Supplementary Content

Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA*. 2009;302(4):385-393.

Supplementary text

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary text

Statistical analysis

Logistic regression models the dependence of a dichotomous variable, Y, on any number of explanatory variables, which are comprised in a column vector **X**. The explanatory variables CSF Aβ42, CSF T-tau, CSF P-tau, baseline MMSE and age were continuous while gender and *APOE* genotype were nominal. The logistic regression model rests on the assumption that

$$\text{Prob}(Y(\mathbf{X})=1)=1/(1+\exp(\alpha + \beta \cdot X))$$

with α being a real constant and β a row vector comprising as many real constants as there are variables in **X**. All possible linear combinations of variables and ratios of variables were tested and Akaike's information criterion (AIC) was considered to choose the best model. The logistic regression models may be used to construct cutoff equations for any two biomarkers (x and y). The statistical cutoff (Prob) is designated p_i. One may derive y as

$$y = (1/\beta_1) (\log p_i / (1- p_i) - \alpha) - \beta_2/\beta_1 * x$$

The sensitivity and specificity of the cutoff is altered by the choice of p_i. In this study p_i was chosen to obtain a pre-set sensitivity of 85% in AD patients with dementia versus controls.

eTable 1. CSF biomarker values from AMS, MUN, and KUOP reanalyzed in Mölndal

Center	Biomarker	No. (%)[a]	*R*	*P* Value	Weighting Formula
AMS	Aβ42	15 (11%)	0.92	<0.0001	Mölndal=1.14*AMS-12.27[b]
	T-tau	15 (11%)	0.95	<0.0001	Mölndal =1.08*AMS-40.58[b]
	P-tau	15 (11%)	0.94	<0.0001	Mölndal =1.06*AMS+0.2
MUN	Aβ42	23 (24%)	0.85	<0.0001	Mölndal =0.66*MUN+66.88[b]
	T-tau	23 (24%)	0.97	<0.0001	Mölndal =1.00*MUN+29.20[b]
	P-tau	23 (24%)	0.97	<0.0001	Mölndal =1.03*MUN-4.10
KUOP	Aβ42	35 (21%)	0.94	<0.0001	Mölndal =0.74*KUOP-83.18[b]
	T-tau	34 (20%)	0.96	<0.0001	Mölndal =1.26*KUOP-32.96[b]
	P-tau	35 (21%)	0.98	<0.0001	Mölndal =0.94*KUOP-3.86

[a]Percentages of total number of study subjects from center.

[b]The comparison indicated that the results from AMS, MUN or KUOP differed more than two coefficients of variance (CV) from the corresponding analysis at Mölndal (using Mölndal CVs for the assays), hence weighted values were used in the statistics; AMS, Amsterdam; MUN, Munich; KUOP, Kuopio.

eTable 2. Ratios Used for Normalization

Center	Biomarker	Study Group	Normalization Ratio[a]
AMS	Aβ42	Controls	616/929=0.66
	T-tau		305/416=0.73
KUOP	Aβ42	Controls	616/459=1.34
MUN	Aβ42	Controls	616/475=1.30
DESC	T-tau	MCI	461/357=1.29
STAV	Aβ42	AD	406/209=1.94
	P-tau		87/63=1.38

[a]Total study group mean biomarker level divided by center study group mean biomarker level; AD, Alzheimer's disease; AMS, Amsterdam; DESC, Descripa study; MUN, Munich; KUOP, Kuopio; STAV, Stavanger.

eTable 3. Demographic Data on Controls From Different Centers

Center	MMSE[a]	Men/ Women	*APOE* ε4		Age[a]
			Heterozygote	Homozygote	
AMS	29 (28-30)	5/11	2 (15%)	0	72 (60-82)
GOT	30 (26-30)	20/31	15 (29%)	2 (4%)	67 (56-80)
KUOP	29 (26-30)	11/19	7 (24%)	1 (3%)	71 (56-79)
LINK	29 (26-30)	21/20	NA	NA	64 (56-91)
MALM	29 (26-30)	15/24	10 (26%)	0	72 (60-87)
MUN	29 (26-30)	28/20	5 (21%)	0	60 (44-84)
NYC	30 (27-30)	22/20	8 (24%)	1 (3%)	66 (56-85)
PER	28 (26-30)	8/6	NA	NA	70 (60-85)
STO	30 (28-30)	12/11	NA	NA	68 (60-77)

[a]Data presented as median (range).

eTable 4. Demographic Data on MCI Subjects From Different Centers

Center	MMSE[a]	Men/ Women	*APOE* ε4		Age[a]
			Heterozygote	Homozygote	
AMS	26 (20-30)	19/17	8 (22%)	8 (22%)	69 (52-80)
DESC	29 (21-30)	15/19	12 (41%)	2 (7%)	70 (54-82)
GOT	29 (23-30)	41/44	33 (39%)	12 (14%)	65 (48-77)
HEID	26 (22-30)	25/19	NA	NA	71 (52-82)
KUOP	25 (17-30)	57/84	45 (39%)	22 (17%)	72 (48-84)
MALM	27 (24-30)	73/92	93 (56%)	2 (1%)	71 (49-89)
MUN	27 (23-30)	20/29	19 (41%)	5 (11%)	68 (49-83)
NYC	28 (25-30)	6/7	3 (25%)	0	81 (56-83)
PER	27 (26-30)	30/40	NA	NA	68 (43-83)
STO	28 (16-30)	55/58	54 (49%)	8 (7%)	65 (47-85)

[a]Data presented as median (range).

eTable 5. Progression Rates in MCI Subjects From Different Centers

Center	Progression (N)						Total Follow-up in Stable MCI, months[a]	Time to Conversion in MCI-AD, months[a]
	Stable	AD	VAD	FTD	DLB	Other		
AMS	12 (33%)	21 (58%)	1 (3%)	1 (3%)	1 (3%)	0	32 (24-57)	21 (2-44)
DESC	26 (77%)	7 (21%)	0	0	0	1 (3%)	32 (25-45)	25 (21-50)
GOT	55 (65%)	24 (28%)	6 (7%)	0	0	0	36 (24-42)	36 (24-42)
HEID	22 (50%)	22 (50%)	0	0	0	0	26 (24-42)	17 (6-52)
KUOP	78 (55%)	55 (39%)	3 (2%)	0	2 (1%)	3 (2%)	66 (24-132)	31 (6-126)
MALM	76 (46%)	63 (38%)	16 (10%)	1 (1%)	6 (4%)	3 (2%)	62 (37-89)	24 (3-60)
MUN	30 (61%)	19 (39%)	0	0	0	0	39 (24-98)	42 (24-83)
NYC	9 (69%)	4 (31%)	0	0	0	0	30 (26-56)	21 (13-27)
PER	42 (60%)	16 (23%)	0	5 (7%)	4 (6%)	3 (4%)	36 (36-72)	12 (10-36)
STO	70 (62%)	40 (35%)	2 (2%)	0	1 (1%)	0	32 (24-42)	16 (2-40)

[a]Data presented as median (range).

eTable 6. Coefficients of Variance (CV) for Biomarker Assays

Laboratory	**Biomarker Assay**	**CV Interassay**
Mölndal	Aβ42	9.69%
	T-tau	10.85%
	P-tau	10.39%
Amsterdam	Aβ42	11.3%
	T-tau	9.3%
	P-tau	9.4%
Kuopio	Aβ42	12.5%
	T-tau	10.5%
	P-tau	6.4%
Münich	Aβ42	7.7%
	T-tau	6.0%
	P-tau	<10%