KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

AddNeuroMed update: ADNI at AAIC 2012

Multimodal Biomarkers for Alzheimer's disease

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AddNeuroMed Study

Six European sites

Compatible with the US ADNI study

716 subjects recruited

259 AD, 225 MCI, 232 CTL

All subjects

Clinical / cognitive assessments

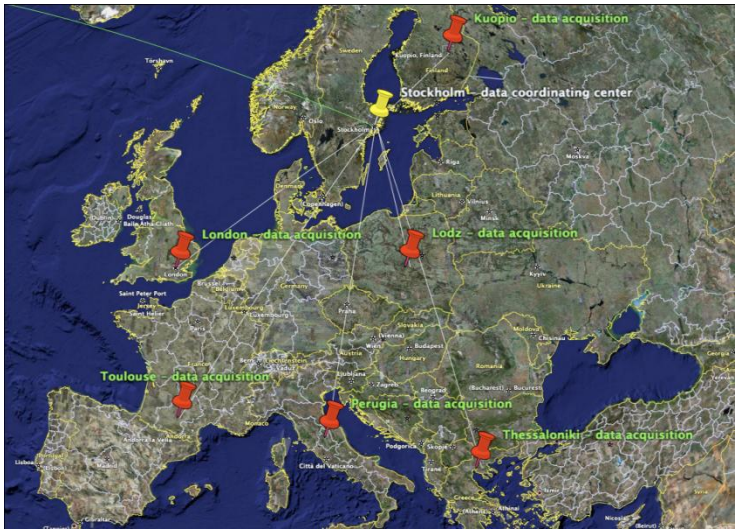
Blood

385 subjects with 1.5T structural MR

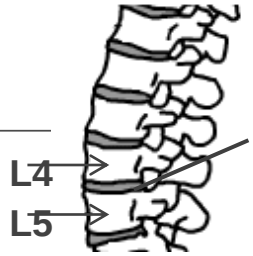
133 AD, 134 MCI, 118 CTL

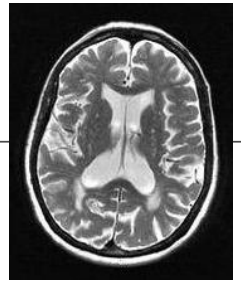
Imaging time points

Baseline, 3 months, 1 year



Blood





Proteomics

Metabolomics

Genomics

Transcriptomics

Abeta/Tau/
pTau

MRI, PIB

Bioinformatics

Multimodal biomarker signature

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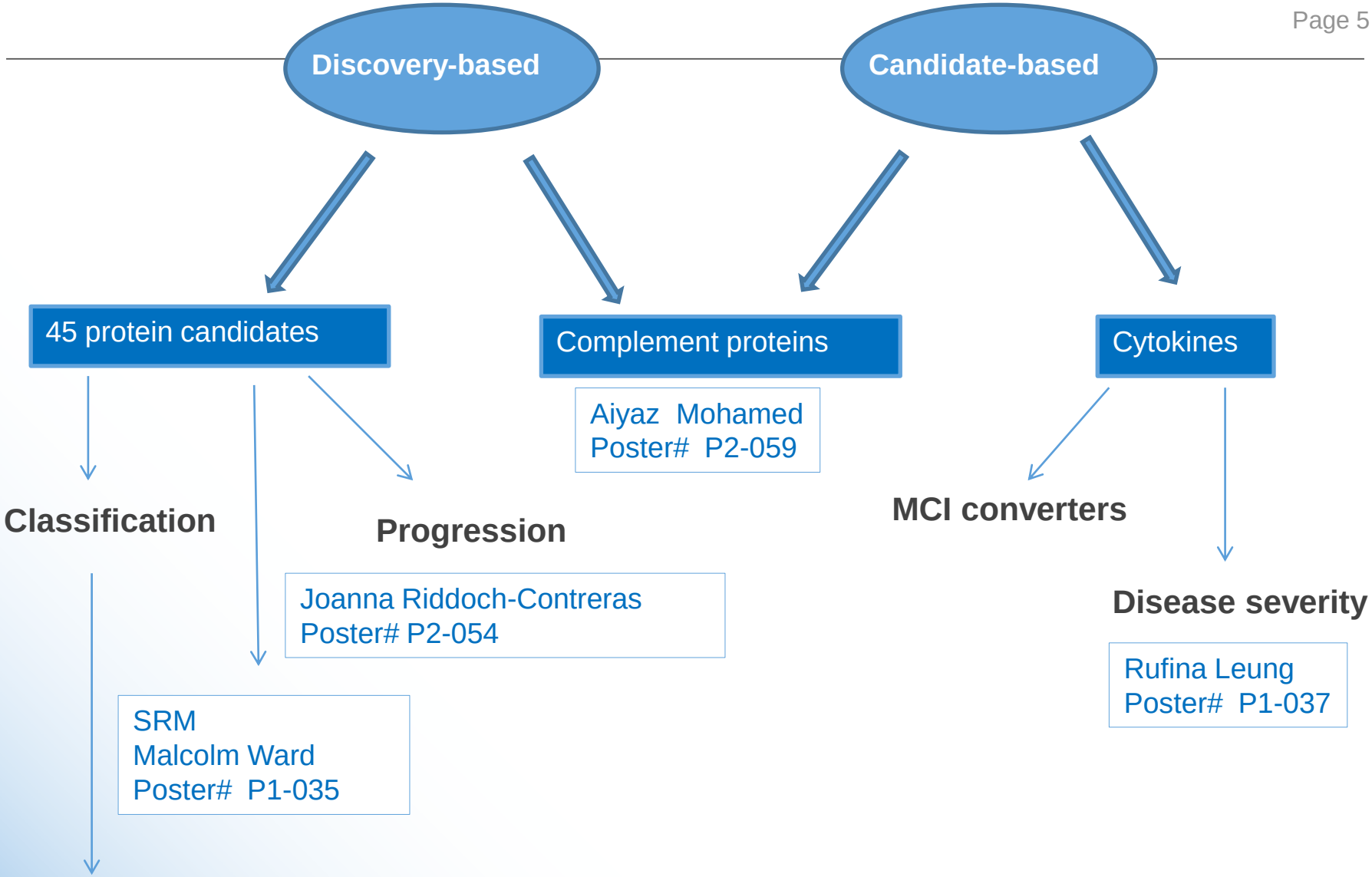
Plasma protein biomarkers



Study designs

Current studies: class prediction

Cases (AD) vs Control
Cases (AD) vs other neurodegenerative diseases

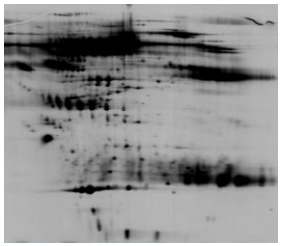
But high heterogeneity of all populations studied among AD, control and MCI groups.

