Supplementary material to '**Association of education and intracranial volume with cognitive trajectories and mortality rates across the Alzheimer´s disease continuum**'

Table of contents

eTable 1. Conversion of the qualitative Verhage scale for educational attainment to years of education

Verhage score	Years of education
1	<6 (elementary school)
2	6
3	8
4	9
5	10–11
6	12–18
7	>18 (university)

eTable 2. Missing data across domains and disease stages

	MMSE	Memory	Attention	Executive	Language	Visuospatial
Total sample						
Number of subjects:	1290	1088	1191	1211	1190	941
percentage available:	99.38	83.82	91.76	93.30	91.68	72.50
Total number of observations:	3777	2513	2611	2681	2488	1688
Min number of observations per subject	1	1	1	1	1	1
number of subjects:	431	484	572	568	597	581
percentage:	33.41	44.49	48.03	46.90	50.17	61.74
Max number of observations per subject:	17	14	13	13	13	8
Number of subjects without BA:	18	54	49	50	64	135
percentage:	1.39	4.16	3.78	3.85	4.93	10.40
Pre-dementia						
Number of subjects:	414	396	413	413	407	339
percentage available:	99.52	95.19	99.28	99.28	97.84	81.49
Total number of observations:	1512	1213	1245	1253	1170	715
Min number of observations per subject	1	1	1	1	1	1
number of subjects:	85	106	110	109	122	192
percentage:	20.53	26.77	26.63	26.39	29.98	56.64
Max number of observations per subject:	17	14	13	13	13	8
Number of subjects without BA:	6	23	15	15	23	51
percentage:	1.44	5.53	3.61	3.61	5.53	12.26
Dementia						
Number of subjects:	876	692	778	798	783	602
percentage available:	99.32	78.46	88.21	90.48	88.78	68.25
Total number of observations:	2265	1300	1366	1428	1318	973
Min number of observations per subject	1	1	1	1	1	1
number of subjects:	346	378	462	459	475	389
percentage:	39.50	54.62	59.38	57.52	60.66	64.62
Max number of observations per subject:	17	7	7	8	7	7
Number of subjects without BA:	12	31	34	35	41	84
percentage:	1.36	3.51	3.85	3.97	4.65	9.52
SCD						
Number of subjects:	141	138	140	140	138	121
percentage available:	99.30	97.18	98.59	98.59	97.18	85.21

Total number of observations:	417	393	393	392	380	205
Min number of observations per subject	1	1	1	1	1	1
number of subjects:	49	51	53	52	52	89
percentage:	34.75	36.96	37.86	37.14	37.68	73.55
Max number of observations per subject:	17	14	13	13	13	6
Number of subjects without BA:	1	4	0	0	1	8
percentage:	0.70	2.82	0.00	0.00	0.70	5.63
MCI						
Number of subjects:	273	258	273	273	269	218
percentage available:	99.64	94.16	99.64	99.64	98.18	79.56
Total number of observations:	1095	820	852	861	790	510
Min number of observations per subject	1	1	1	1	1	1
number of subjects:	36	55	57	57	70	103
percentage:	13.19	21.32	20.88	20.88	26.02	47.25
Max number of observations per subject:	13	9	10	10	8	8
Number of subjects without BA:	5	19	15	15	22	43
percentage:	1.82	6.93	5.47	5.47	8.03	15.69

eTable 3. Description of the pre-dementia sample

	Pre-dementia (n=416)	SCD (n=142)	MCI (n=274)
Participant characteristics [a]			
Age	66.0 ± 7.7	63.9 ± 7.9	67.1 ± 7.4
Sex (% female)	49.3	52.8	47.4
Education (Verhage) [b]	6 (1)	6 (1)	5 (2)
APOE ε4 (% positive)	69.5	62	73.4
Brain measures [a]			
Intracranial volume (cm3)	1496.3 ± 151.8	1489.7 ± 157.3	1499.7 ± 148.9
Whole-brain GM atrophy [c]	.40 ± .05	.43 ± .05	.39 ± .05
Baseline cognition [a]			
MMSE (global cognition)	26.9 ± 2.4	28.19 ± 1.47	26.20 ± 2.50
Memory	0.73 ± 0.77	1.41 ± 0.59	0.36 ± 0.59
Attention	0.43 ± 0.43	0.54 ± 0.39	0.38 ± 0.44
Executive functioning	0.56 ± 0.51	0.74 ± 0.45	0.46 ± 0.51
Language	0.52 ± 0.48	0.76 ± 0.45	0.39 ± 0.44
Visuospatial ability	0.43 ± 0.27	0.49 ± 0.23	0.40 ± 0.29
Annual cognitive decline [d]			
MMSE (global cognition)	-0.16 ± 0.01	-0.05 ± 0.02	-0.19 ± 0.01
Memory	-0.16 ± 0.01	-0.08 ± 0.03	-0.19 ± 0.02
Attention	-0.06 ± 0.01	-0.03 ± 0.01	-0.08 ± 0.01
Executive functioning	-0.08 ± 0.01	-0.03 ± 0.02	-0.11 ± 0.01
Language	-0.08 ± 0.01	-0.07 ± 0.01	-0.08 ± 0.01
Visuospatial ability	-0.07 ± 0.01	-0.07 ± 0.04	-0.07 ± 0.02
Mortality			
Deceased during follow up (n,%)	129 (31.0)	21 (14.8)	108 (39.4)

