Nutritional support in early Alzheimer's disease:
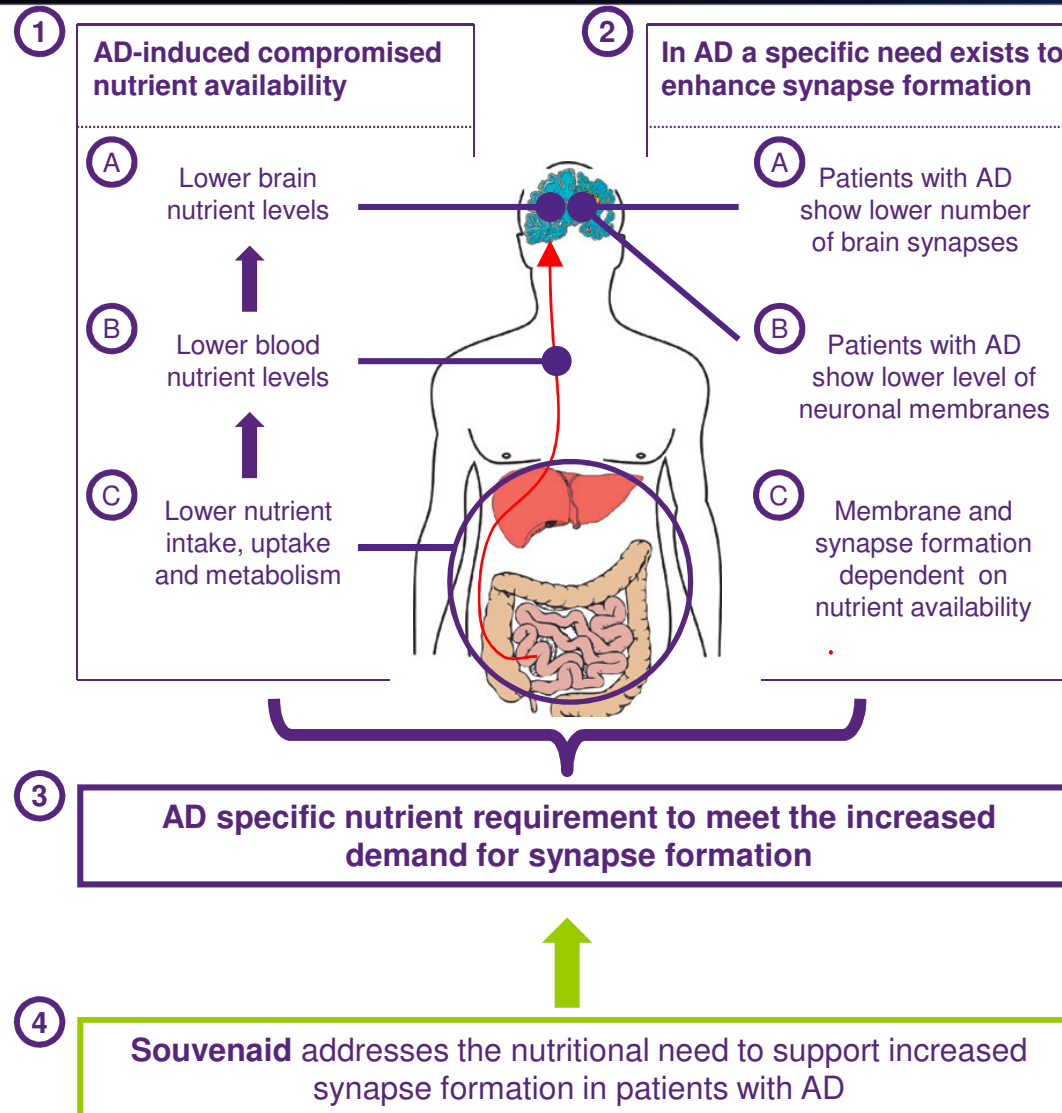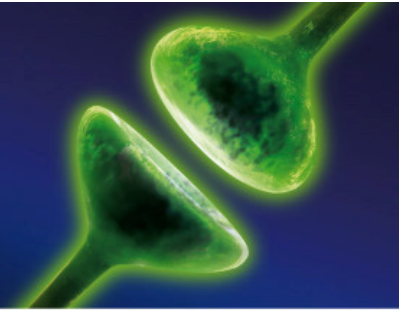## what, why and when?

Laus Broersen, PhD
Senior Neuroscientist
Nutricia Research, Advanced Medical Nutrition
Utrecht, The Netherlands

NUTRICIA
Souvenaid®

AD specific nutritional needs for membrane and synapse formation

1 AD-induced compromised nutrient availability

A Lower brain nutrient levels

B Lower blood nutrient levels

C Lower nutrient intake, uptake and metabolism

2 In AD a specific need exists to enhance synapse formation

A Patients with AD show lower number of brain synapses

B Patients with AD show lower level of neuronal membranes

C Membrane and synapse formation dependent on nutrient availability

3 AD specific nutrient requirement to meet the increased demand for synapse formation

4 **Souvenaid** addresses the nutritional need to support increased synapse formation in patients with AD

# Synapse loss is structural basis of functional deficits in AD
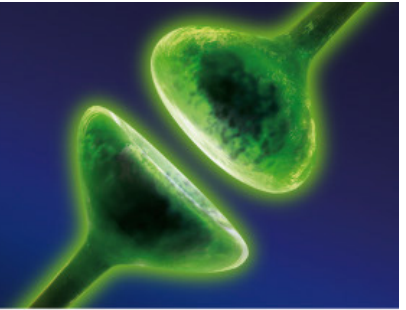
Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Robert D. Terry, MD,* Eliezer Masliah, MD,* David P. Salmon, PhD,* Nelson Butters, PhD,† Richard DeTeresa, BS,* Robert Hill, PhD,* Lawrence A. Hansen, MD,* and Robert Katzman, MD*

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580
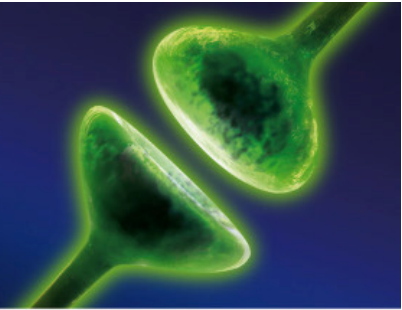
Reduced number of synapses
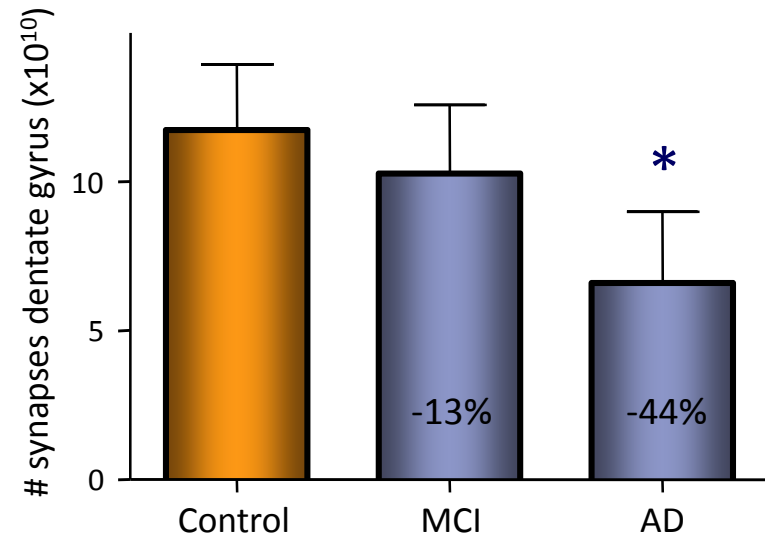
VIEWPOINT

Alzheimer's Disease Is a Synaptic Failure

Dennis J. Selkoe
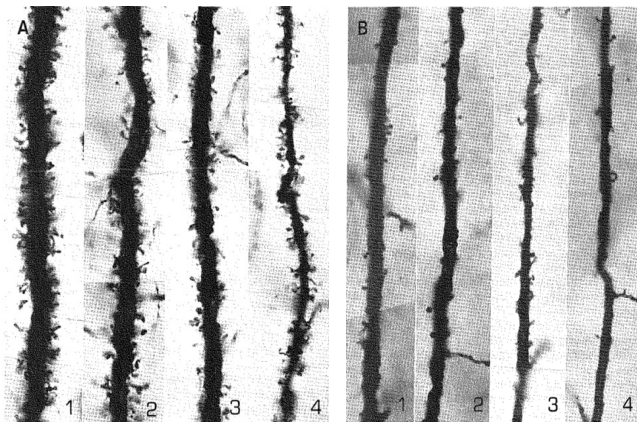
SCIENCE   VOL 298   25 OCTOBER 2002

Synapse loss in AD is confirmed in >30 publications
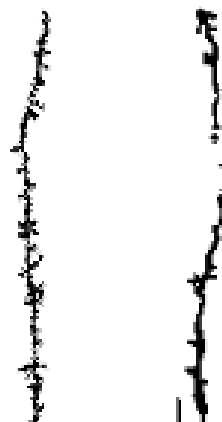
Loss of dendritic spines in AD