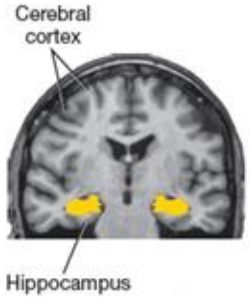
Innovation: looking at other independent variables that reflect pathology

- Cortical atrophy
- Cognition (MMSE)
- Speed of decline

Plasma Biomarkers and Brain Atrophy

Discovery- Gel based approach
Small study





Proteomics

Whole brain volume

- complement component C3
- complement component C3a
- complement factor-I,
- γ-fibrinogen
- alpha-1-microglobulin.

Validation- quantitative immunoassays
Larger independent study

Table 3. Univariate associations between plasma concentrations of assayed candidate biomarkers and whole brain volume in AD; R = Pearson correlation coefficient; p = 2-tailed statistical significance.

Plasma protein	R/p
C3	0.31/0.006
C3a	0.27/0.02
A1M	−0.23/0.04
CFI	0.24/0.04
Gamma-fibrinogen	0.24/0.03
SAP	0.05/0.65

Univariate associations

OPEN ACCESS Freely available online

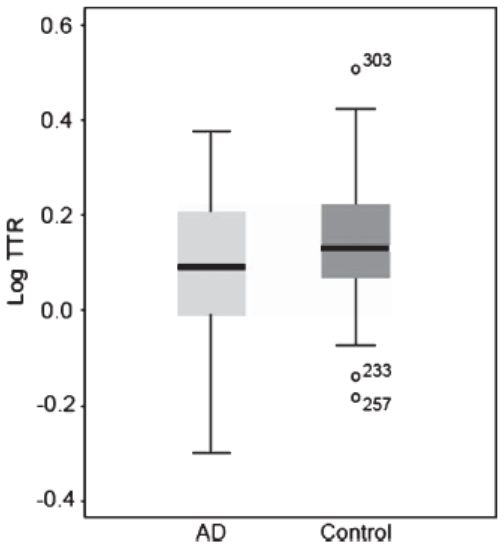
PLoS one

Plasma Biomarkers of Brain Atrophy in Alzheimer's Disease

Madhav Thambisetty[1]*, Andrew Simmons[2], Abdul Hye[2], James Campbell[3], Eric Westman[2], Yi Zhang[4], Lars-Olof Wahlund[5], Anna Kinsey[2], Mirsada Causevic[2], Richard Killick[2], Iwona Kloszewska[6], Patrizia Mecocci[7], Hilkka Soininen[8], Magda Tsolaki[9], Bruno Vellas[10], Christian Spenger[4], Simon Lovestone[1] for the AddNeuroMed consortium

Disease progression: rate of cognitive decline

Plasma transthyretin is reduced in AD



Journal of Alzheimer's Disease 28 (2012) 369–375
DOI 10.3233/JAD-2011-110611
IOS Press

Plasma Transthyretin as a Candidate Marker for Alzheimer's Disease

Latha Velayudhan[a,d,*], Richard Killick[a], Abdul Hye[a], Anna Kinsey[a], Andreas Güntert[a], Steven Lynham[a], Malcolm Ward[b], Rufina Leung[a], Anbarasu Lourdusamy[c], Alvina W.M. To[a], John Powell[a] and Simon Lovestone[a]

Plasma transthyretin is reduced in rapid decliners

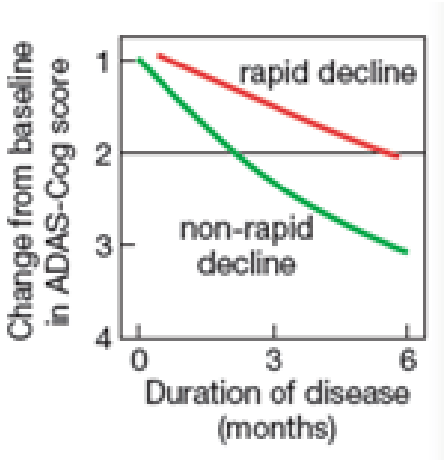
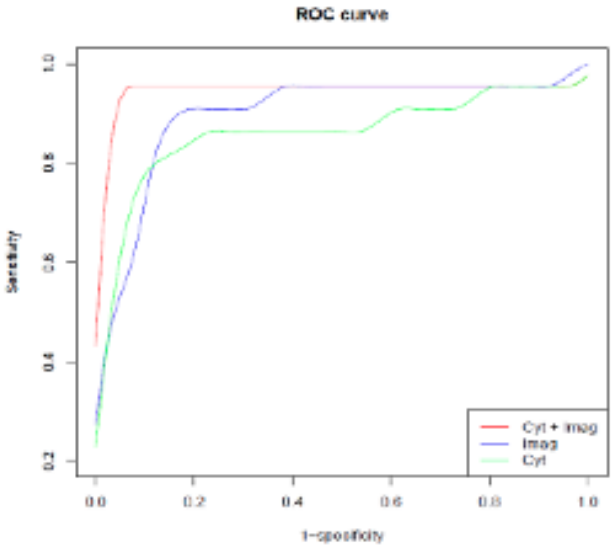


Table 2
Linear regression analysis with the loss of MMSE scores over 6 months follow up as the dependent variable and plasma transthyretin levels, age, baseline MMSE scores, duration of illness, gender and APOE4 alternatively (Model 1) or simultaneously (Model 2) entered as predictive variables within the whole Alzheimer's disease sample

