

# Supplementary Material

## White Matter Hyperintensities Are No Major Confounder for Alzheimer's Disease Cerebrospinal Fluid Biomarkers

**Supplementary Table 1.** Overview of diagnostic criteria

<b>Research centers</b>	<b>Diagnostic criteria</b>	<b>CSF biomarkers used as support in diagnosis?</b>
<b>1 Radboudumc</b>	AD: [1, 2] MCI: [3, 4]	Yes
<b>2 Hospital de Sant Pau</b>	MCI: [3, 4]	No
<b>3 IRCCS Foundation San Giovanni di Dio Fatebenefratelli</b>	AD: [2] MCI: [5]	No
<b>4 University of Lisbon</b>	AD: [2] MCI: [3]	Yes
<b>5 University of Eastern Finland (UEF)</b>	Dementia: [6] AD: [1] MCI: [3]	No
<b>6 University of Genoa</b>	AD: [7, 8]	Yes
<b>7 IRCCS Fondazione Santa Lucia</b>	AD: [1] MCI: [3]	Yes
<b>8 University of Milan, Fondazione Ca' Granda IRCCS Ospedale Policlinico</b>	AD: [7, 8] MCI: [3]	Yes
<b>9 Università degli Studi di Perugia</b>	AD: [2] MCI: [3]	Yes

**Supplementary Table 2.** Overview of cut-off values of CSF biomarker concentrations

Research centers	Assay type	A $\beta$ <sub>42</sub> (ng/L)	t-tau (ng/L)	p-tau (ng/L)	Definition of cut-off point for abnormal
1	Fujirebio ELISA	≤500*	≥350**	≥85	Defined from population of healthy controls
2	Fujirebio ELISA	≤550	≥350	≥61	ROC curve [9]
3	Fujirebio ELISA	≤500	≥500***	≥70	Rank-based [10]
4	Fujirebio ELISA	≤445	≥300	≥61	ROC curve
5	Fujirebio ELISA	≤450	≥400	≥70	ROC curve
6	Fujirebio ELISA	≤600	≥300-400	≥40	ROC curve
7	Fujirebio ELISA	≤500	ND	≥40	Unknown
8	Fujirebio ELISA	≤500	≥500***	≥61	Rank-based [10]
9	Fujirebio ELISA	≤800	≥300	≥60	Rank-based [10]

CSF, cerebrospinal fluid; A $\beta$ <sub>42</sub>, amyloid- $\beta$ ; t-tau, total tau; p-tau, phosphorylated tau; ROC, receiver operating characteristic; ND, not determined.

\* A $\beta$ <sub>42</sub>: age <15: ≤400 ng/L; age >15: ≤500 ng/L.

\*\* t-tau: age <50: ≥300 ng/L; age >50: ≥ 50 ng/L.

\*\*\* t-tau: age <50: ≥300 ng/L; 50 <age <70: ≥450 ng/L; age >70: ≥500 ng/L.

**Supplementary Table 3.** Comparison of control and SMC subjects

	<b>Controls</b>	<b>SMCs</b>	<b><i>p</i>*</b>
<b>Sample size: <i>n</i></b>	44	8	
<b>CSF A<math>\beta</math><sub>42</sub>: mean, ng/L (SD)</b>	746 (191)	817 (209)	0.417
<b>CSF t-tau: mean, ng/L (SD)</b>	41 (15)	48 (18)	0.275
<b>CSF p-tau: mean, ng/L (SD)</b>	214 (89)	287 (156)	0.281
<b>WMH volume: mean, mL (SD)</b>	5.59 (2.87)	6.45 (4.15)	0.771

SMC, subjective memory complainers; CSF, cerebrospinal fluid; SD, standard deviation; A $\beta$ <sub>42</sub>, amyloid- $\beta$ ; t-tau, total tau; p-tau, phosphorylated tau; WMH, white matter hyperintensities.

\* Mann Whitney test.

**Supplementary Table 4.** Overview of MRI scanners

<b>Research centers</b>	<b>Type of MRI scanner</b>	<b>Company</b>	<b>Magnetic field (Tesla)</b>	<b>Protocol</b>
<b>1</b>	Magnetom Avanto 1	SIEMENS	1.5 T	1 protocol, acquisition matrix 192x256
	Magnetom Avanto 2	SIEMENS	1.5 T	1 protocol, acquisition matrix 192x256
	Magnetom TrioTim	SIEMENS	3.0 T	1 protocol, acquisition matrix 192x256
<b>2</b>	ACHIEVA X-series	PHILIPS	3.0 T	1 protocol, acquisition matrix 240x234
<b>3</b>	Signa HDxt	GE HealthCare	1.5 T	1 protocol, acquisition matrix 256x256
<b>4</b>	Signa HDxt	GE HealthCare	1.5 T	No protocol
<b>5</b>	Magnetom Vision plus	SIEMENS	1.5 T	4 protocols, acquisition matrix 256x256
<b>6</b>	Genesis Signa	GE HealthCare	1.5 T	No protocol
	Signa Excite	GE HealthCare	1.5 T	No protocol
	Signa HDxt	GE HealthCare	1.5 T	No protocol
	Signa HDxt	GE HealthCare	3.0 T	No protocol
	ACHIEVA A-series 1	PHILIPS	1.5 T	No protocol
	ACHIEVA A-series 2	PHILIPS	1.5 T	No protocol
	ACHIEVA A-series 3	PHILIPS	1.5 T	No protocol
<b>7</b>	Magnetom Allegra	SIEMENS	3.0 T	1 protocol, acquisition matrix 224x256
<b>8</b>	ACHIEVA X-series	PHILIPS	3.0 T	1 protocol, acquisition matrix 272x268
<b>9</b>	ACHIEVA	PHILIPS	3.0 T	1 protocol, acquisition matrix 256x256