Control   AD   Control   AD   Control   AD   Control   AD

Catala et al (1988)
Hum Neurobiol
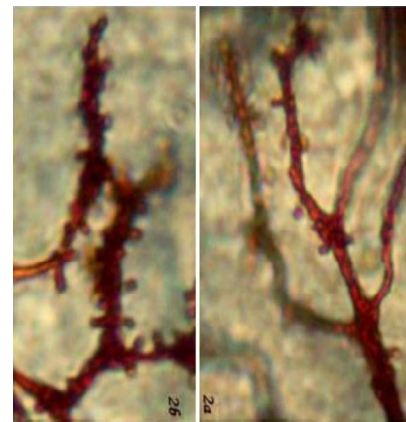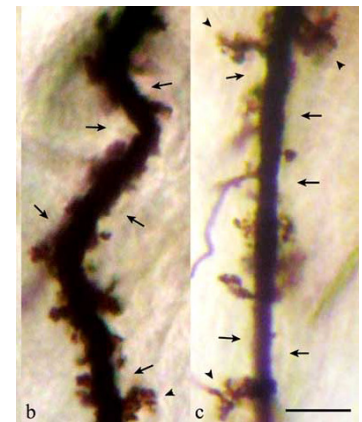
Einstein et al (1994)
J Neurosci

Mavroudis et al (2010)
Am J Alz Dis oth Dement

Tsamis et al (2010)
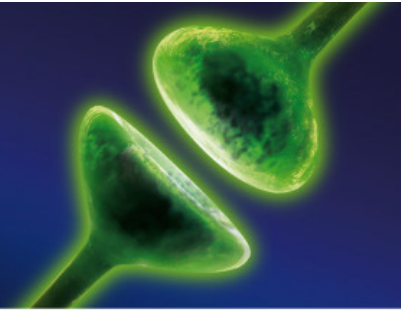Curr Alzheim Res

Decreased brain phospholipids in AD indicates disrupted membrane integrity

Phospholipids and Alzheimer's Disease: Alterations, Mechanisms and Potential Biomarkers

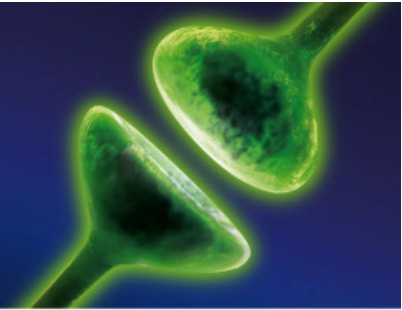Marko Kosicek and Silva Hecimovic *

Table 1

Phospholipid changes in the brain of individuals with Alzheimer's disease.

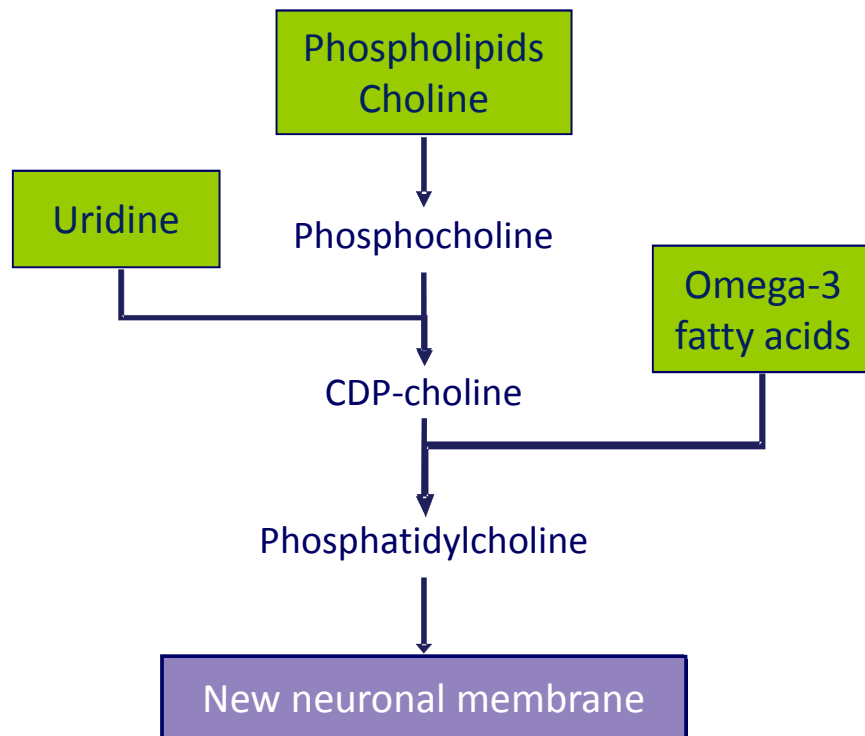| Lipid class	Change/Normalization	Sample size/Examined brain regions/Analytical method	Reference
PI	decreased/wet weight	9 AD and 9 controls/HPG, SMTG, IPL and cerebellum/TLC	[14]
PI	decreased/wet weight	17 AD and 18 controls/anterior temporal cortex/TLC	[15]
PI	decreased/relative	45 AD and 11 controls/SMFG, STG, IPL, occipital cortex and cerebellum/^{31}P NMR	[21]
PE	decreased/wet weight	9 AD and 9 controls/HPG, SMTG, IPL and cerebellum/TLC	[14]
PE	decreased/DNA	10 AD and 10 controls/frontal, primary auditory and parietal cortex/photometrical phosphorus determination	[16]
PPE	decreased/relative	9 AD and 9 controls/middle-temporal cortex/HPLC and TLC	[18]
PPE	decreased/phosphate	15 AD and 13 controls/frontal cortex, hippocampus and white matter/HPLC and GC	[19]
PPE	decreased/relative	45 AD and 11 controls/SMFG, STG, IPL, occipital cortex and cerebellum/^{31}P NMR	[21]
PPE	decreased/protein	6 CDR = 0; 6 CDR = 0.5; 6 CDR = 1; 6 CDR = 2; 6 CDR = 5/white and gray matter from SFG, STG, IPL and cerebellum/ESI-MS	[22]
PC	unchanged/wet weight	9 AD and 9 controls/HPG, SMTG, IPL and cerebellum/TLC	[14]
PC	decreased/DNA	10 AD and 10 controls/frontal, primary auditory and parietal cortex/HPLC–fluorimetric detection	[16]
PC	unchanged/wet weight	6 AD and 4 controls/gray matter from frontal cortex, parietal and temporal region/HPLC	[17]
PC	decreased/phosphate	15 AD and 13 controls/frontal cortex, hippocampus and white matter/HPLC and GC	[19]

4. Conclusions

"… Phospholipids provide an optimal membrane environment for protein interactions, trafficking and function. There is increasing evidence that phospholipid changes occur during pathogenic processes in Alzheimer's disease. …"

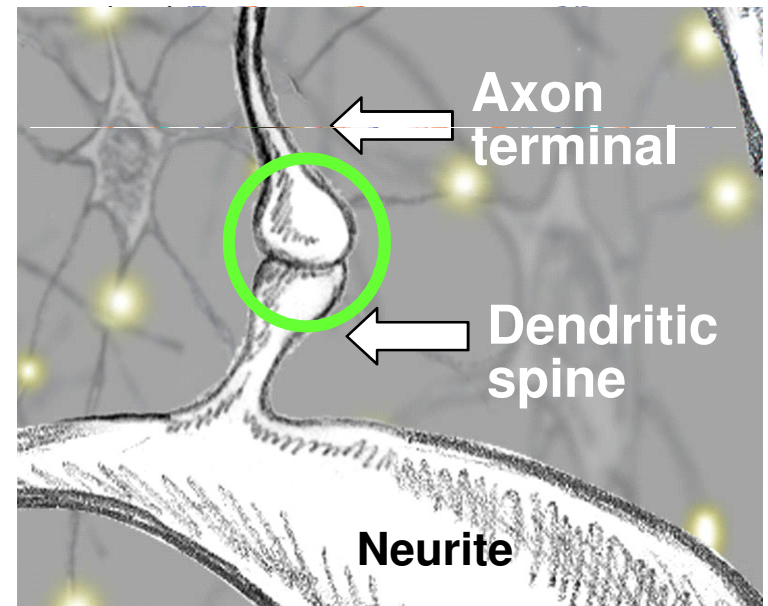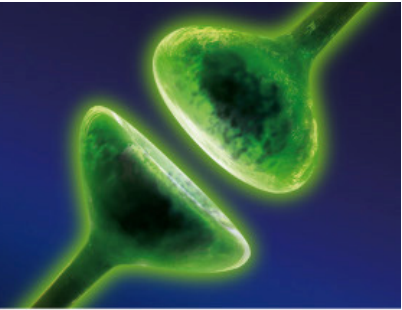# Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis of neuronal membrane