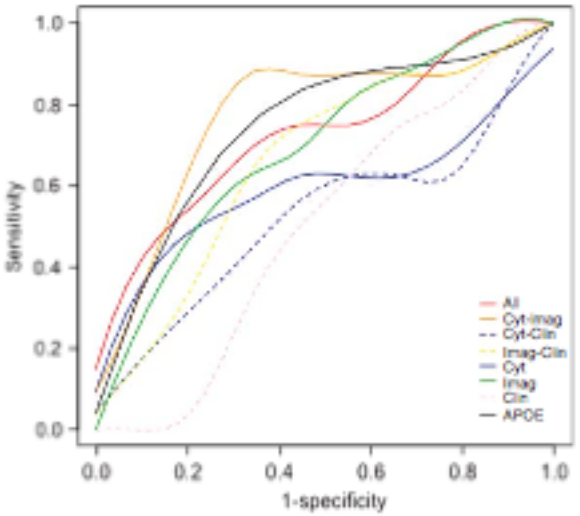
	R^2 (%)		Beta	*T*-value	*P* value
Model 1					
Plasma transthyretin	3.6		0.012	2.32	0.022*
Age in years	0.6		−0.039	−1.072	0.285
Duration of illness	0.4		−0.074	−0.924	0.356
MMSE baseline	1.8		0.092	1.903	0.058
Gender	0.2		−0.295	−0.592	0.555
APOE4	0.2		0.294	0.609	0.543
Model 2					
Plasma transthyretin + MMSE baseline	5.7	TTR	0.011	2.168	0.032*
		MMSE	0.100	1.779	0.077

R^2 (%) = R^2 value in percent for the overall model; *$p<0.05$; MMSE, Mini Mental State Examination; TTR, Transthyretin; APOE4, presence of one E4 allele.

Disease progression: conversion to Dementia



Total n= 48; 22 convertors



Total 253 (99 convertors: 48 with imaging)

Journal of Alzheimer's Disease 26 (2011) 395–405
DOI 10.3233/JAD-2011-0044
IOS Press

Combinatorial Markers of Mild Cognitive Impairment Conversion to Alzheimer's Disease - Cytokines and MRI Measures Together Predict Disease Progression

Simon J. Furney[a], Deborah Kronenberg[b], Andrew Simmons[a], Andreas Güntert[a], Richard J. Dobson[a], Petroula Proitsi[a], Lars Olof Wahlund[c], Iwona Kloszewska[d], Patrizia Mecocci[e], Hilkka Soininen[f], Magda Tsolaki[g], Bruno Vellas[h], Christian Spenger[i] and Simon Lovestone[a,*]

1.5 T sMRI and automated analysis

Regional cortical thickness-34 areas

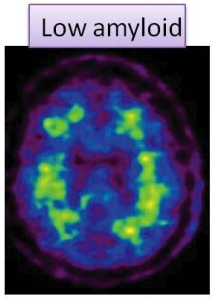
Regional cortical volume- 24 areas

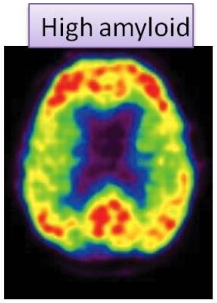
36 cytokines measures by Luminex

Extreme Clinical Phenotypes

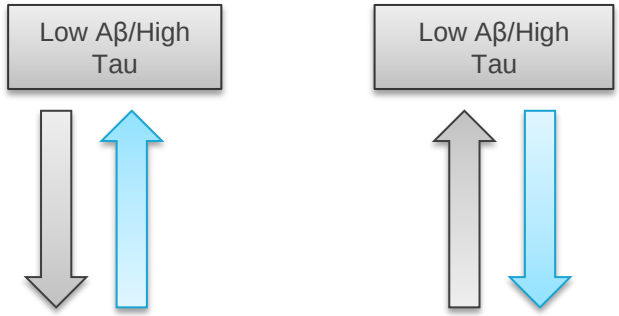
Future studies

PiB-PET measures





CSF Abeta/Tau ratios



Discovery GeLC/MS-MS (Orbitrap Velos)
Tandem Mass Tagging (TMT)
2-DGE
Aptamer based
Longitudinal sampling

Nicholas Ashton
Alison Baird
Sarah Westwood
Emmanuella Leoni
Malcolm Ward

Project vision

To enable and conduct novel research into human health by utilising human health data at an ***unprecedented scale***

'Think Big'

- Access to information on > 40 million patients
- AD research on 10-times more subjects than ADNI
- Linkage of clinical and omics data
- Development of a secure (privacy, legal) modular platform

Project objectives

1. **EMIF-Platform: Develop a framework for evaluating, enhancing and providing access to human health data across Europe, to support specific topics as well as research using human health data in general**

2. **EMIF-AD: Identify predictors of Alzheimer's Disease (AD) in the pre-clinical and prodromal phase, with the support of EMIF-Platform**

AD research objectives

1. Set-up a **large data repository** of patient data to allow biomarker discovery.

2. **Link data** from research cohorts to EHR data and use EHR data to define extreme phenotypes

3. Discover and validate **new biomarkers** in plasma, cerebrospinal fluid (CSF) and using MRI for the diagnosis and prognosis of AD in the presymptomatic and prodromal stages

4. Identify **new potential targets** for AD drug development using genomics and proteomics approaches in presymptomatic and prodromal AD;

5. Test the utility of the new biomarkers for **selection of subjects** for AD prevention trials.

Conflict of interests

Research collaborations relevant to biomarkers for AD:

- Proteome Sciences, Millipore Merck and GSK
- J&J and GE
- Precompetitive collaborative projects with multiple European Federation of Pharmaceutical Industry Associations (EFPIA) partners

Other, non-biomarker, collaborations

- Astra Zeneca
- J&J

AddNeuroMed – Combining Markers

Combining markers

MRI

MRS

Neuropsych

Cytokines

GWAS

Gene expression

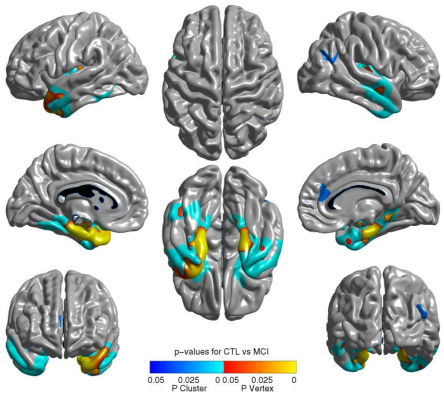
Vitamin E forms

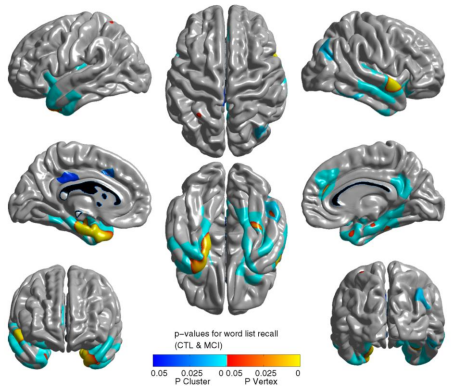
Plasma proteins #1

Plasma proteins #2

Plasma proteins #3

Plasma proteins #4





Combinatorial Markers of Mild Cognitive Impairment Conversion to Alzheimer's Disease - Cytokines and MRI Measures Together Predict Disease Progression

