

Supplementary information

Table 1: Elecsys CSF summary statistics of CSF variables, by group

	Controls n=137	SMC n=92	EMCI n=252	LMCI n=143	AD n=119	<i>p</i> value across groups
CSF Aβ1-42 (pg/ml)	1252.2 (450.9)	1228.8 (424.7)	1109.8 (440.2)	908.3 (382.8)	693.7 (329.5)	<0.001
Median (IQR)	1345.0 (810.1)	1313.5 (825.2)	1085.5 (925.1)	810.6 (440.7)	624.1 (292.4)	
CSF t-tau (pg/ml)	235.7(91.5)	241.9 (95.2)	255.5 (117.4)	309.9 (137.6)	384.4 (155.7)	<0.001
Median (IQR)	210.1 (103.1)	217.8 (133.2)	233.9 (121.7)	283.7 (171.8)	353.7 (177.7)	
CSF p-tau (pg/ml)	21.7 (9.2)	22.1 (9.8)	24.1 (13.2)	30.3 (13.7)	37.9 (16.2)	<0.001
Median (IQR)	19.3 (10.6)	19.3 (11.5)	20.7 (12.8)	27.7 (17.5)	34.3 (20.4)	

Values are mean (SD) unless reported.

Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease

Table 2: Regression model results for the relationship between WMH and CSF Aβ1-42, by group

WMH and Aβ1-42	Controls	SMC	EMCI	LMCI	AD
TIV and gender adjusted					
% reduction in WMH (ml) per 1SD change in Aβ1-42	30.1	20.0	22.0	14.9	17.5
95% confidence intervals	(19.9 to 39.0)	(6.1 to 31.2)	(12.7 to 30.7)	(-0.6 to 28.0)	(-0.9 to 32.5)
<i>p</i> value	<0.001	0.006	<0.001	0.06	0.06

Estimates are percentage decrease in WMH volume per one SD change (1 SD = 78.3pg/ml) in Aβ1-42. The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of Aβ1-42 by group

Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; TIV, total intracranial volume; WMH, white matter hyperintensities.

Table 3: Regression model results for the relationship between WMH and CSF Aβ1-42 (Elecsys assay), by group

WMH and Aβ1-42	Controls	SMC	EMCI	LMCI	AD
TIV adjusted					
% reduction in WMH (ml) per 1SD change in Aβ1-42	25.5	30.9	23.4	27.4	20.5
95% confidence intervals	(10.3 to 38.2)	(13.5 to 44.8)	(10.9 to 34.2)	(6.1 to 44.0)	(-3.9 to 39.2)
<i>p</i> value	0.002	0.002	0.001	0.02	0.09
TIV and age adjusted					
% reduction in WMH (ml) per 1SD change in Aβ1-42	22.3	26.4	15.1	19.5	29.1
95% confidence intervals	(6.8 to 35.2)	(7.7 to 41.3)	(2.8 to 25.9)	(-2.2 to 36.6)	(10.5 to 43.8)
<i>p</i> value	0.007	0.008	0.02	0.07	0.004
Between group differences in % reductions per 1SD change in Aβ1-42			<i>p</i> value = 0.9 (0.9 with age adjustment)		

Estimates are percentage decrease in WMH volume per one SD change (1 SD = 413.2pg/ml) in Aβ1-42. The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of Aβ1-42 by group.

Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; TIV, total intracranial volume; WMH, white matter hyperintensities.

Table 4: Regression model results examining the association between CSF A β 1-42 (Elecsys assay) and WMH with various covariates

a)

