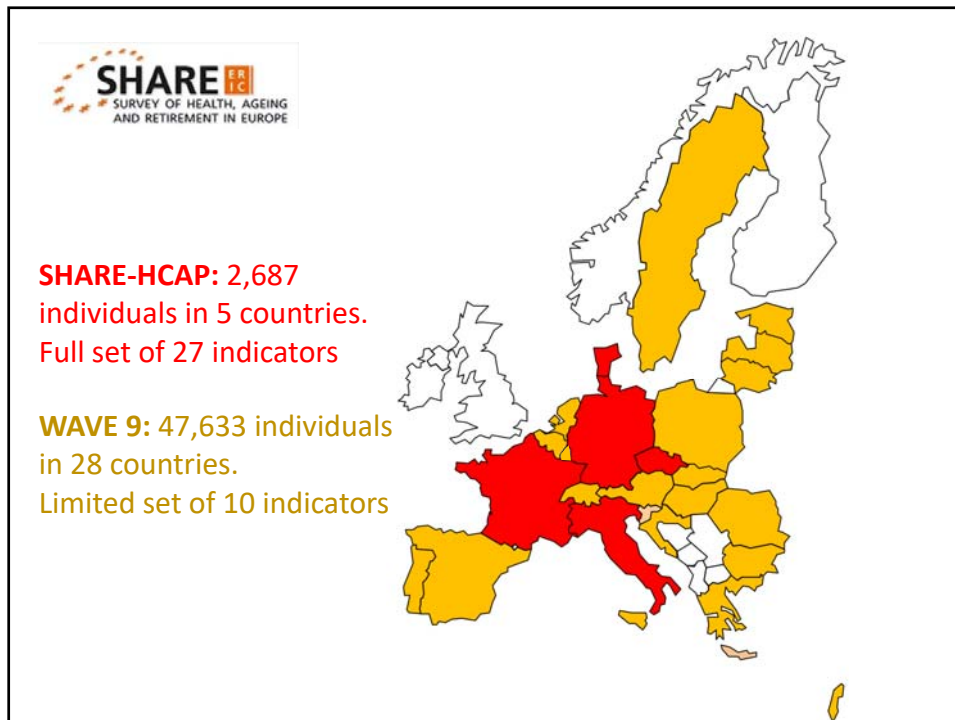
www.nature.com/scientificreports
scientific reports

Harmonized Cognitive Assessment Protocol
(Five domains, plus self-rated and informant rating)



Classification
[Manly et al. 2022]

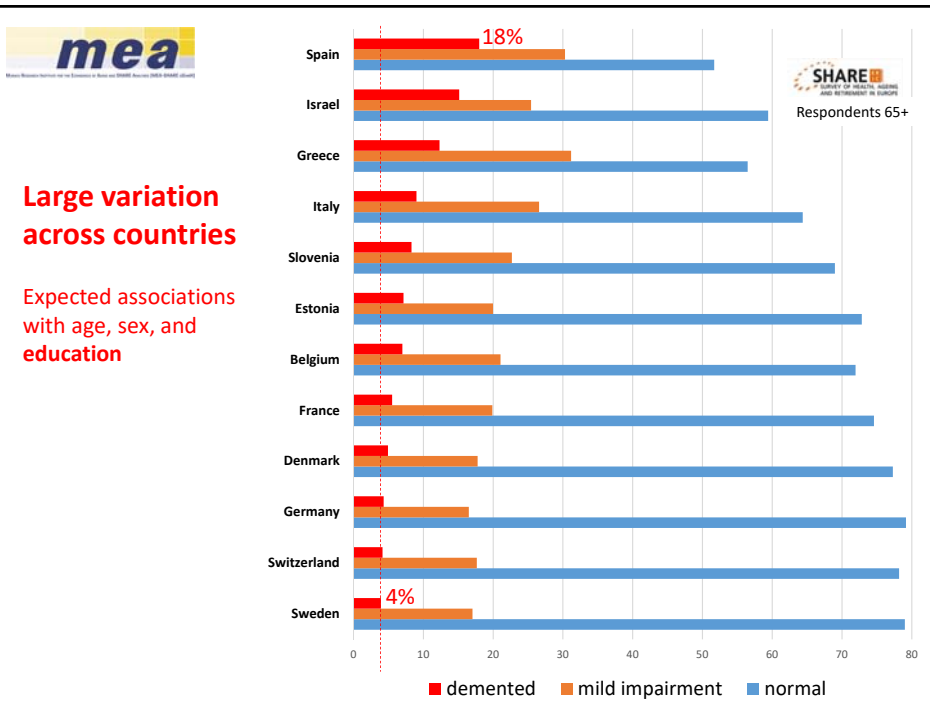






Prediction accuracy:

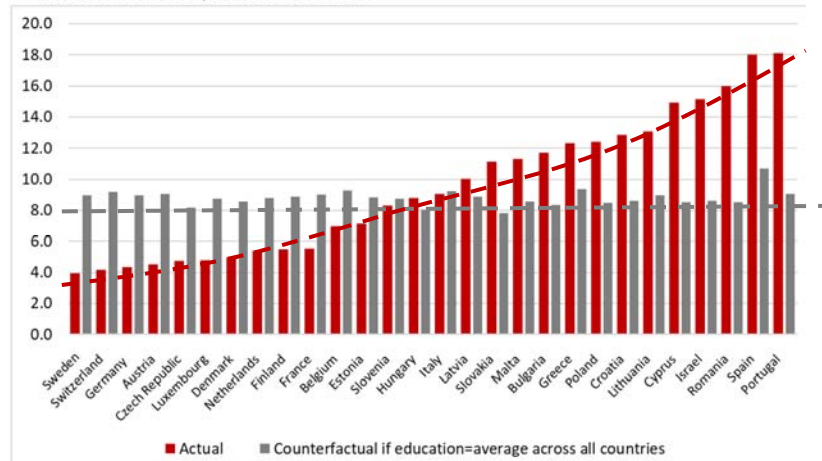
	classified by Manly et al. approach			predicted by Hurd et al. approach		
	normal	MCI	SCI	normal	MCI	SCI
Germany	76.9%	18.8%	4.3%	77.6%	17.6%	4.8%
Italy	65.6%	22.6%	11.8%	58.5%	29.7%	11.8%
France	71.8%	22.0%	6.2%	72.2%	21.2%	6.6%
Denmark	77.1%	18.0%	4.9%	76.1%	19.1%	4.8%
Czech Republi	71.5%	20.4%	8.1%	73.1%	19.7%	7.2%
Total	72.6%	20.4%	7.0%	71.5%	21.5%	7.0%



Dementia prevalence strongly associated with childhood education



Figure 2. Prevalence of dementia for 27 European countries and Israel. Actual and counterfactual if education had been equal across all countries



The red bars show the actual estimated share of demented individuals in each country. The grey bars show the counterfactual share of demented individuals if education in each country had been equal to the average of the 28 countries.

Nevertheless: ApoE4 protein measured in 2015 strongly correlates with dementia in 2022



Cognitive Impairment 0/1 on Gene 0/1 - Weighted

	(1) GCI_01 b/ci95	HCAP-validated indicator	(3) LW_01 b/ci95
apoe4_det	1.45***	1.48***	1.43***
female	1.08	0.60***	0.85
agecat_70-74	1.15	2.48***	1.57***
agecat_75-79	2.14***	2.62***	2.50***
agecat_80+	4.03***	5.10***	4.81***
laced1997_none	0.60	0.30***	0.45*
laced1997_primary	0.29***	0.43***	0.38***
laced1997_lower_sec	0.35***	0.18***	0.17***
laced1997_higher_sec	0.14***	0.13***	0.17***
laced1997_some_college	0.15***	0.23***	0.12***
laced1997_college	0.14	0.30	0.08***
N	6378	6390	6376
Pseudo R2	0.35	0.40	0.28
Log Likelihood	-2076.23	-2710.81	-3915.60

Coefficients represent odds ratios
Plus country dummies, number of waves, BMI, and health conditions

**ApoE4 protein measured in 2015
strongly correlates with
dementia probability in 2022**



Cognitive Impairment C on Gene 0/1 - Weighted

	(1) Zmean (GCI) b/se	HCAP-validated probability	(3) LWscore b/se
Gene Detected 0/1	-0.076*** (0.018)	-0.064*** (0.023)	-0.103*** (0.024)
N	6378	6390	6376
R2	0.47	0.60	0.43
Log Likelihood	-5279.90	-6856.35	-7502.10

Demographic variables are sex dummy, age class dummies, ISCED1997 dummies, country dummies, number of waves, and BMI. Health variables are EuroD dummies, IADL dummies, Affective, CVR Score, Cholesterol, and Hypertension. Activity variables are social activities, physical activities, taking medication for Hypertension, Heart diseases, Diabetes, Joint pain, Pain, Sleeping, Depression, Inflammation, and Cholesterol.

**4. ApoE4 and education effects
are independent from each other**

ApoE4 effect stronger/education effect weaker with other covariates



	Only ApoE4			Only Educ			Both ApoE4 and Educ		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Gene Detected 0/1	0.022*	0.029**	0.034***				0.030**	0.032***	0.035***
Primary				-0.332***	-0.287***	-0.214***	-0.332***	-0.287***	-0.214***
Lower Sec				-0.370***	-0.299***	-0.177***	-0.372***	-0.300***	-0.178***
Higher Sec				-0.460***	-0.380***	-0.237***	-0.462***	-0.381***	-0.238***
Some College				-0.508***	-0.417***	-0.258***	-0.509***	-0.419***	-0.259***
College				-0.451***	-0.372***	-0.226***	-0.453***	-0.372***	-0.227***
Post-College				-0.450***	-0.375***	-0.202***	-0.453***	-0.378***	-0.205***
N	6420	6420	6420	6420	6420	6420	6420	6420	6420
R squared	0.00	0.06	0.27	0.06	0.09	0.28	0.07	0.09	0.28
Countries		x	x		x	x		x	x
Health			x			x			x

Coefficients are marginal effects



Thank you

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