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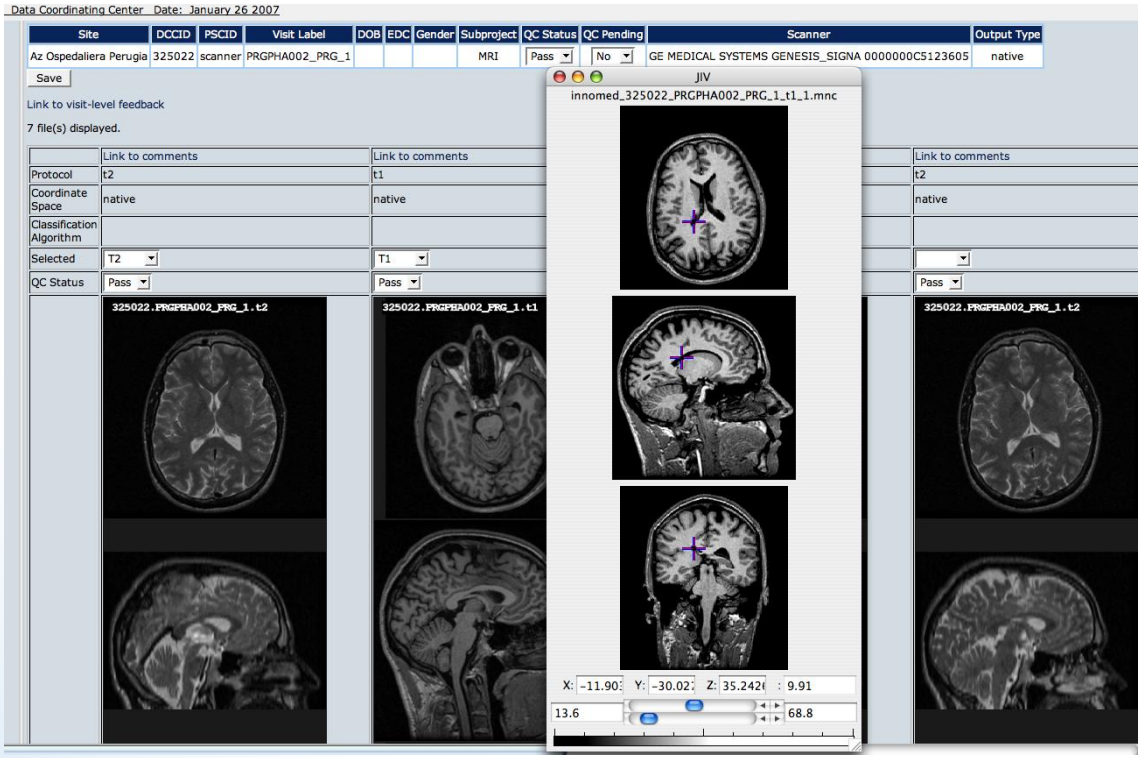
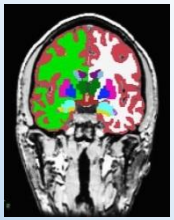
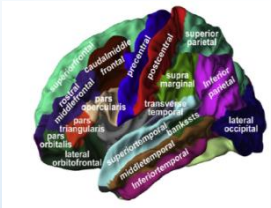
Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy for Detection of Early Alzheimer's Disease

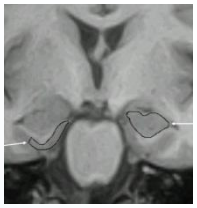
Eric Westman[a,*], Lars-Olof Wahlund[a], Catherine Foy[b], Michaela Poppe[b], Allison Cooper[b], Declan Murphy[b], Christian Spenger[d], Simon Lovestone[b] and Andrew Simmons[b,c]