Phospholipids Choline

Uridine

Phosphocholine

Omega-3 fatty acids

CDP-choline

Phosphatidylcholine

New neuronal membrane

Membranes are main constituents of synapses

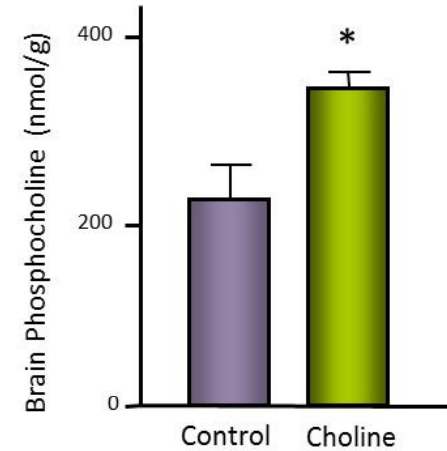Axon terminal

Dendritic spine

Neurite

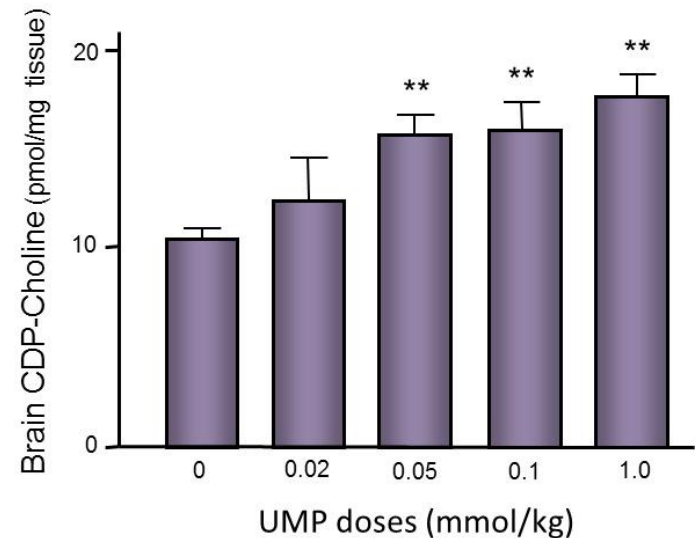# Dietary precursor control of neural membrane synthesis

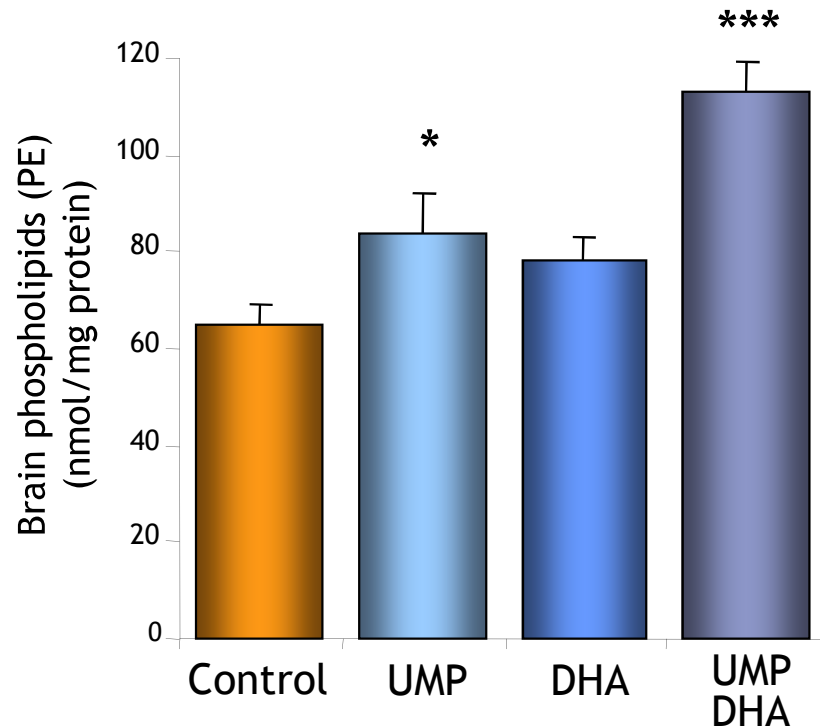The Kennedy pathway for biosynthesis neuronal membrane
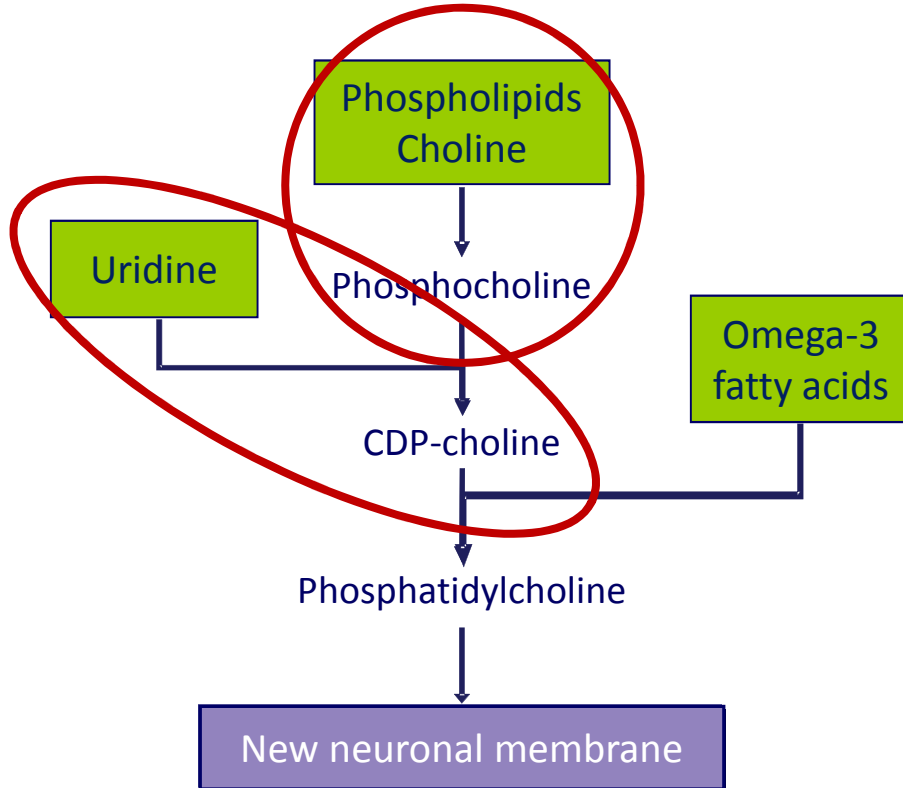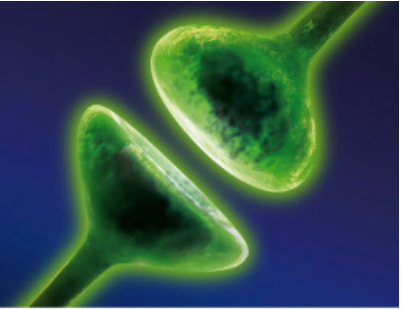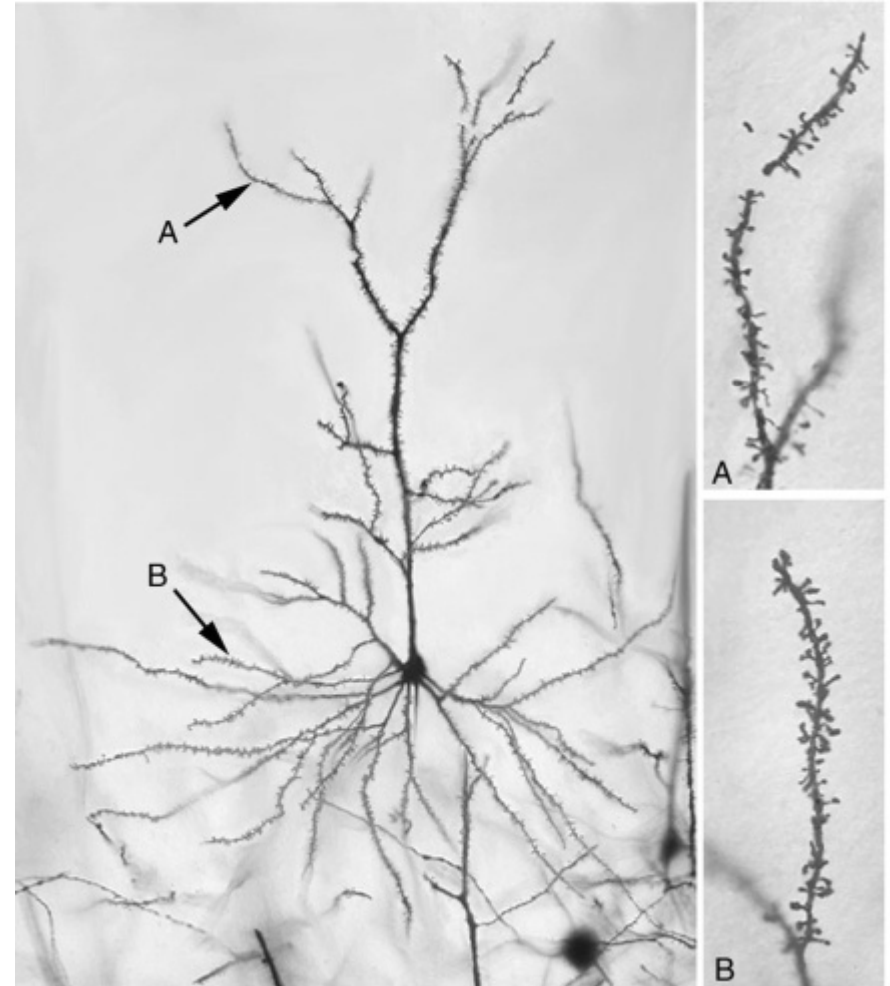