**Supplementary Table 5.** Overview of MRI scanner characteristics

<b>Research centers</b>	<b>T1-weighted MRI parameters</b>				
	<b>TR (ms)</b>	<b>TE (ms)</b>	<b>Flip angle (°)</b>	<b>Matrix size</b>	<b>Voxel size (mm<sup>3</sup>)</b>
<b>1*</b>	1900	3.42	15	192x256	1.0x1.0x1.0
<b>2</b>	8.1	3.7	8	240x234	1.0x1.0x1.0
<b>3</b>	11.6	5.1	8	256x256	1.0x1.0x1.0
<b>4</b>	NA	NA	NA	NA	Max. 2.0x2.0x2.0
<b>5</b>	9.7	4.0	10	256x256	1.0x1.0x1.0
<b>6*</b>	NA	NA	NA	NA	Max. 2.0x2.0x2.0
<b>7</b>	1338	2.4	15	224x256	1.0x1.0x1.0
<b>8</b>	596.4	15	69	272x268	1.0x1.0x1.0
<b>9</b>	8.0	3.7	0	256x256	1.0x1.0x1.0

TR, repetition time; TE, echo time; NA, not applicable (no protocol was used).

\*Different scanners are used in group 1 and 6.

**Supplementary Table 6.** Overview of MRI scanner characteristics

<b>Research centers</b>	<b>T2-weighted-FLAIR MRI parameters</b>				
	<b>TR (ms)</b>	<b>TE (ms)</b>	<b>Flip angle (°)</b>	<b>Matrix size</b>	<b>Voxel size (mm<sup>3</sup>)</b>
<b>1*</b>	UN	UN	UN	UN	Max. 2.0x2.0x2.0
<b>2</b>	11000	120	0	240x138	1.0x1.0x1.0
<b>3</b>	10000	100	0	256x256	1.0x1.0x1.0
<b>4</b>	NA	NA	NA	NA	Max. 2.0x2.0x2.0
<b>5</b>	9000	119	0	256x256	1.0x1.0x1.0
<b>6*</b>	NA	NA	NA	NA	Max. 2.0x2.0x2.0
<b>7</b>	8170	96	180	256x192	1.0x1.0x1.0
<b>8</b>	8000	125	90	227x260	1.0x1.0x1.0
<b>9</b>	9000	90	0	256x256	1.0x1.0x1.0

TR, repetition time; TE, echo time; UN, unknown, data was not available; NA, not applicable (no protocol was used).

\*Different scanners are used in group 1 and 6.

**Supplementary Table 7.** Detailed overview of patients

<b>Research centers</b>	<b>Total (n)</b>		<b>Control (n)</b>	<b>MCI (n)</b>	<b>AD (n)</b>
	<b>Included</b>	<b>Excluded</b>	<b>Included</b>	<b>Included</b>	<b>Included</b>
<b>1</b>	48	34	11	13	24
<b>2</b>	49	10	39	10	0
<b>3</b>	22	24	1	12	9
<b>4</b>	1	20	0	1	0
<b>5</b>	18	9	0	18	0
<b>6</b>	11	10	1	4	6
<b>7</b>	4	7	0	3	1
<b>8</b>	1	15	0	0	1
<b>9</b>	18	8	0	11	7
<b>Total</b>	172	137	52	72	48

AD, Alzheimer's disease; MCI, mild cognitive impairment.

## REFERENCES

- [1] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.
- [2] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.
- [3] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.
- [4] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* **56**, 303-308.
- [5] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.
- [6] Harper C (2014) Diagnostic and statistical manual of mental disorders. *A Companion to Criminal Justice, Mental Health & Risk*, pp. 143-147.



- [7] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, Gauthier S, Hampel H, Jicha GA, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Sarazin M, de Souza LC, Stern Y, Visser PJ, Scheltens P (2010) Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* **9**, 1118-1127.
- [8] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* **6**, 734-746.
- [9] Alcolea D, Martinez-Lage P, Sanchez-Juan P, Olazaran J, Antunez C, Izagirre A, Ecay-Torres M, Estanga A, Clerigue M, Guisasola MC, Sanchez Ruiz D, Marin Munoz J, Calero M, Blesa R, Clarimon J, Carmona-Iragui M, Morenas-Rodriguez E, Rodriguez-Rodriguez E, Vazquez Higuera JL, Fortea J, Lleó A (2015) Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. *Neurology* **85**, 626-633.
- [10] Sjogren M, Vanderstichele H, Agren H, Zachrisson O, Edsbacke M, Wikkelso C, Skoog I, Wallin A, Wahlund LO, Marcusson J, Nagga K, Andreasen N, Davidsson P, Vanmechelen E, Blennow K (2001) Tau and Abeta42 in cerebrospinal fluid from healthy adults 21-93 years of age: establishment of reference values. *Clin Chem* **47**, 1776-1781.