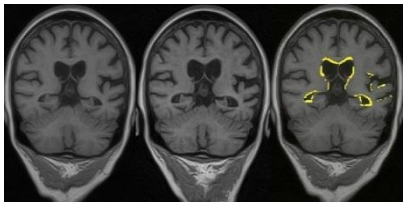
Image database







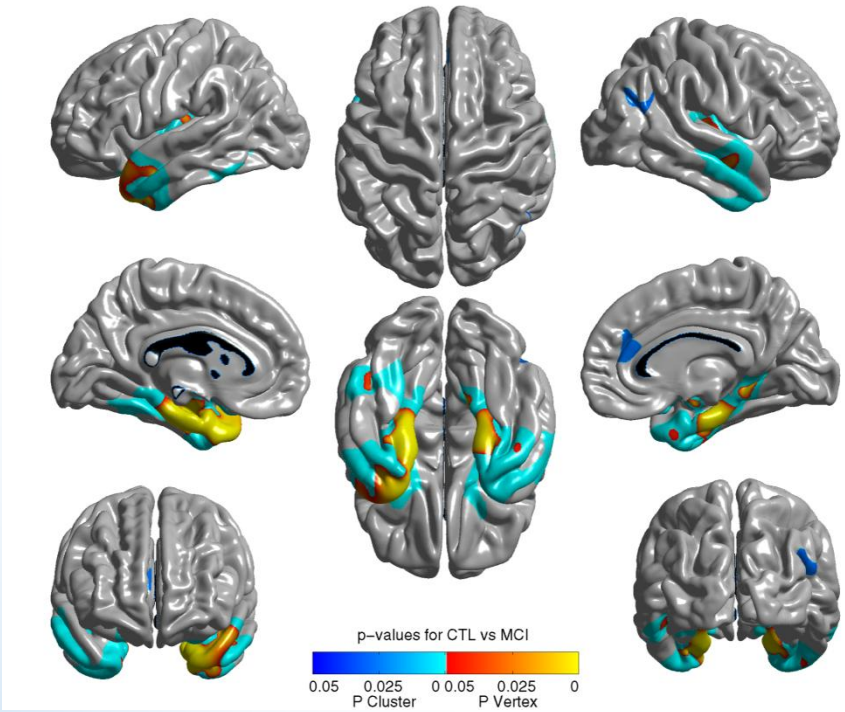




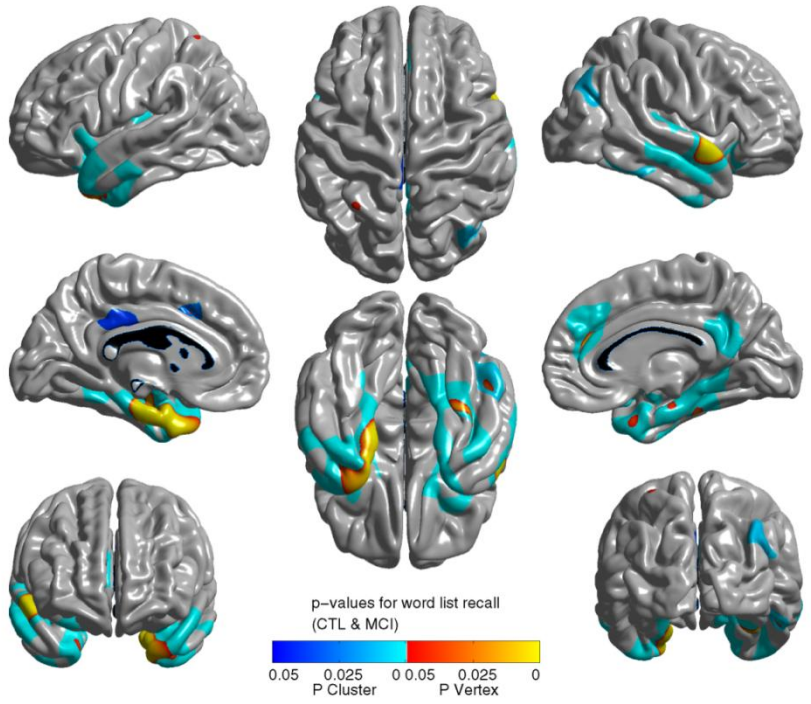
385 AddNeuroMed
- 0, 3, 12m
821 ADNI 1
- 0, 6, 12, 18, 24, 36, 48m
288 AIBL
- 0, 18, 36, 54m
200 London cohort
- 0, 12, 24, 36m
500 Memory clinic
- 0m
2000 Young controls
- 0m, 48m
Total – 4,000

Neuroimaging and Neuropsych

Paajanen et al, submitted



CTl v MCI cortical thickness differences



Correlation of word list recall with cortical thickness in CTL+MCI group

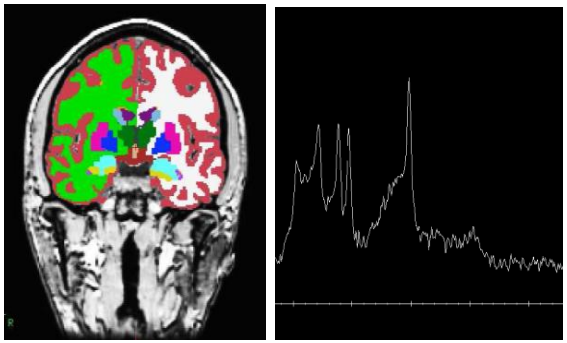
Multivariate Analysis

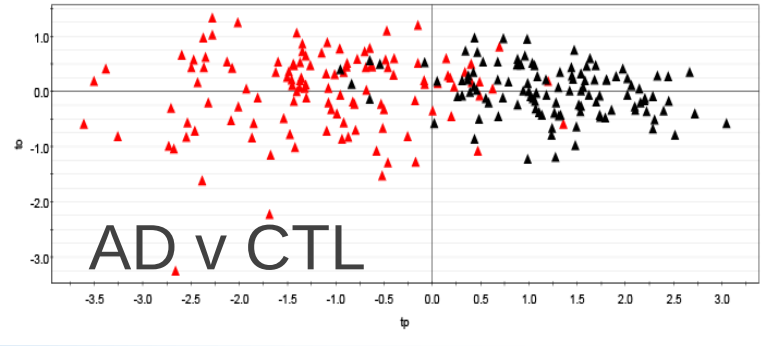
Orthogonal partial least squares (OPLS)

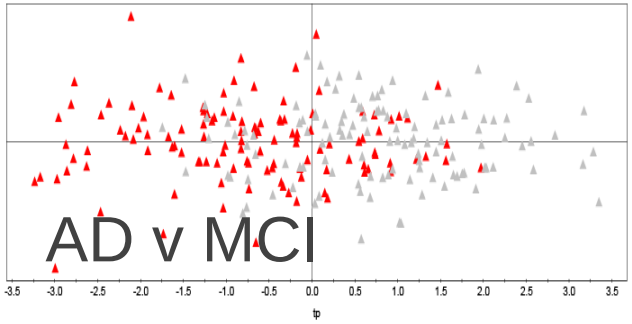
Regional cortical thickness measures

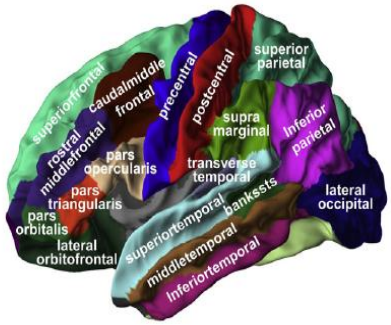
Regional MRI volumes

Total of 75 MRI measures









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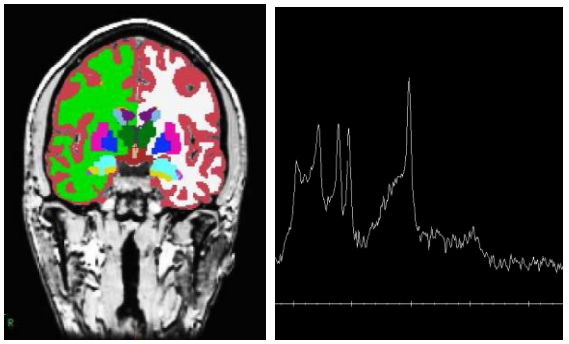
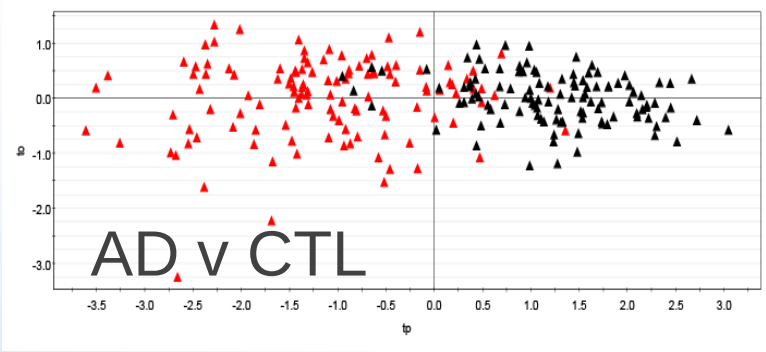
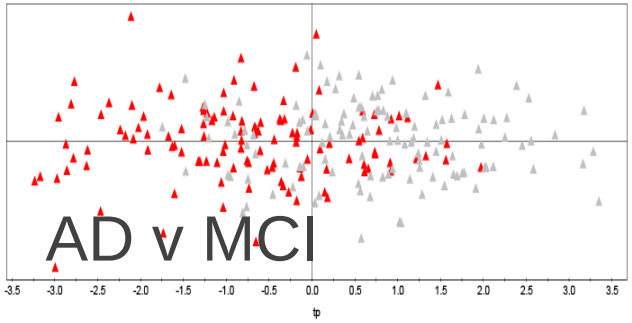
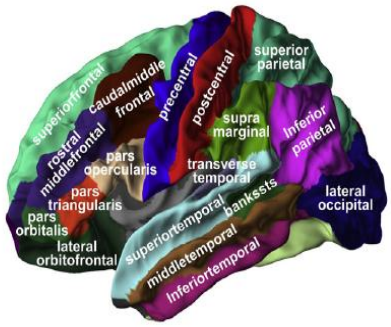