Kennedy & Weiss (1956) J Biol Chem
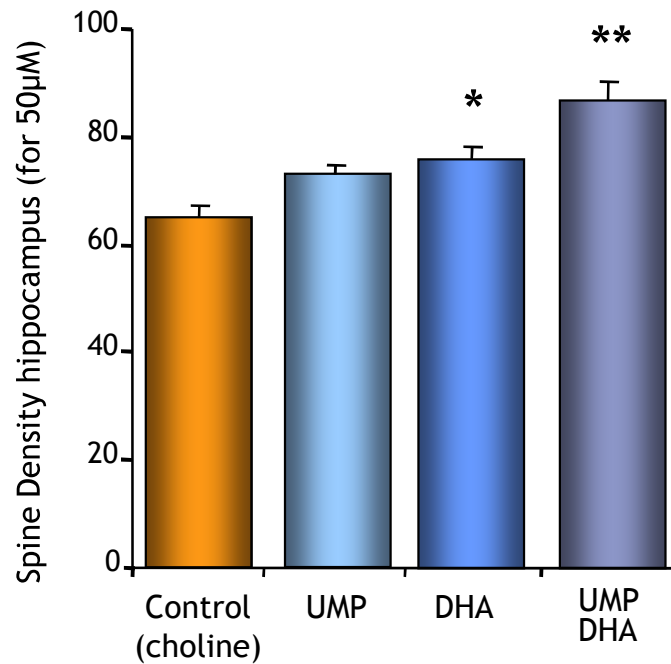

Millington & Wurtman (1982) J Neurochem

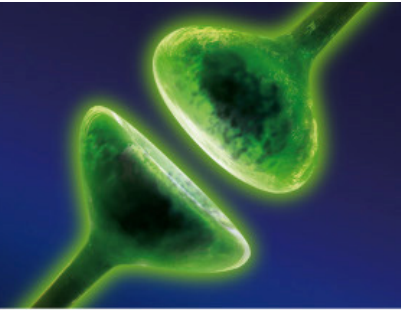Cansev et al (2005) Brain Res

Dietary precursors can be rate-limiting: Synergy between dietary precursors

Wurtman et al (2005, 2006) Brain Res

Dietary precursors increase membrane dominant structures: Dendritic spines

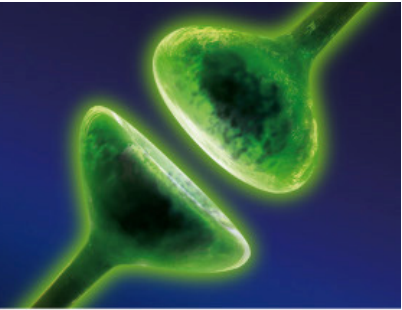Sakamoto et al (2007) Brain Res

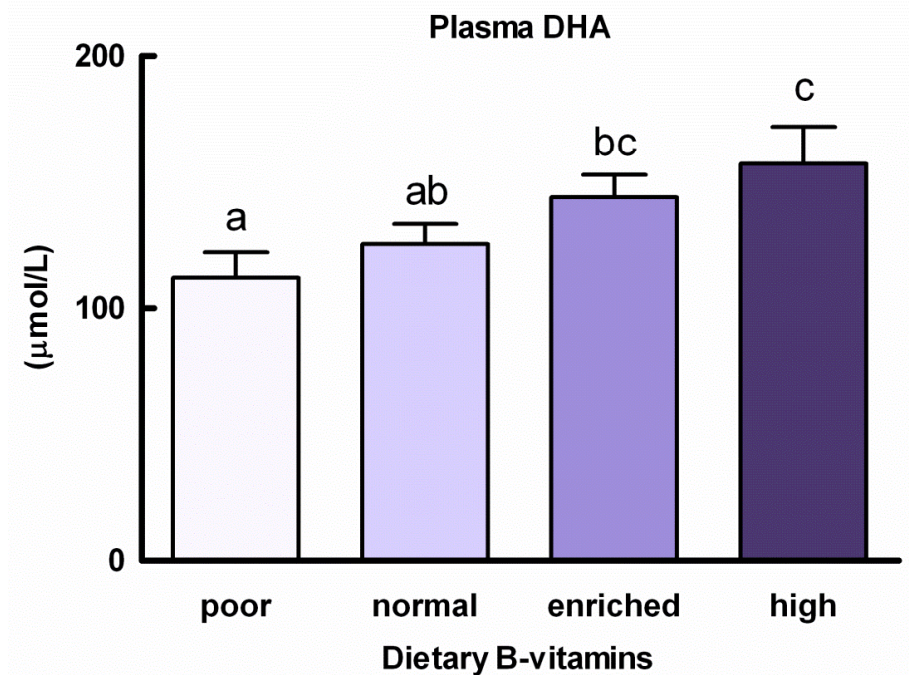# B-vitamins: cofactors for endogenous production of membrane precursors
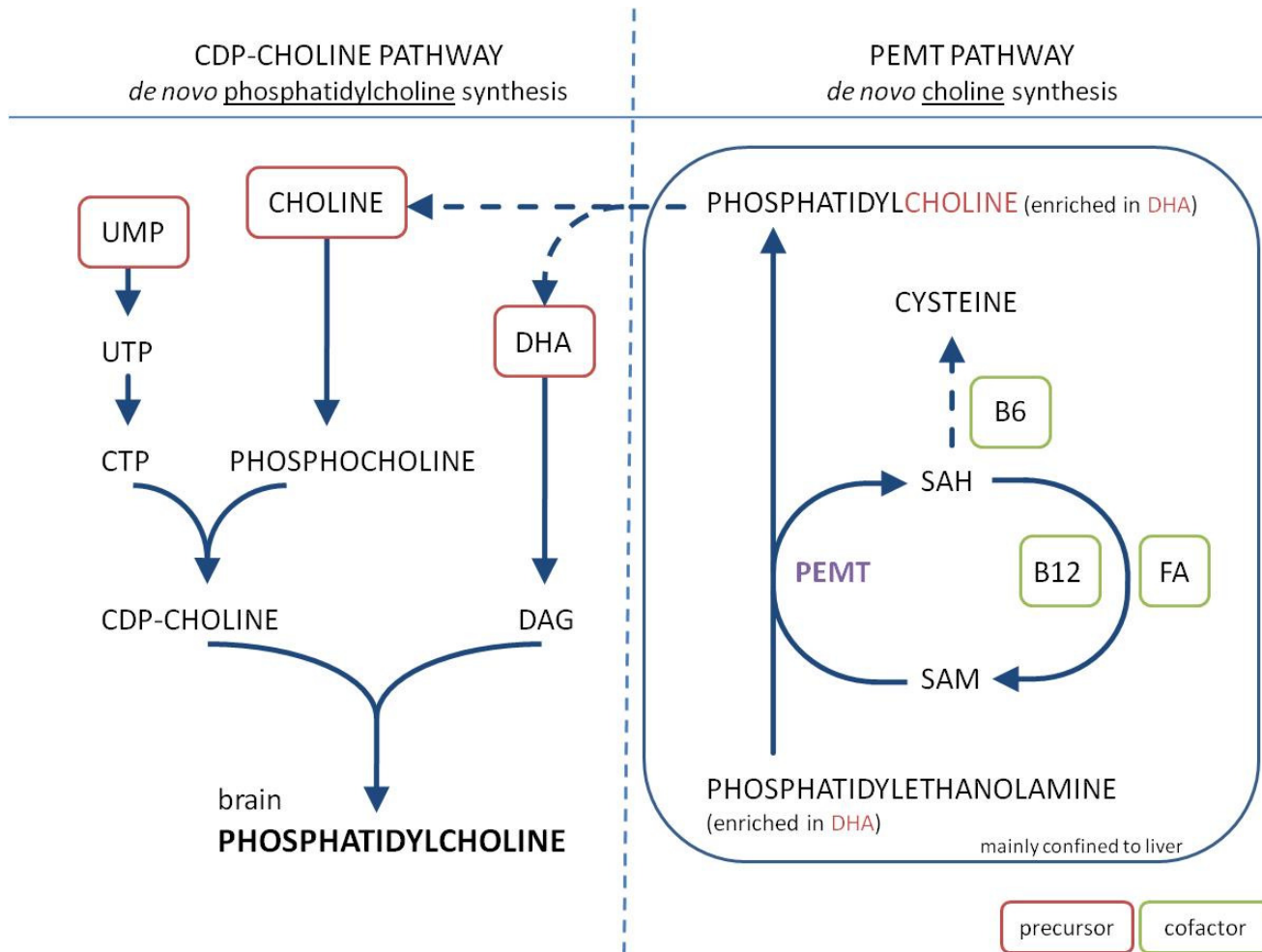
PEMT = phosphatidylethanolamine-N-methyltransferase