Data are presented as mean ± SD unless indicated otherwise. There were significant differences between the SCD and MCI group for all variables except sex, education and intracranial volume. There was statistically significant cognitive decline in all domains across all stages except in the executive function and visuospatial ability domains in the SCD group. GM=gray matter, MMSE=Mini-Mental State Examination, SCD=subjective cognitive decline, MCI=mild cognitive impairment, AD=Alzheimer's disease. [a]these data represent characteristics of the sample at baseline. [b]median (interquartile range), [c]this measure was operationalized as the GM/intracranial volume ratio (lower scores reflect greater atrophy), [d]these data reflect β (SE) as obtained from unadjusted linear mixed models.

eTable 4. Relationships of education and intracranial volume with baseline and longitudinal cognition in multivariate models

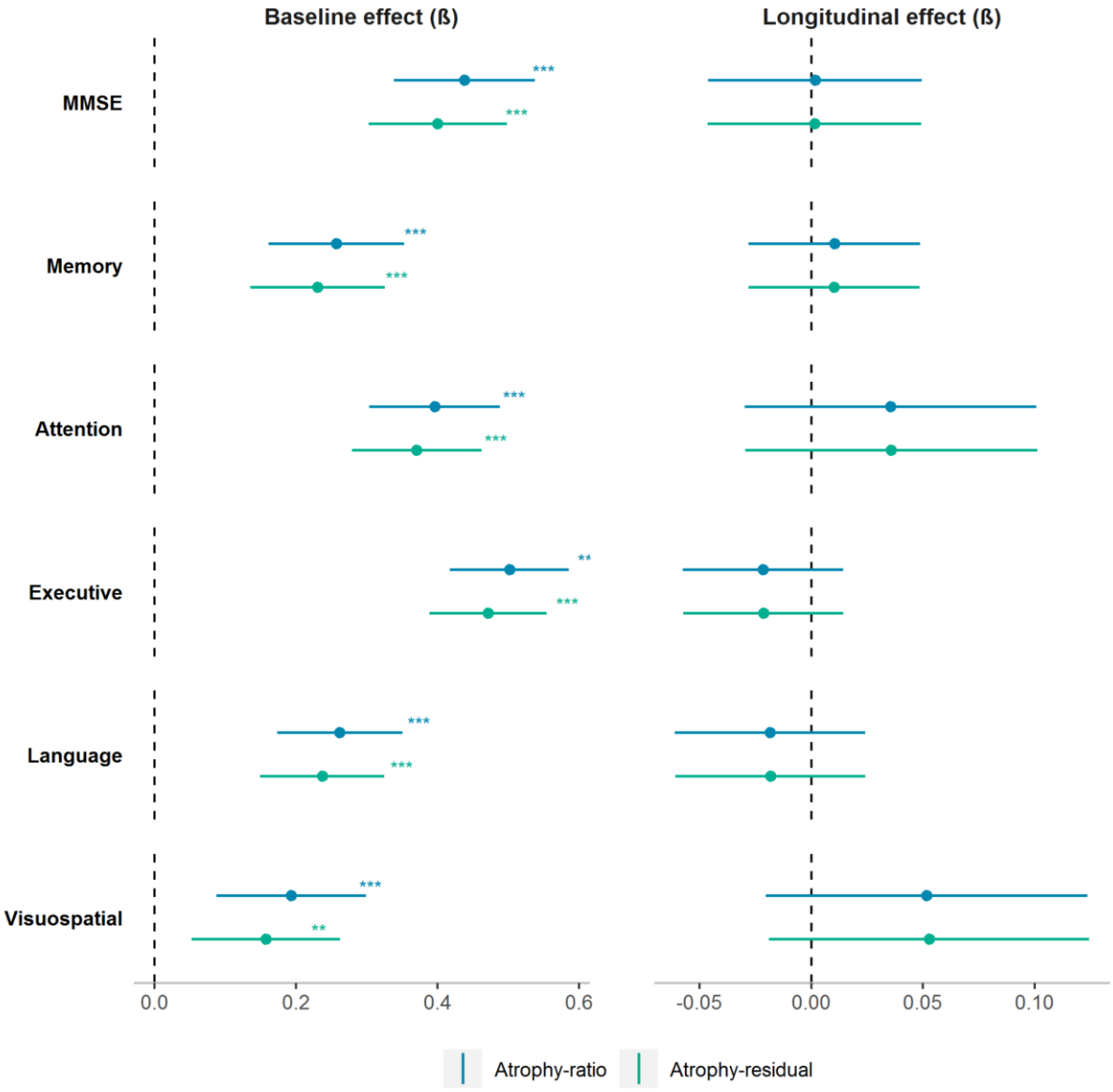
	Education		
	Total sample	**Pre-dementia**	**Dementia**
Baseline cognition[a]			
MMSE (global cognition)	0.39 (0.29 - 0.49) ***#	0.18 (0.09 - 0.27) ***#	0.38 (0.26 - 0.50) ***#
Memory	0.23 (0.14 - 0.33) ***#	0.12 (-0.03 - 0.27)	0.15 (0.06 - 0.24) **#
Attention	0.36 (0.27 - 0.46) ***#	0.27 (0.19 - 0.35) ***#	0.35 (0.22 - 0.48) ***#
Executive function	0.47 (0.39 - 0.56) ***#	0.43 (0.34 - 0.52) ***#	0.40 (0.30 - 0.51) ***#
Language	0.24 (0.15 - 0.33) ***#	0.21 (0.12 - 0.30) ***#	0.16 (0.04 - 0.28) **#
Visuospatial ability	0.16 (0.06 - 0.27) **#	0.02 (-0.04 - 0.09)	0.17 (0.02 - 0.33) *#
Longitudinal cognition[b]			
MMSE (global cognition)	0.00 (-0.04 - 0.05)	0.05 (0.01 - 0.10) *	-0.12 (-0.19 - -0.05) **#
Memory	0.01 (-0.03 - 0.05)	0.04 (-0.01 - 0.10)	-0.06 (-0.11 - -0.01) *#
Attention	0.04 (-0.02 - 0.11)	0.00 (-0.03 - 0.04)	-0.01 (-0.14 - 0.13)
Executive function	-0.02 (-0.06 - 0.02)	0.00 (-0.04 - 0.03)	-0.10 (-0.16 - -0.04) **#
Language	-0.02 (-0.06 - 0.03)	0.00 (-0.03 - 0.04)	-0.12 (-0.20 - -0.04) **#
Visuospatial ability	0.05 (-0.02 - 0.13)	0.07 (0.01 - 0.13) *	-0.02 (-0.15 - 0.10)
	Intracranial volume		
	Total sample	**Pre-dementia**	**Dementia**
Baseline cognition[a]			
MMSE (global cognition)	0.39 (0.27 - 0.51) ***#	0.07 (-0.03 - 0.18)	0.38 (0.23 - 0.53) ***#
Memory	0.23 (0.11 - 0.35) ***#	0.18 (-0.01 - 0.37)	0.13 (0.02 - 0.24) *#
Attention	0.29 (0.18 - 0.40) ***#	0.10 (0.00 - 0.20) *	0.30 (0.14 - 0.46) ***#
Executive function	0.26 (0.16 - 0.37) ***#	0.09 (-0.02 - 0.20)	0.24 (0.11 - 0.36) ***#
Language	0.18 (0.08 - 0.29) ***#	-0.01 (-0.12 - 0.10)	0.18 (0.04 - 0.32) *#
Visuospatial ability	0.27 (0.14 - 0.40) ***#	-0.02 (-0.09 - 0.06)	0.34 (0.15 - 0.53) ***#
Longitudinal cognition[b]			
MMSE (global cognition)	-0.02 (-0.07 - 0.03)	0.00 (-0.05 - 0.04)	-0.01 (-0.08 - 0.06)
Memory	0.01 (-0.03 - 0.04)	-0.02 (-0.08 - 0.03)	0.04 (-0.01 - 0.09)
Attention	-0.06 (-0.13 - 0.00)	-0.02 (-0.05 - 0.02)	-0.07 (-0.20 - 0.06)
Executive function	-0.02 (-0.06 - 0.01)	0.02 (-0.02 - 0.06)	-0.05 (-0.11 - 0.01)