Multivariate analysis of MRI data for Alzheimer's disease, mild cognitive impairment and healthy controls

Eric Westman [a,*], Andrew Simmons [b,c], Yi Zhang [a], J-Sebastian Muehlboeck [a], Catherine Tunnard [b], Yawu Liu [f], Louis Collins [e], Alan Evans [e], Patrizia Mecocci [g], Bruno Vellas [h], Magda Tsolaki [i], Iwona Kloszewska [j], Hilkka Soininen [f], Simon Lovestone [b,c], Christian Spenger [a], Lars-Olof Wahlund [a] for the AddNeuroMed consortium

Combining MRI and MRS to Distinguish Between Alzheimer's Disease and Healthy Controls

Eric Westman[a,*], Lars-Olof Wahlund[a], Catherine Foy[b], Michaella Poppe[b], Allison Cooper[b], Declan Murphy[b], Christian Spenger[a], Simon Lovestone[b] and Andrew Simmons[b,c]

Combining MRI and Vitamin E Forms

Table 1
Subject characteristics by diagnosis

	CTL (n: 86)	MCI (n: 86)	AD (n: 81)
Age, y	74.4±5.5	74.6±5.2	75.1±5.7
Gender, % female [a]	55%	52%	74%
Education, y	10.5±4.8	8.5±4.3 ††	7.6±3.7 *
Any APOE-ε4 allele, % [a]	28%	35%	57%
MMSE score	29.1±1.2	27.1±1.6 †	21.0±4.7 * §
Serum albumin, g/dl	4.3±0.4	4.4±0.4	4.3±0.4
Serum total cholesterol, mmol/L	5.2±1.1	5.3±1.1	5.4±1.1

If not otherwise specified, data are presented as mean ± standard deviation (SD).
AD: Alzheimer's disease, MCI: Mild Cognitive Impairment, CTL: healthy control, MMSE = Mini Mental State Examination.

AD vs CTL: *p<.001; AD vs MCI: §p<.001 ; MCI vs CTL: †p<.001; †† p<0.05

[a] Pearson Chi-Square: p<0.05

Combining MRI and Vitamin E Forms

Table 3 Subjects vitamin E plasma levels (absolute values) by diagnosis

Vitamin E plasma levels #	CN (n: 187)	MCI (n: 166)	AD (n: 168)
α-tocopherol	33.21 (5.15)	30.24 (3.33)ᵀ	28.18 (2.42)* §
β-tocopherol	2.46 (0.44)	2.18 (0.24)ᵀ	2.33 (0.25)** §
γ-tocopherol	2.30 (0.26)	1.92 (0.19)ᵀ	1.80 (0.16)* §
δ-tocopherol	0.29 (0.02)	0.26 (0.02)ᵀ	0.27 (0.02)* §
α-tocotrienol	349.0 (68.5)	278.9 (27.6)ᵀ	276.1 (26.0)*
β-tocotrienol	143.7 (18.6)	141.0 (11.1)	131.1 (10.0)* §
γ-tocotrienol	83.63 (12.80)	65.87 (10.17)ᵀ	48.15 (7.40)* §
δ-tocotrienol	12.33 (4.27)	11.0 (4.34)ᵀᵀ	9.00 (3.23)* §
Total tocopherols	38.26 (5.50)	34.61 (3.63)ᵀ	32.58 (2.70)* §
Total tocotrienols	588.7 (74.7)	496.8 (37.6)ᵀ	464.3 (31.2)* §
Total vitamin E	38.85 (5.55)	35.10 (3.64)ᵀ	33.04 (2.71)* §