Precursor availability: B-vitamins increase plasma choline and DHA

B vitamins increase choline

B vitamins dose-dependently increase DHA

van Wijk et al (2011) Br J Nutr

van Wijk et al (2012) Nutr Metabol
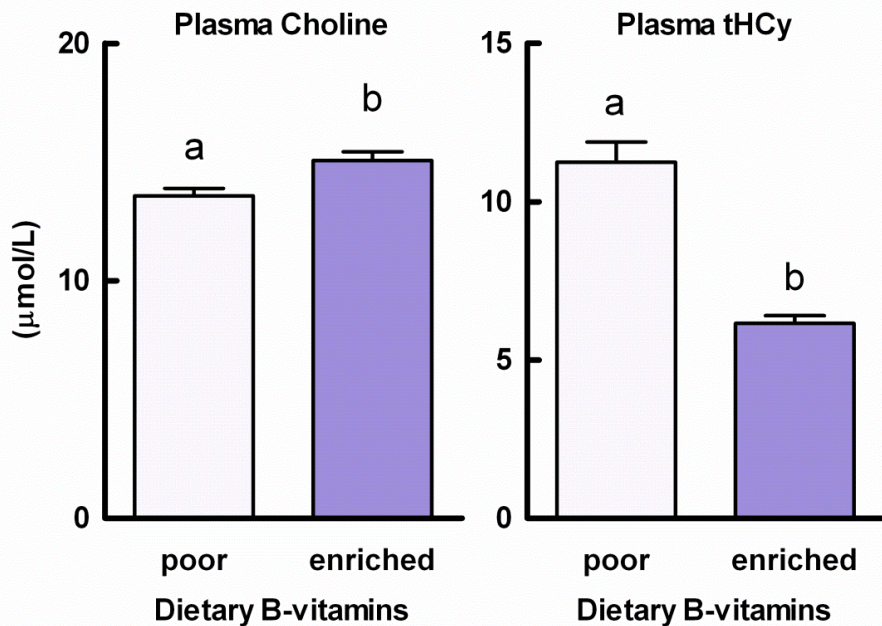
Nutritional precursors and cofactors: enhanced availability by Fortasyn Connect
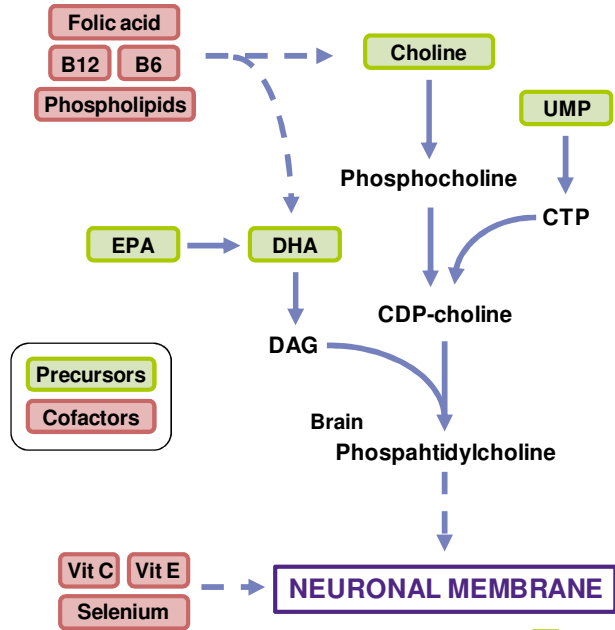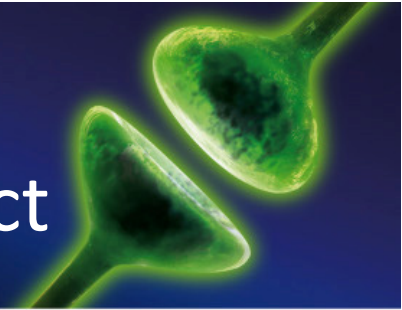
- Synapses are continuously being remodeled

- Synapses are part of the neuronal membrane

- Membranes consist of phospholipids

- Phospholipid synthesis depends on the presence of uridine, choline and DHA

- B-vitamins enhance precursor bioavailability

- Antioxidants protect the neuronal membrane and maintain its integrity, stability and function
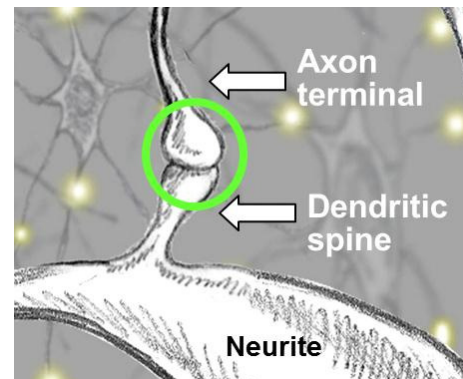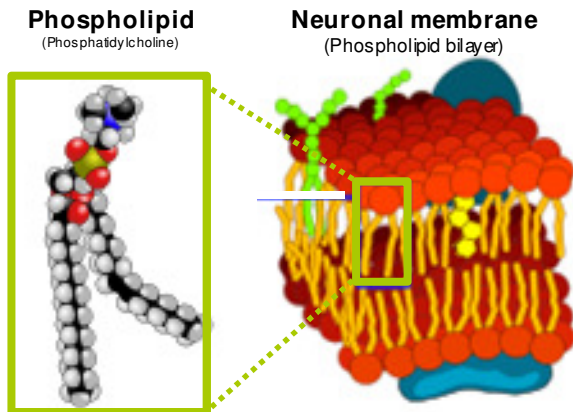
Precursors and cofactors enhance synapse formation and function – basic science data
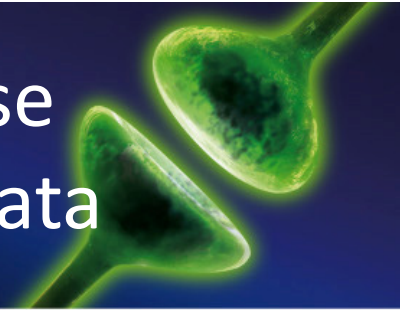
459 nnect

Review

3

Targeting Synaptic Dysfunction in Alzheimer's Disease by Administering a Specific Nutrient Combination

8

8

Nick van Wijk[a,*], Laus M. Broersen[a], Martijn C. de Wilde[a], Robert J.J. Hageman[a], Martine Groenendijk[a], John W.C. Sijben[a] and Patrick J.G.H. Kamphuis[a,b]

[a]Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands
[b]Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

3,29

- Improve learning & memory / behavior

| ✓ | 11,13-17 | ✓ | 19,22,29-31 |

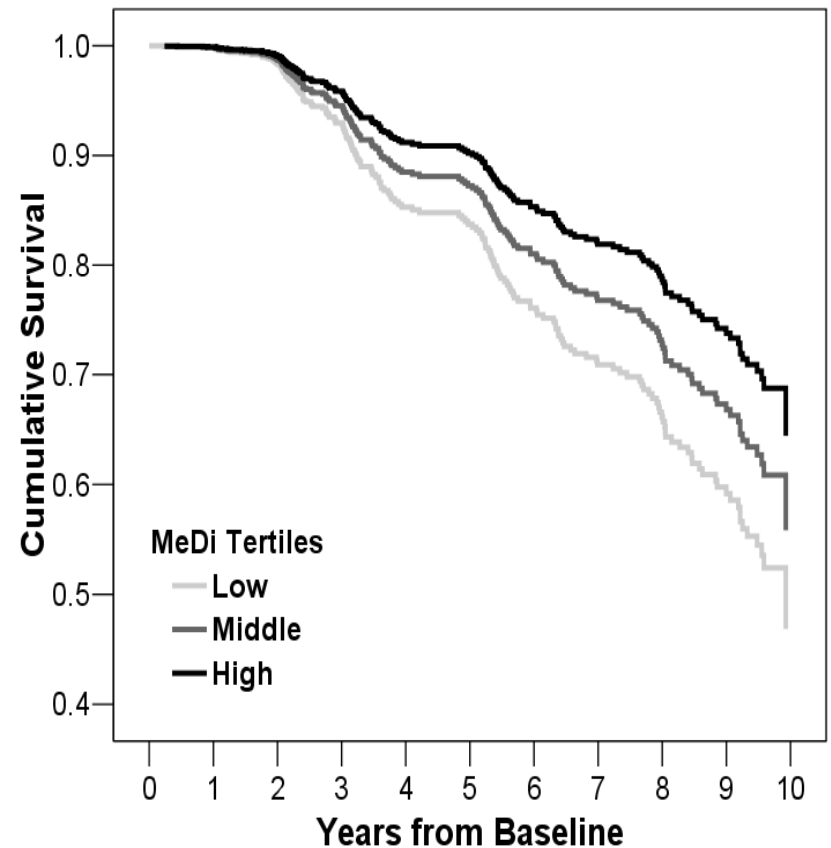|				
1.Cansev (2005) Brain Res	8.Sakamoto (2007) Brain Res	15.de Wilde (2002) Brain Res	22.Jansen (2013) PLOS ONE	29.Jansen (2013) Brain Struc Fun
2.Ulus (2006) Cell Mol Neurobiol	9.Farkas (2002) Brain Res	16.de Bruin (2003) J Learn Mem	23.Broersen (2013) J Alz Dis	30.Koivisto (2013) in press
3.Van Wijk (2011) Br J Nutr	10.Wang (2007) Brain Res	17.Holguin (2008) BehavBrainRes	24.Savelkoul (2012) AAIC	31.Wiesmann (2013) JAD
4.Van Wijk (2012) Nutr Metab	11.Kariv-Inbal (2012) JAD	18.van Wijk (2014) JAD	25.Zerbi (2013) Neurobiol Aging	
5.Wurtman (2006) Brain Res	12.Grimm (2011) JBC	19.de Wilde (2011) J Alz Dis	26.Savelkoul (2011) ADPD	
6.Wang (2005) J Mol Neurosci	13.Teather (2003) PNBP	20.Cansev (2012) data on file	27.Verheijen (2012) data on file	
7.Pooler (2005) Neuroscience	14.de Wilde (2003) Brain Res	21.Cansev (2013) data on file	28.Savelkoul (2012) J Neurochem	

AD risk and nutrient intake

Observational studies suggest a link between Mediterranean diet & AD risk, but data not fully consistent

Mediterranean diet:

- High vegetables, legumes, fruits, and cereals
- High unsaturated fatty acids
- Low saturated fatty acids
- Moderately high fish
- Low-to-moderate dairy
- Low meat and poultry
- Regular but moderate amount of ethanol, primarily in the form of wine and generally, during meals