Language	-0.02 (-0.07 - 0.02)	0.03 (-0.01 - 0.06)	-0.06 (-0.14 - 0.02)
Visuospatial ability	0.00 (-0.07 - 0.07)	0.02 (-0.03 - 0.08)	-0.01 (-0.13 - 0.11)

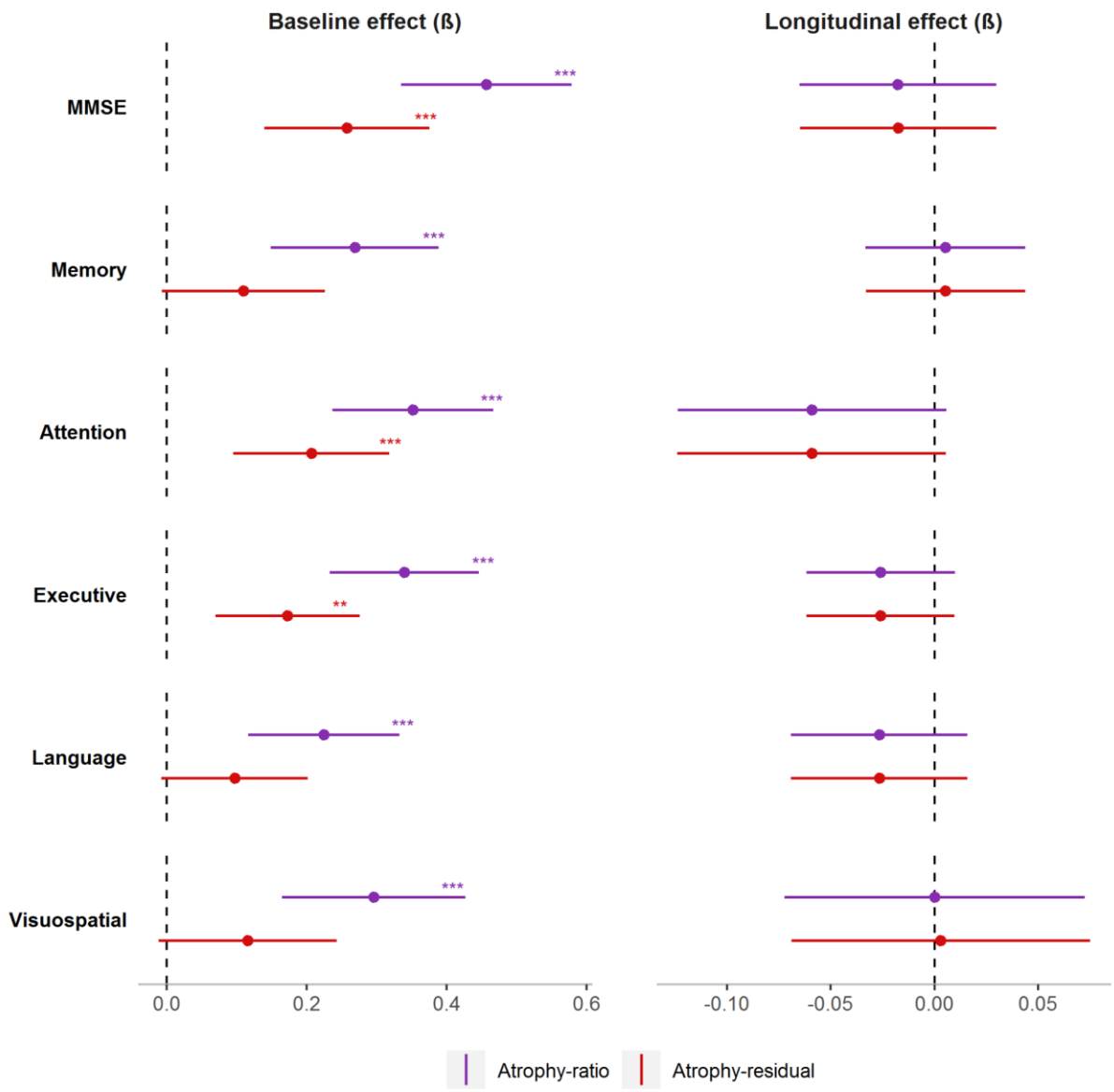
Data are displayed as β (95% CI) as obtained from our multivariate linear mixed models (including education and intracranial volume simultaneously as predictors). All models contained random intercepts and slopes per participant, and were corrected for age, sex, whole-brain GM atrophy and MRI field strength. [a]results reflect simple main effects, [b]results reflect interaction effects with time. MMSE=Mini-Mental State Examination. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, $^{\#}p<0.05$ after correction for multiple comparisons using the false discovery rate.

eFigure 1. Relationships of education and intracranial volume with baseline and longitudinal cognition by atrophy operationalization