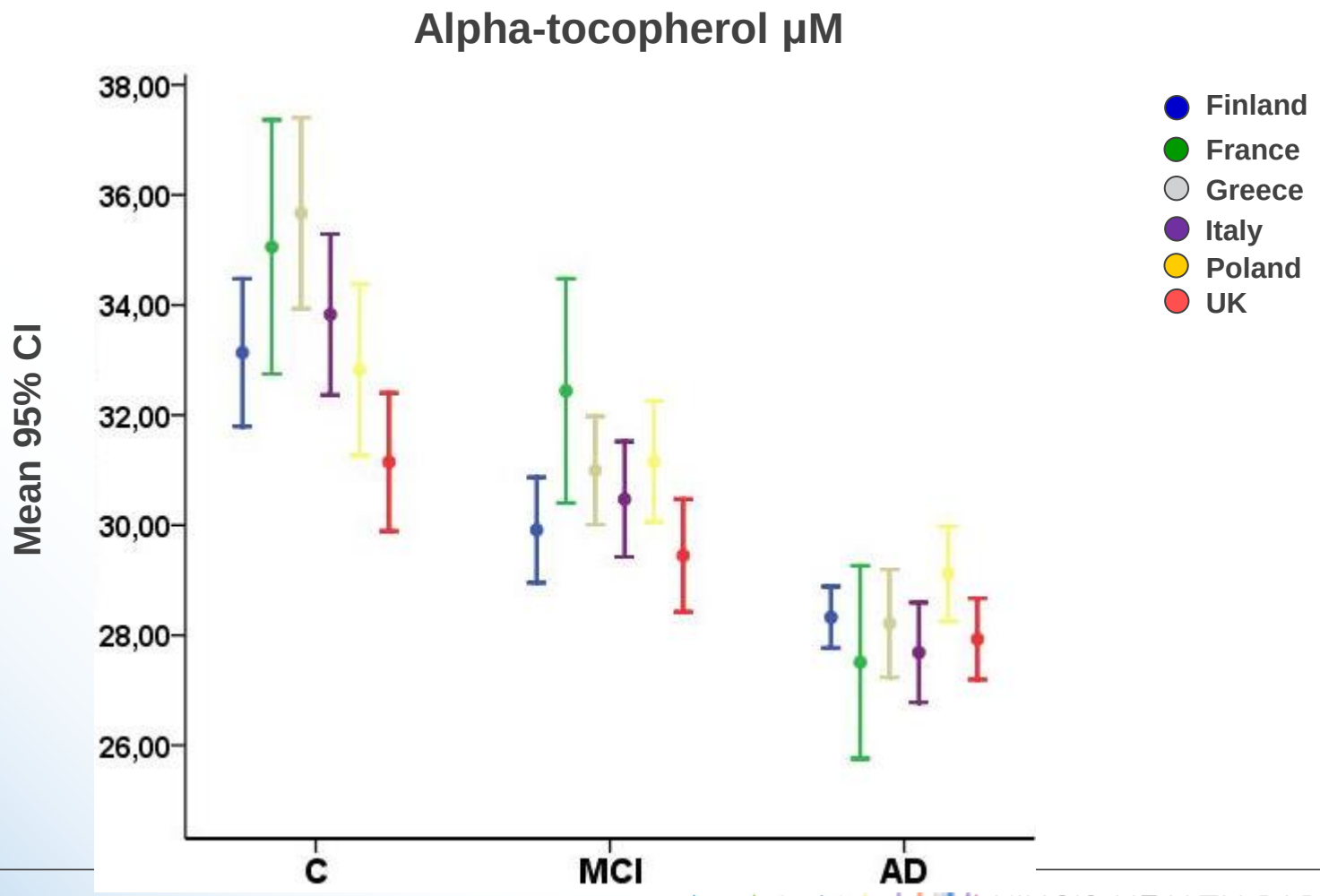
#Tocopherols and total vitamin E are expressed as μM; tocotrienols are expressed as nM