AD incidence by diet tertile

Scarmeas et al (2006) Ann Neurol

Scarmeas et al, *Ann Neurol,* 2006; Psaltopoulou et al, *Public Health Nutr,* 2008;
Feart et al, *JAMA,* 2009; Cherbuin et al, *Am J Geriatr* Psychiatry, 2011; Tangney et al, *Am J Clin Nutr,* 2011

Systematic review and meta-analysis on nutrient availability in AD
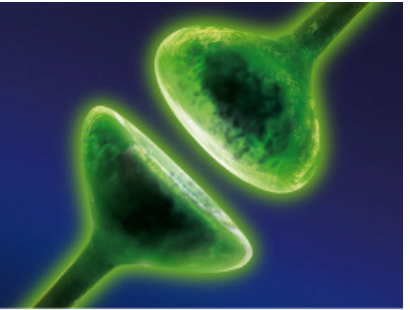
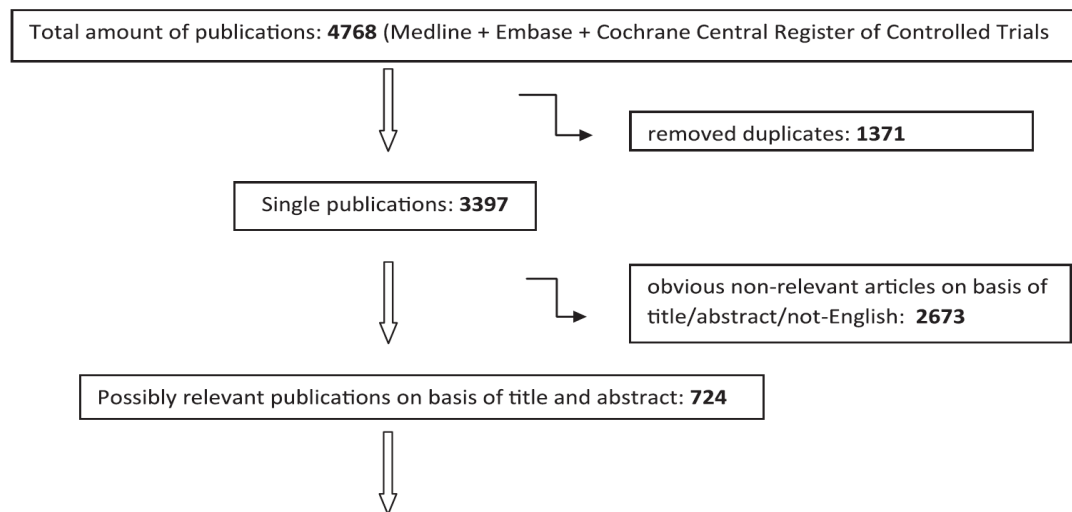- According to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines
- Analyses by independent statisticians
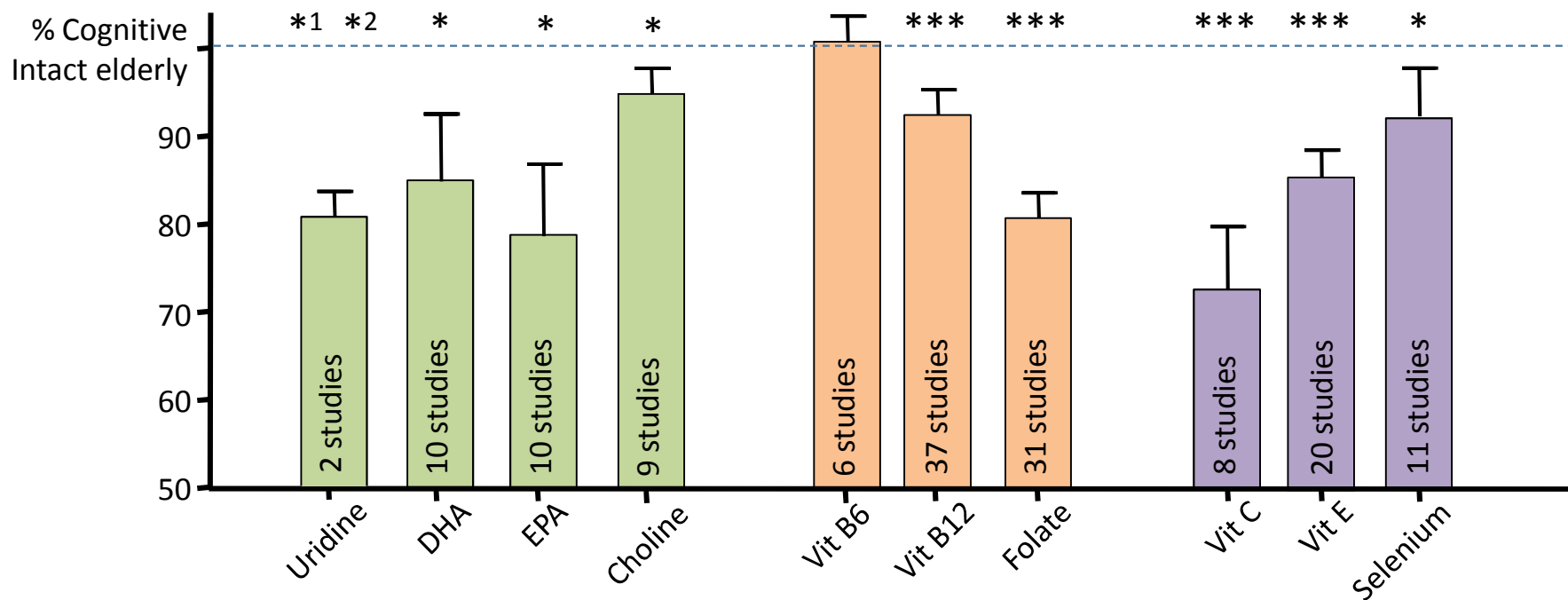
Flow Chart Literature Search

Total amount of publications: **4768** (Medline + Embase + Cochrane Central Register of Controlled Trials

→ removed duplicates: **1371**

Single publications: **3397**

→ obvious non-relevant articles on basis of title/abstract/not-English: **2673**

Possibly relevant publications on basis of title and abstract: **724**

Alzheimer's & Dementia

Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis

Sofia Lopes da Silva[a,b], Bruno Vellas[c], Saskia Elemans[a], José Luchsinger[d], Patrick Kamphuis[a,b], Kristine Yaffe[e], John Sijben[a,*], Martine Groenendijk[a], Theo Stijnen[f]

Systematic review and meta-analysis of literature:
Lower plasma levels of precursors & cofactors in AD

Plasma nutrient status in AD
Meta-analyses, systematic review and observations

*1	*2	*	*	*		***	***		***	***	*

% Cognitive Intact elderly

Bars (left to right with annotations inside):
- Uridine — 2 studies
- DHA — 10 studies
- EPA — 10 studies
- Choline — 9 studies
- Vit B6 — 6 studies
- Vit B12 — 37 studies
- Folate — 31 studies
- Vit C — 8 studies
- Vit E — 20 studies
- Selenium — 11 studies

Y-axis: 50, 60, 70, 80, 90

1:Trushina (2013) PLOS
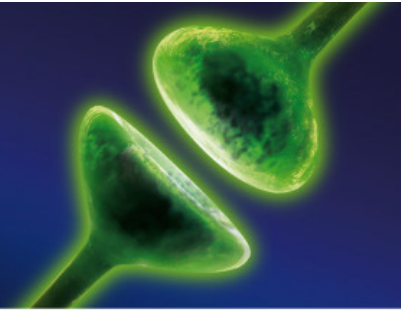2:Olde Rikkert (2013)ADPD