Model set	Covariates	% reduction in WMH per 1SD change in A β 1-42	95% confidence interval	p value
1	i) None	26.4	19.8 to 32.5	<0.001
	ii) TIV	25.6	19.1 to 31.5	<0.001
	iii) TIV, group	25.3	18.3 to 31.7	<0.001
	iv) TIV, group, age	20.1	13.3 to 26.5	<0.001
	v) TIV, group, age, APOE- ϵ 4 status	21.4	14.4 to 27.9	<0.001
2	i) T-tau	26.8	19.9 to 33.0	<0.001
	ii) T-tau, TIV	25.3	18.6 to 31.5	<0.001
	iii) T-tau, TIV, group	25.2	18.1 to 31.7	<0.001
	iv) T-tau, TIV, group, age	20.4	13.5 to 26.8	<0.001
	v) T-tau, TIV, group, age, APOE- ϵ 4 status	21.5	14.4 to 28.0	<0.001
3	i) P-tau	27.2	20.4 to 33.5	<0.001
	ii) P-tau, TIV	25.8	19.0 to 32.0	<0.001
	iii) P-tau, TIV, group	25.6	18.5 to 32.1	<0.001
	iv) P-tau, TIV, group, age	20.8	13.8 to 27.2	<0.001
	v) P-Tau, TIV, group, age, APOE- ϵ 4 status	21.9	14.8 to 28.4	<0.001

b)

Model set	Covariates from v)	Partial R ₂
1	A β 1-42	0.04
	TIV	0.05
	Group	0.0004
	Age	0.2
	APOE- ϵ 4 status	0.003
2	A β 1-42	0.04
	t-tau	0.0004
	TIV	0.05
	Group	0.0005
	Age	0.2
3	A β 1-42	0.04
	p-tau	0.0004
	TIV	0.05
	Group	0.0004
	Age	0.2
	APOE- ϵ 4 status	0.0003

All models assess associations between WMH and A β 1-42 with various covariates, with model 2 additionally adjusting for t-tau and model 3 additionally adjusting for p-tau. In a) estimates are percentage changes in WMH volume per one SD change (1 SD = 413.2pg/ml) in A β 1-42. The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of A β 1-42 by group. In b) partial R₂ are shown for each covariate in the fully-adjusted model v) from each of the three model sets. R₂ values are shown to 2 significant figures for values >0.1 and 1 significant figure for values <0.1.

Key: TIV, total intracranial volume; WMH, white matter hyperintensities

Table 5: Regression model results for associations between WMH and age

a)	Controls	SMC	EMCI	LMCI	AD
Change in WMH (ml) per decade increase in age	0.4	0.4	0.7	0.6	0.6
Confidence intervals	(0.2 to 0.6)	(0.1 to 0.7)	(0.6 to 0.8)	(0.4 to 0.8)	(0.4 to 0.8)
<i>p</i> value	<0.001	0.006	<0.001	<0.001	<0.001
Between-group differences in slope <i>p</i> value = 0.2					
b)	Controls	SMC	EMCI	LMCI	AD
Adjusted for hypertension					
Change in WMH (ml) per decade increase in age	0.3	0.4	0.7	0.6	0.6
Confidence intervals	(0.1 to 0.6)	(0.1 to 0.7)	(0.5 to 0.8)	(0.4 to 0.7)	(0.4 to 0.7)
<i>p</i> value	0.001	0.007	<0.001	<0.001	<0.001
c)	Controls	SMC	EMCI	LMCI	AD
Adjusted for smoking					
Change in WMH (ml) per decade increase in age	0.4	0.4	0.7	0.6	0.6
Confidence intervals	(0.2 to 0.6)	(0.1 to 0.7)	(0.6 to 0.8)	(0.4 to 0.8)	(0.4 to 0.8)
<i>p</i> value	<0.001	0.006	<0.001	<0.001	<0.001
d)	Controls	SMC	EMCI	LMCI	AD
Adjusted for BMI					
Change in WMH (ml) per decade increase in age	0.4	0.5	0.7	0.6	0.6
Confidence intervals	(0.2 to 0.7)	(0.2 to 0.8)	(0.6 to 0.8)	(0.4 to 0.7)	(0.4 to 0.8)
<i>p</i> value	<0.001	0.003	<0.001	<0.001	<0.001
e)	Controls	SMC	EMCI	LMCI	AD
Adjusted for diabetes					
Change in WMH (ml) per decade increase in age	0.4	0.4	0.7	0.6	0.6
Confidence intervals	(0.2 to 0.6)	(0.1 to 0.8)	(0.6 to 0.8)	(0.4 to 0.8)	(0.4 to 0.8)
<i>p</i> value	<0.001	0.007	<0.001	<0.001	<0.001
f)	Controls	SMC	EMCI	LMCI	AD
Adjusted for hypertension, smoking, BMI and diabetes					
Change in WMH (ml) per decade increase in age	0.3	0.5	0.7	0.6	0.6
Confidence intervals	(0.1 to 0.6)	(0.2 to 0.8)	(0.5 to 0.8)	(0.4 to 0.7)	(0.4 to 0.8)
<i>p</i> value	0.002	0.005	<0.001	<0.001	<0.001