AD vs C: *p<0.0001; **p<0.01

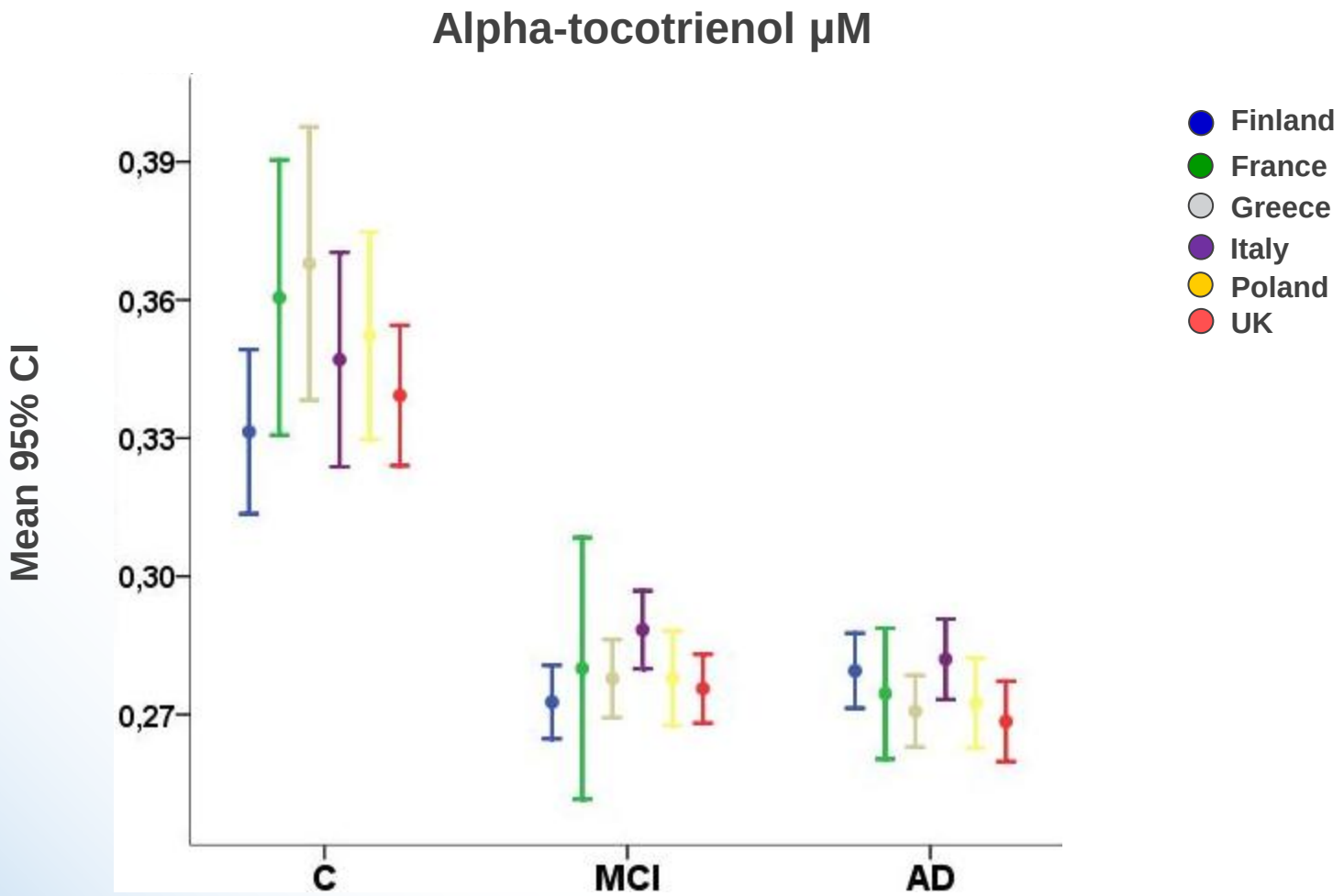
AD vs MCI: §p<0.0001

MCI vs C: ᵀp<0.0001; ᵀᵀ p<0.01

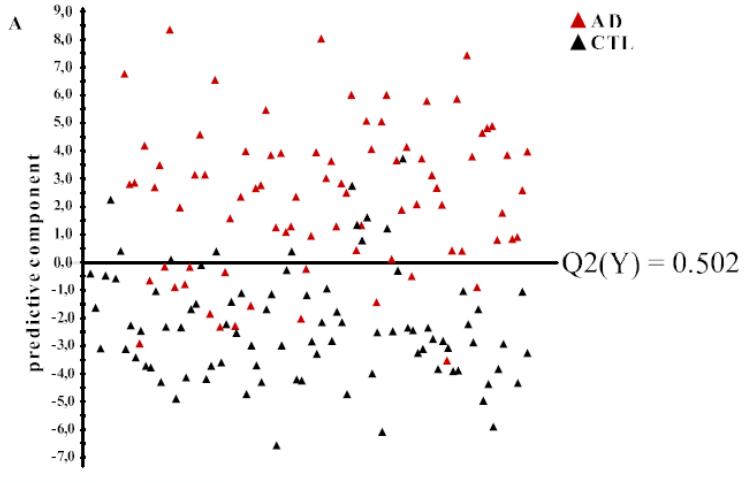
Plasma levels of Vitamin E forms

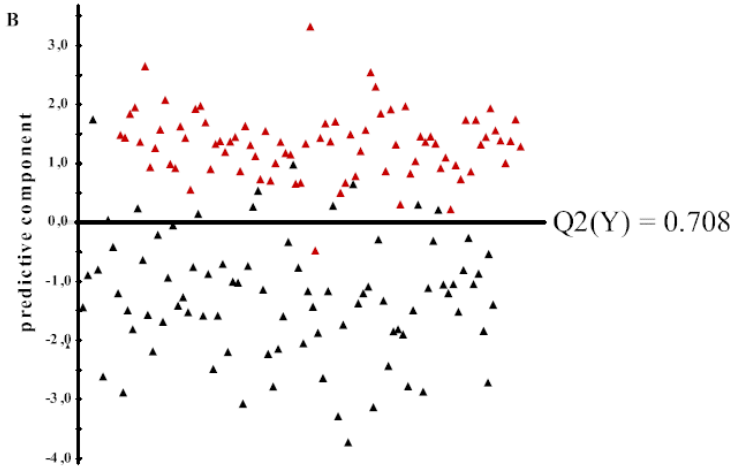


Plasma levels of Vitamin E forms



AD v Controls, MRI





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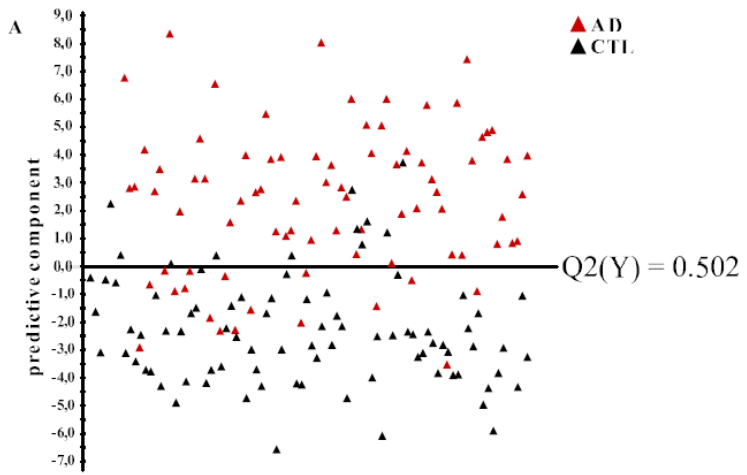

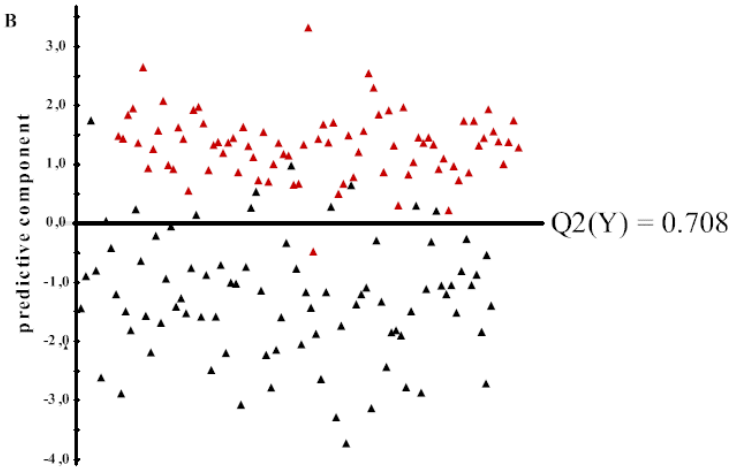

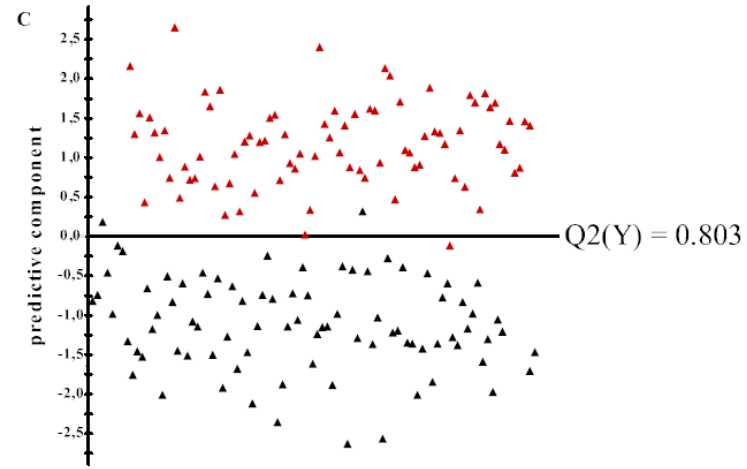

Table 3
Accuracy, sensitivity/specificity and likelihood ratio for the different models

	Accuracy	Sensitivity	Specificity	LR+	LR-
CTL vs. AD					
Neuroimaging	83.2 (76.8-88.1)	79.0 (69.9-86.5)	87.2 (78.5-92.7)	6.2 (3.5-10.8)	0.24 (0.16-0.37)
Vitamin E	92.3 (87.9-95.8)	98.8 (93.3-99.8)	87.2 (78.5-92.7)	7,7 (4.4-13.4)	0.01 (0.00-0.10)
Combined	98.2 (94.8-99.4)	98.8 (93.3-99.8)	97.7 (91.9-99.4)	42.5 (10.8-167)	0.01 (0.00-0.09)

85% of MCI converters predicted as AD like

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