Meta-analyses
Lin (2012) JCP
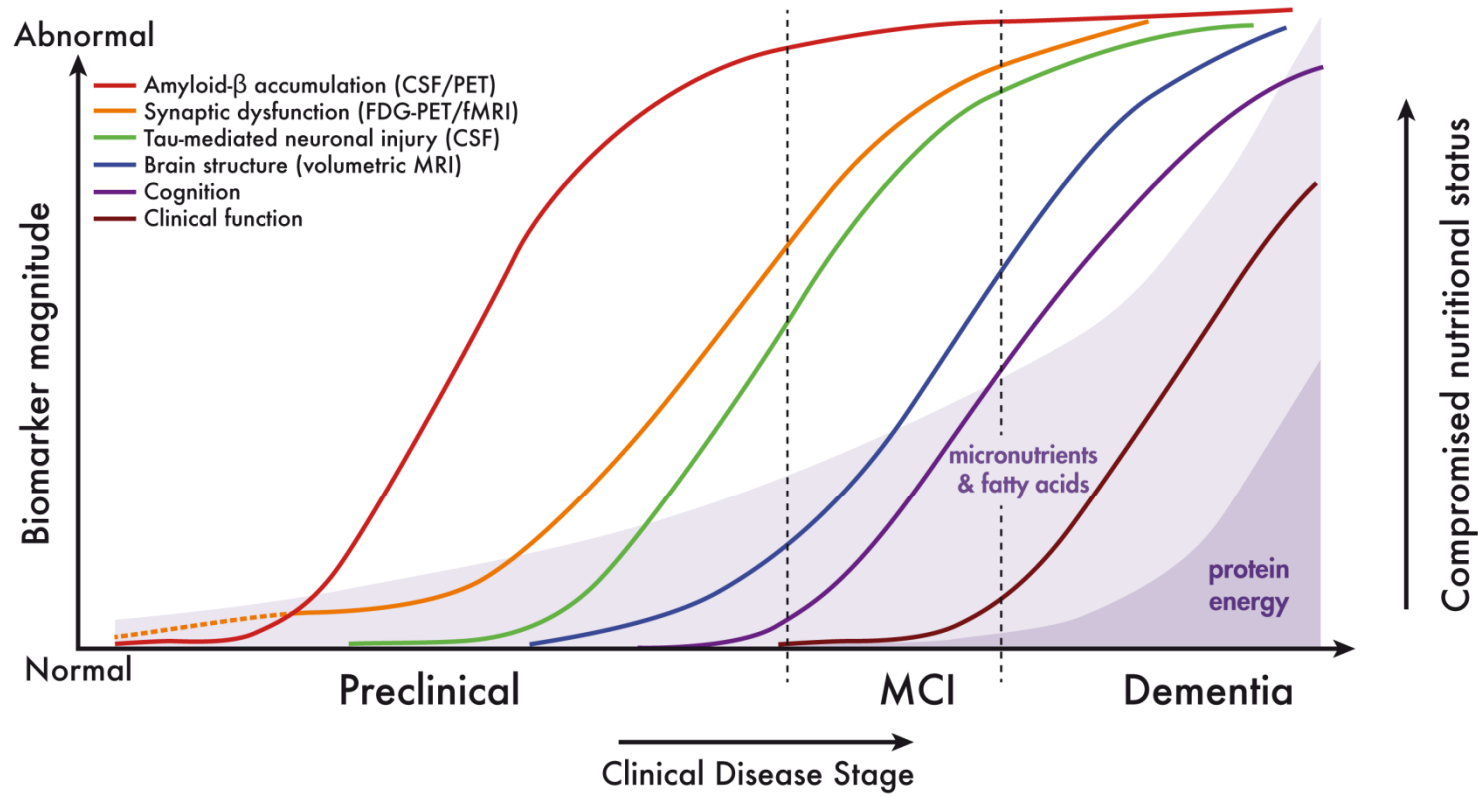
Meta-analyses
data on file

Meta-analyses
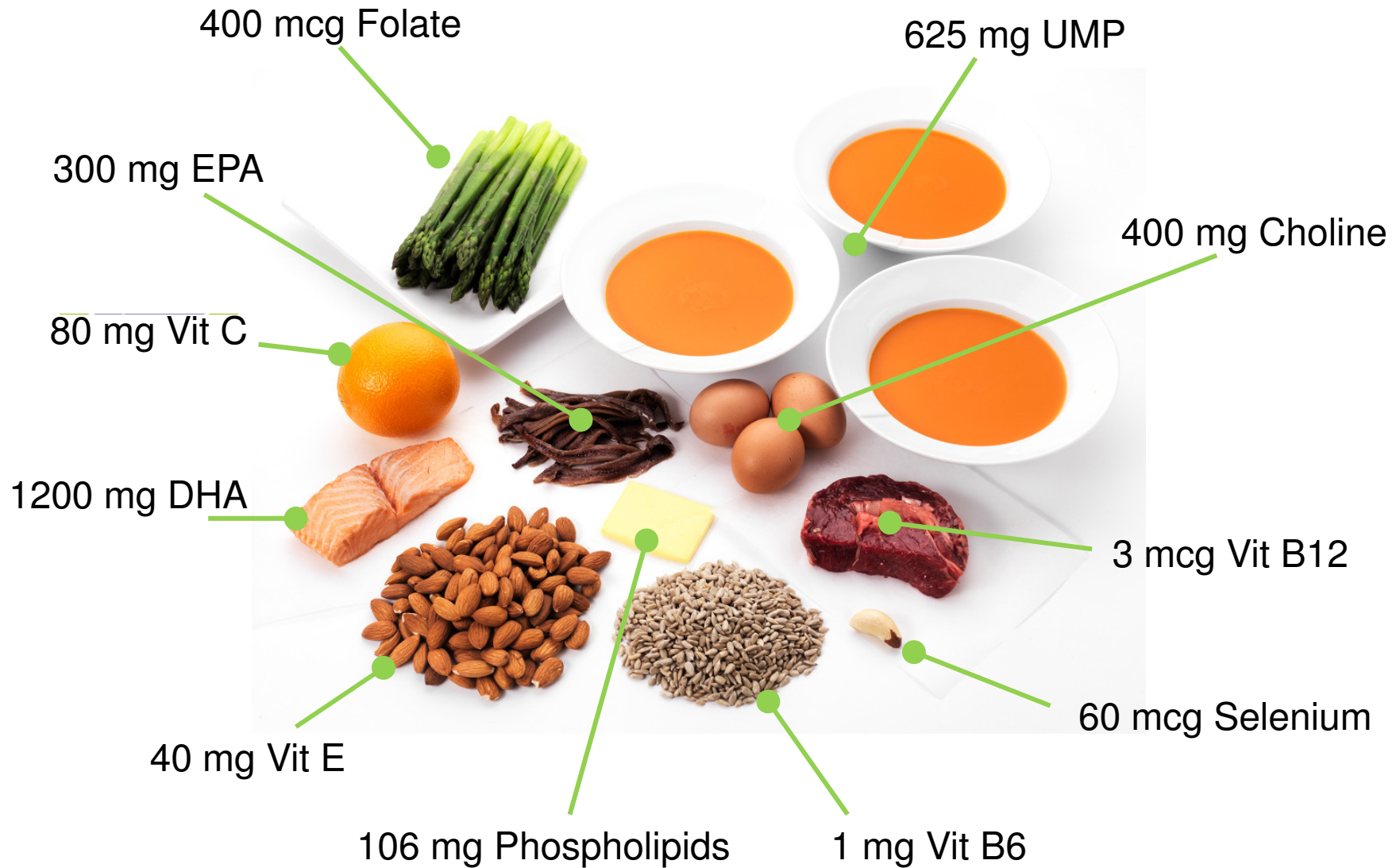Lopes da Silva (2013) Alz Dement

Systematic review
Loef (2011) JAD

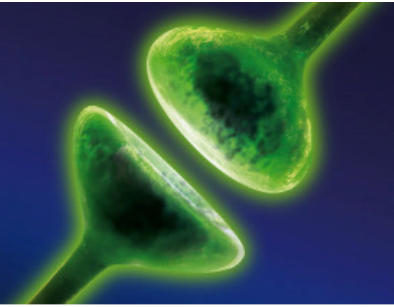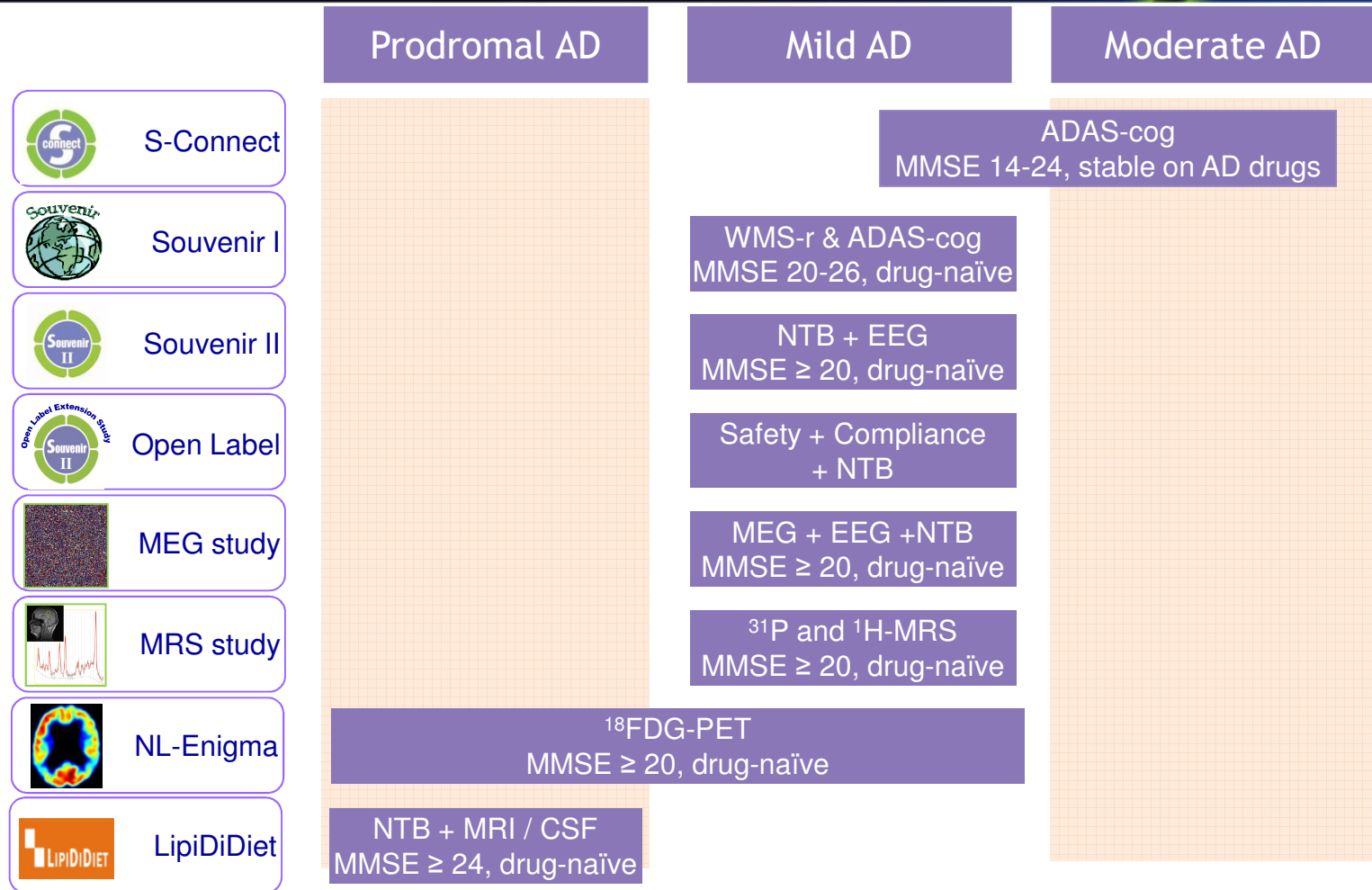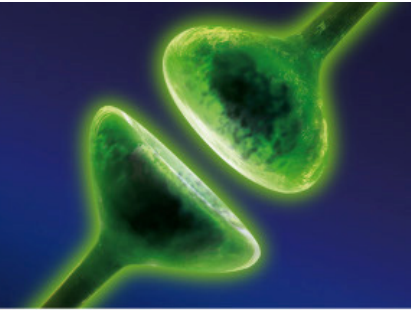# Lower nutrient status preceding classic protein energy malnutrition