Estimates are shown for log_eWMH volume increase, with 95% confidence intervals, for every decade increase in age and all adjusted for TIV. Table a) had no additional adjustment, with subsequent tables adjusted for b) hypertension, c) smoking, d) BMI e) diabetes f) hypertension, smoking, BMI and diabetes.

Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; TIV, total intracranial volume; WMH, white matter hyperintensities; BMI, body mass index.

Table 6: Regression models of the associations between CSF biomarkers and either the parietal lobe WMHs or the rest of the brain WMHs.

Outcome	Predictors	SD change in biomarker per doubling in WMH	CI	p value	
Aβ1-42	Non-age adjusted	Parietal log _e WMH	-5.5	-13.9 to 3.8	0.2
		Non-parietal log _e WMH	-18.1	-29.2 to -5.4	0.007
	Age adjusted	Parietal log _e WMH	-5.0	-13.5 to 4.3	0.3
		Non-parietal log _e WMH	-16.2	-27.6 to -2.9	0.02
T-tau	Non-age adjusted	Parietal log _e WMH	-7.0	-15.7 to 2.6	0.1
		Non-parietal log _e WMH	14.4	-1.7 to 33.1	0.08
	Age adjusted	Parietal log _e WMH	-7.4	-16.1 to 2.2	0.1
		Non-parietal log _e WMH	11.5	-4.5 to 30.1	0.2
P-tau	Non-age adjusted	Parietal log _e WMH	-2.7	-11.7 to 7.2	0.6
		Non-parietal log _e WMH	5.8	-8.9 to 22.9	0.5
	Age adjusted	Parietal log _e WMH	-2.4	-11.4 to 7.6	0.6
		Non-parietal log _e WMH	7.4	-7.7 to 25.1	0.4

Estimates are for an SD increase in CSF biomarker for every 1 unit increase in WMH volume (ml). The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of CSF biomarker by group. All are adjusted for TIV and diagnostic group. Results for one predictor are adjusted for the other predictor. Non-parietal WMH is total brain WMH minus the parietal lobe WMH. Key: WMH, white matter hyperintensities.

Table 7: Regression model results assessing associations of CSF biomarkers and age, by group

	Controls	SMC	EMCI	LMCI	AD
Aβ1-42					
SD change in Aβ1-42 per decade increase in age	-0.4	-0.2	-0.3	-0.2	0.08
Confidence intervals	(-0.7 to -0.2)	(-0.6 to 0.3)	(-0.5 to -0.2)	(-0.4 to 0.1)	(-0.1 to 0.3)
p value	0.001	0.4	<0.001	0.07	0.4
Between group differences in slope p=0.01					
T-tau					
SD change in t-tau per decade increase in age	0.3	0.2	0.3	-0.02	-0.3
Confidence intervals	(0.1 to 0.5)	(0.008 to 0.4)	(0.1 to 0.4)	(-0.3 to 0.2)	(-0.6 to -0.06)
p value	0.001	0.04	0.002	0.9	0.02
Between group differences in slope p<0.001					
P-tau					
SD change in p-tau per decade increase in age	0.2	0.05	0.1	-0.2	-0.4
Confidence intervals	(0.01 to 0.4)	(-0.3 to 0.4)	(0.005 to 0.3)	(-0.4 to 0.03)	(-0.7 to -0.07)
p value	0.04	0.8	0.04	0.09	0.02
Between group differences in slope <0.001					

Estimates are for SD change in CSF biomarker per decade increase in age. The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of CSF biomarker by group.

Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; TIV, total intracranial volume; WMH, white matter hyperintensities.