A. Education effects



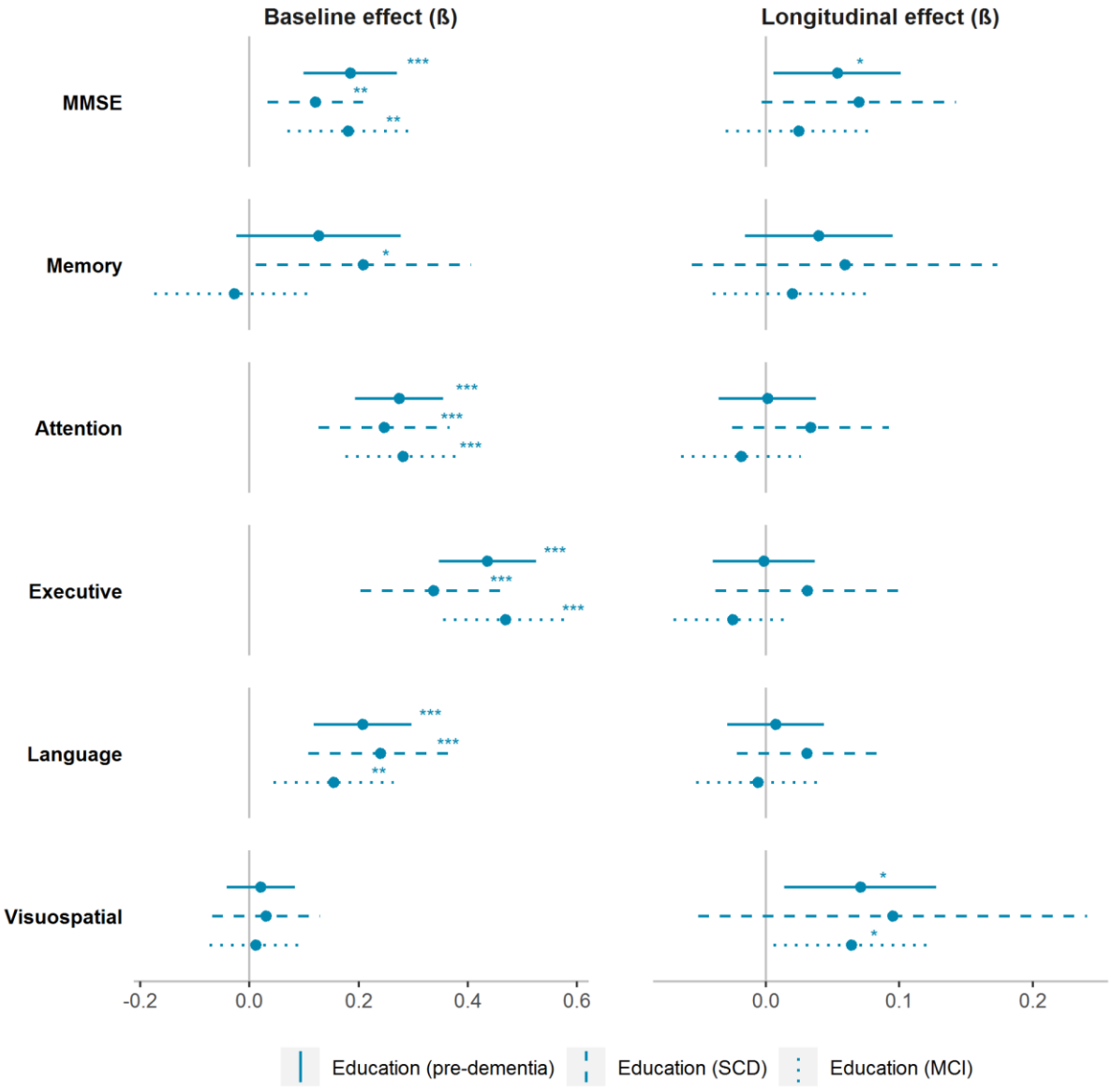
B. ICV effects



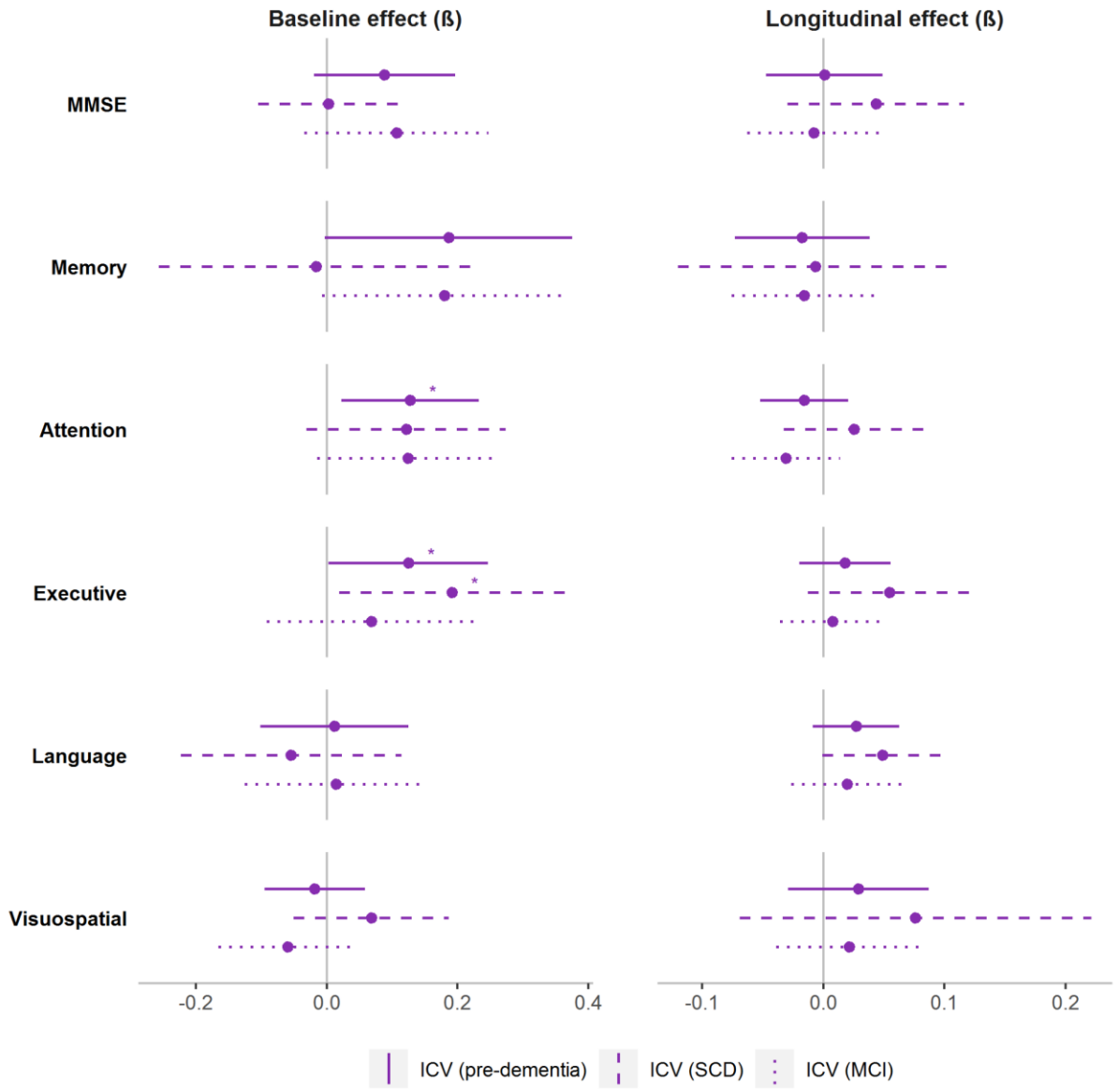
Results presented are either using an ICV-residualized measure of gray matter as a measure of atrophy (i.e. atrophy-residual) or the total gray matter volume to ICV ratio as a measure of atrophy (i.e. atrophy-ratio). Results are based on univariate linear mixed models and reflect effects that were estimated after correction for all covariates. ICV=intracranial volume, MMSE = mini mental state examination. *p≤0.01, *p≤0.05, **p≤0.01, ***p≤0.001.

eFigure 2. Relationships of education (A) and intracranial volume (B) with baseline and longitudinal cognition in the pre-dementia sample, stratified for SCD and MCI participants.

C. Education effects



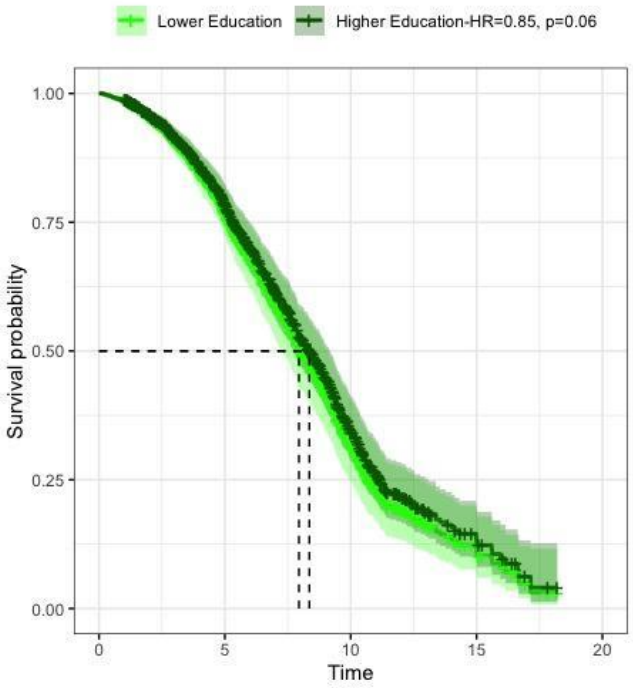
B. ICV effects



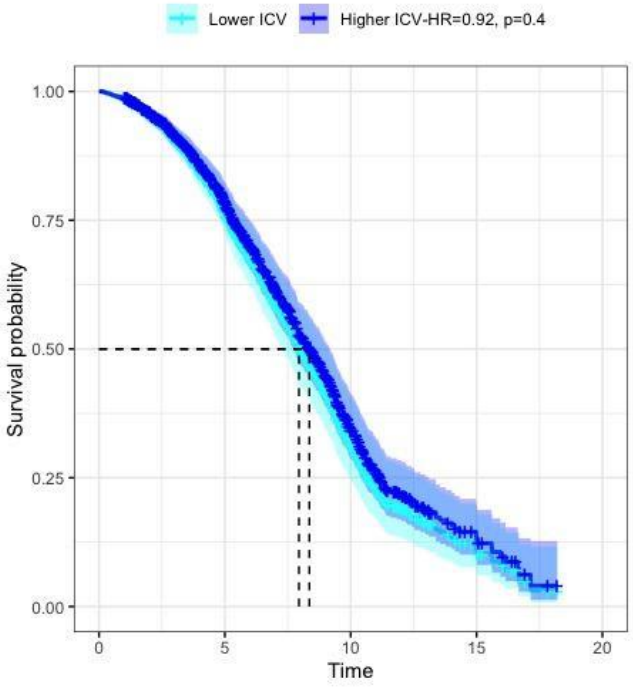
Results are based on univariate linear mixed models and reflect effects that were estimated after correction for all covariates. SCD = subjective cognitive decline, MCI = Mild cognitive impairment, ICV=intracranial volume, MMSE = mini mental state examination. *p≤0.01, *p≤0.05, **p≤0.01, ***p≤0.001.

eFigure 3. Relationships of education and intracranial volume with mortality adjusting for atrophy operationalized with the residual method

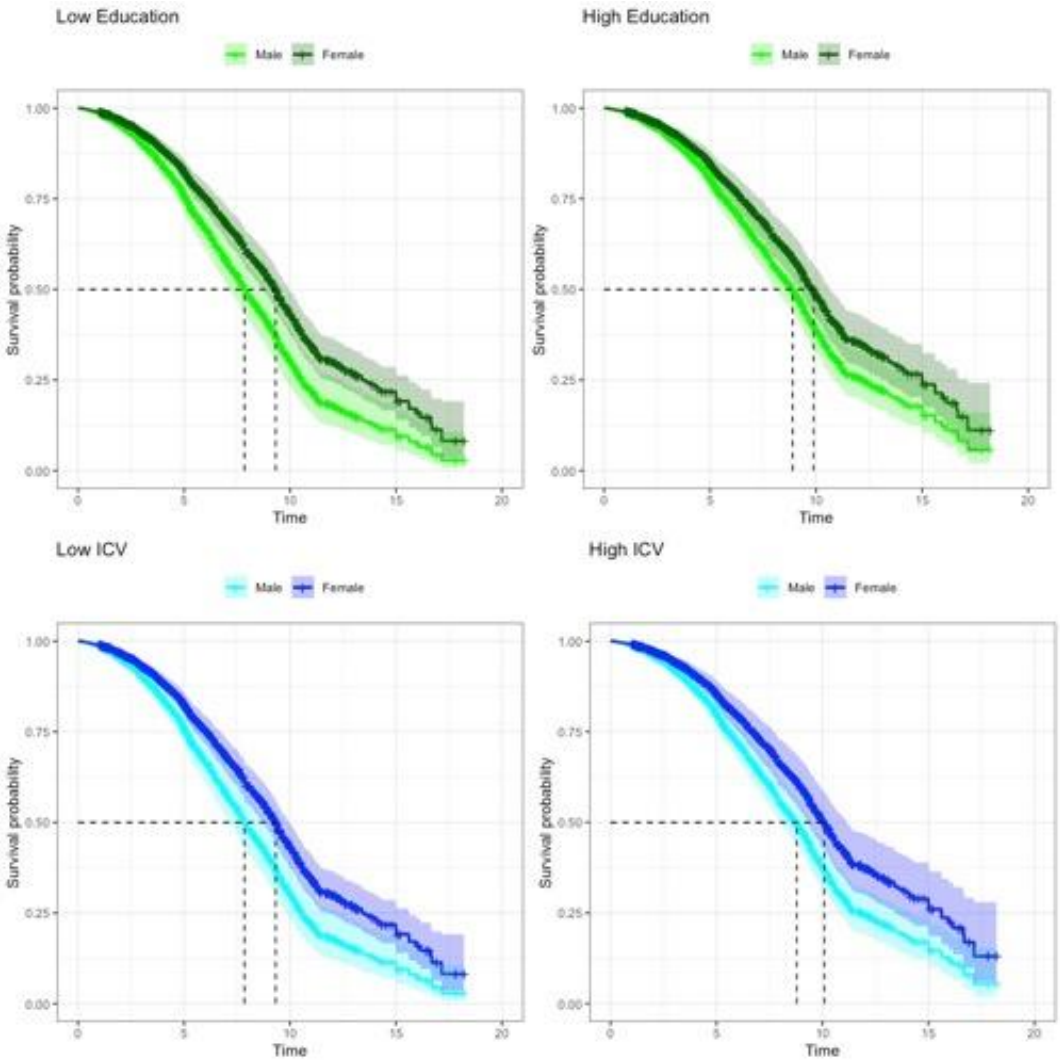
A. Education



B. ICV



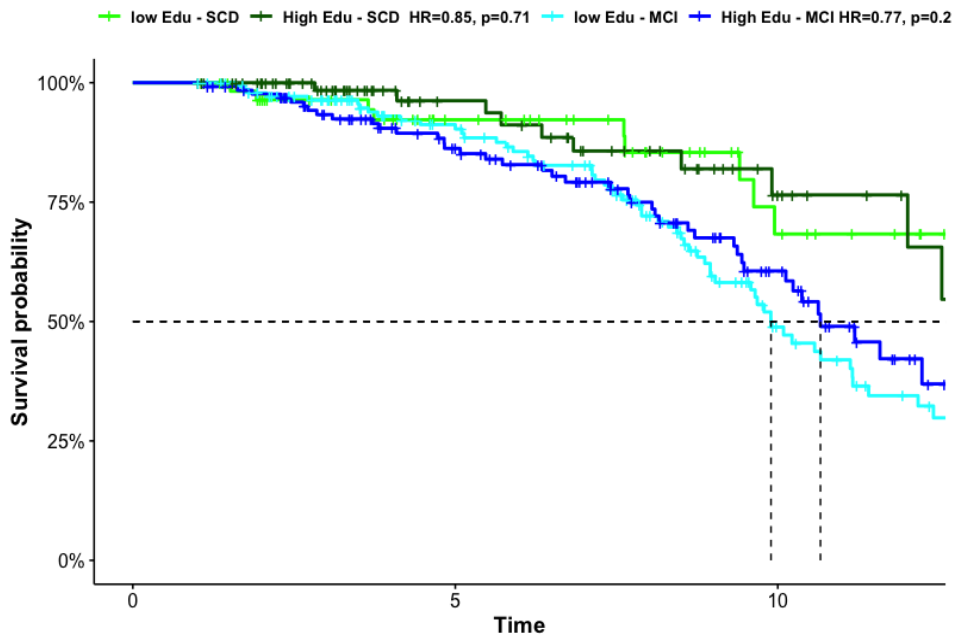
eFigure 4. Survival of males vs. females, stratified for level of reserve (low education vs. high education and low ICV vs. high ICV)



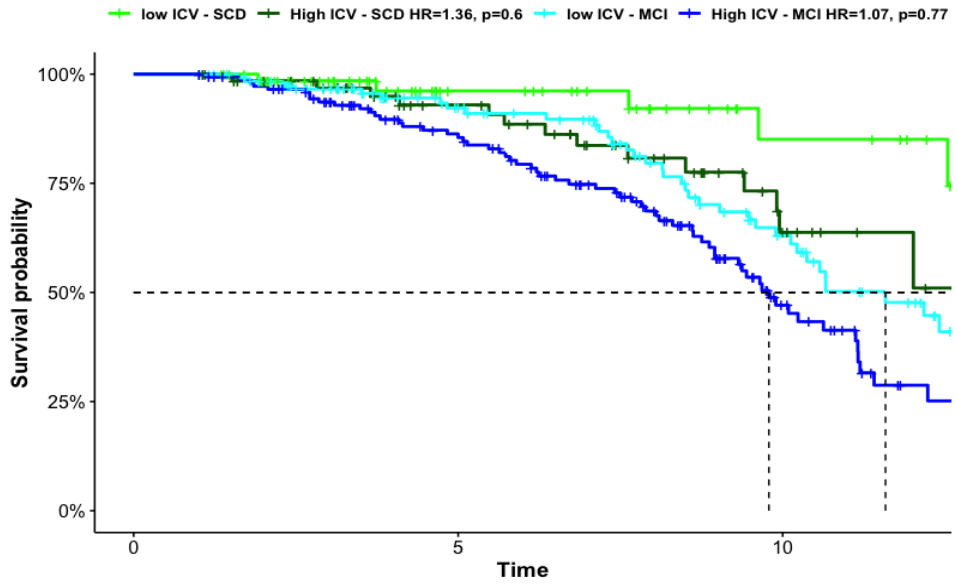
Results presented here show that sex does not seem to affect the association between level of reserve (either education or ICV) and mortality risk. This is additionally supported by the lack of an interaction effect between sex and education/ICV on survival probabilities assessed in (separate) Cox models.

eFigure 5. Survival of participants in higher and lower education and intracranial volume groups, stratified for groups of SCD and MCI participants.

A



B



Kaplan-meyer (unadjusted) curves for (A) education and (B) ICV. The hazard ratios are based on univariate Cox proportional hazard models estimated after correction for all covariates. Lower education and intracranial volume groups were used as the reference and HRs were calculated separately in groups of SCD and MCI. HR = hazard ratio, Edu = Education, ICV=intracranial volume, SCD = subjective cognitive decline, MCI = Mild cognitive impairment.

eTable 5. Relationship of education and intracranial volume with mortality, stratified across disease stages

	Univariate model		
	Total	**Pre-dementia**	**Dementia**
Education	0.84 (0.72 - 0.99) *	0.76 (0.53 - 1.09)	0.95 (0.79 - 1.13)
ICV	0.82 (0.67 - 0.99) *	1.10 (0.71 - 1.69)	0.85 (0.69 - 1.06)
	Multivariate model		
	Total	**Pre-dementia**	**Dementia**
Education	0.86 (0.73 - 1.01)	0.76 (0.53 - 1.09)	0.96 (0.80 - 1.16)
ICV	0.83 (0.68 - 1.00)	1.11 (0.72 - 1.71)	0.86 (0.69 - 1.07)

Data are displayed as HR (95% CI) as obtained from either univariate or multivariate linear mixed models (including education and intracranial volume simultaneously as predictors) Cox regression models. All models were corrected for age, sex, whole-brain GM atrophy and MRI field strength. ICV=Intracranial Volume. *$p<0.05$

eTable 6. Description of groups with and without longitudinal follow-up cognitive data

	Without follow-up (n=434)	**With follow-up (n=864)**
Participant characteristics		
Diagnosis (n , %)	SCD (49 , 11.3), MCI (37 , 8.5), AD (348 , 80.2)	SCD (193 , 10.8), MCI (237 , 27.4), AD (534 , 61.8)
Age	66.2 ± 8.0	65.3 ± 7.4
Sex (% female)	58.5	49.3
Education [Verhage scale] [a]	5 (2)	5 (2)
APOE ε4 (% positive)	67.6	72.2
Brain measures		
Intracranial volume (cm3)	1,474.32 (161.35)	1,494.32 (151.71)
Whole-brain GM atrophy [b]	0.38 (0.05)	0.38 (0.05)
Baseline cognition		
MMSE (global cognition)	20.25 (6.30)	23.72 (4.28)
Memory	-0.09 (0.97)	0.09 (0.80)
Attention	-0.30 (0.99)	0.09 (0.74)
Executive functioning	-0.32 (0.87)	0.07 (0.78)
Language	-0.28 (0.99)	0.14 (0.66)
Visuospatial ability	-0.15 (0.90)	0.07 (0.72)
Mortality		
Deceased during follow up (n,%)	220 (50.7)	437 (50.6)
Follow up (to death, years)	4.8 (2.8)	6.6 (3.3)

Data are presented as mean ± SD unless indicated otherwise. There were statistically significant differences between the group without cognitive follow-up and the group with follow-up for all variables except age, APOE e-4 genotype and percentage of deceased during follow-up. GM=gray matter, MMSE=Mini-Mental State Examination, AD=Alzheimer's disease. [a]median (interquartile range), [b]this measure was operationalized as the GM/intracranial volume ratio (lower scores reflect greater atrophy)