Epidemiological relate dietary patterns with AD risk

Mi et al (2013) Nutrition

Development of Souvenaid: addressing AD specific requirements

400 mcg Folate
625 mg UMP
300 mg EPA
400 mg Choline
80 mg Vit C
1200 mg DHA
3 mcg Vit B12
60 mcg Selenium
40 mg Vit E
106 mg Phospholipids
1 mg Vit B6

Souvenaid Clinical Development

	Prodromal AD	Mild AD	Moderate AD
S-Connect			ADAS-cog MMSE 14-24, stable on AD drugs
Souvenir I		WMS-r & ADAS-cog MMSE 20-26, drug-naïve	
Souvenir II		NTB + EEG MMSE ≥ 20, drug-naïve	
Open Label		Safety + Compliance + NTB	
MEG study		MEG + EEG +NTB MMSE ≥ 20, drug-naïve	
MRS study		^{31}P and ^{1}H-MRS MMSE ≥ 20, drug-naïve	
NL-Enigma		^{18}FDG-PET MMSE ≥ 20, drug-naïve	
LipiDiDiet	NTB + MRI / CSF MMSE ≥ 24, drug-naïve		

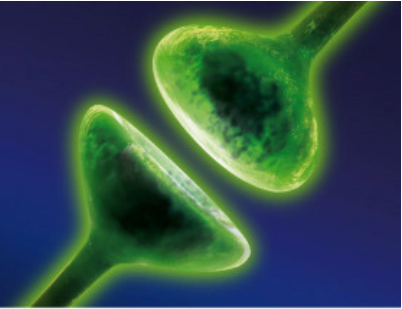# S-Connect study: mild to moderate AD on AD medication

- Principle investigators: David Bennett and Raj Shah, Rush, Chicago
- Multi-centre (48 sites in the US), randomized, controlled trial
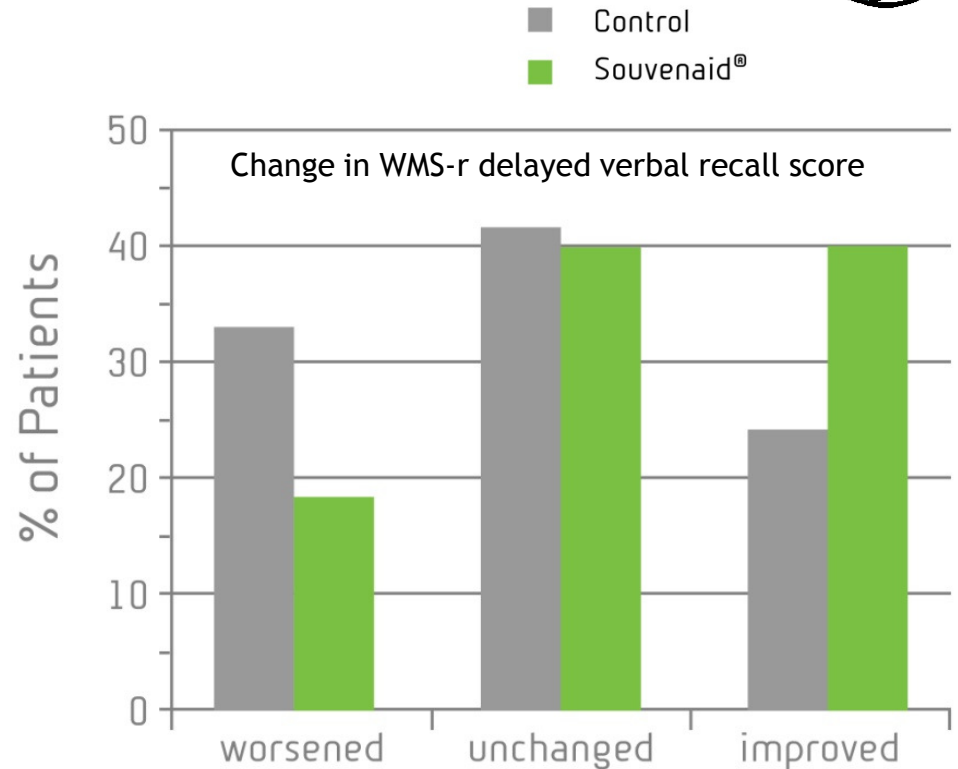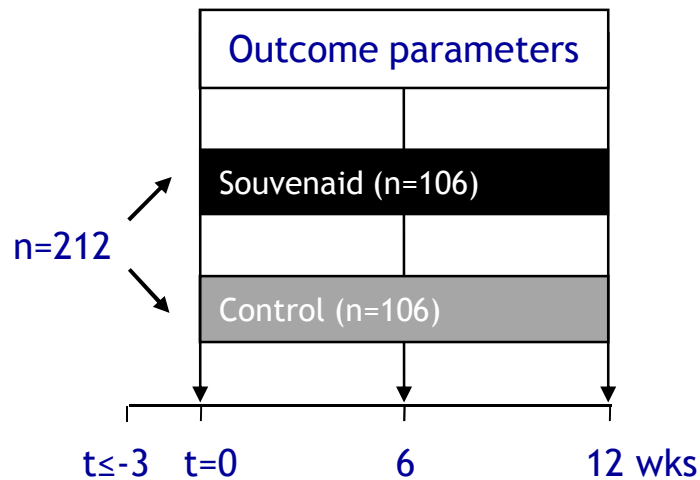- Intervention 24 weeks
- Primary outcome:
  - ADAS-cog-11

Outcome parameters

Souvenaid (n=265)

n=527

Control (n=262)

t≤-3 t=0   12   24 wks

ITT, MMRM, data are mean ±SE

No significant effect (p=0.513) during 24 weeks

Shah et al (2013) Alz Res Ther

# Souvenir I: Proof of concept study in drug-naive mild AD

- Multi-country (NL, Bel, Ger, UK, US), randomized, controlled trial
- Intervention 12 weeks *(+ optional 12 wk extension)*
- Co-primary outcomes:
  - WMS-r delayed verbal recall
  - ADAS-cog-13

Outcome parameters

Souvenaid (n=106)

n=212

Control (n=106)

t≤-3   t=0   6   12 wks

Scheltens et al (2010) Alzh Dement

Control
Souvenaid®

Change in WMS-r delayed verbal recall score

% of Patients

worsened   unchanged   improved

Significantly more responders after 12 weeks (p=0.021)

Souvenir II study: drug-naive mild AD

- Multi-country (NL, Ger, Bel, Fr, It, Sp), randomized, controlled trial
- Intervention 24 weeks
- Primary outcome: Memory Domain NTB (z-score):
  - RAVLT immediate, delayed, recognition and VPA immediate and delayed
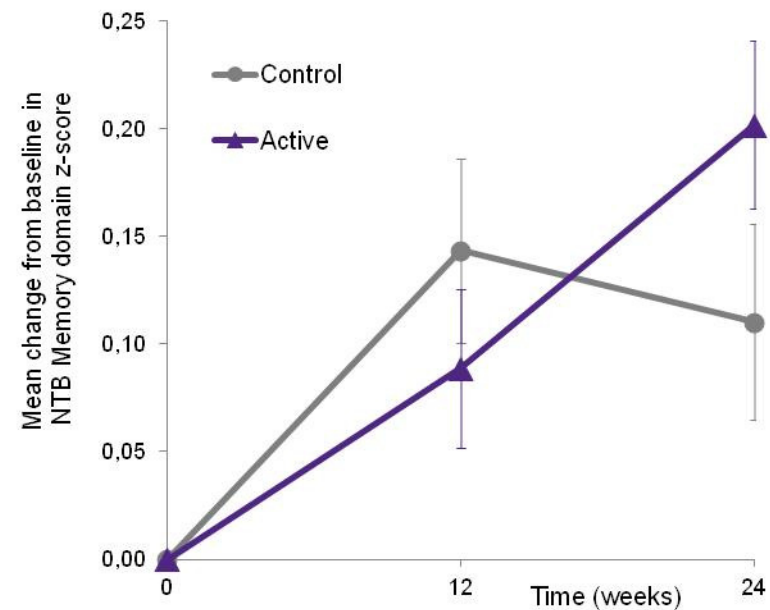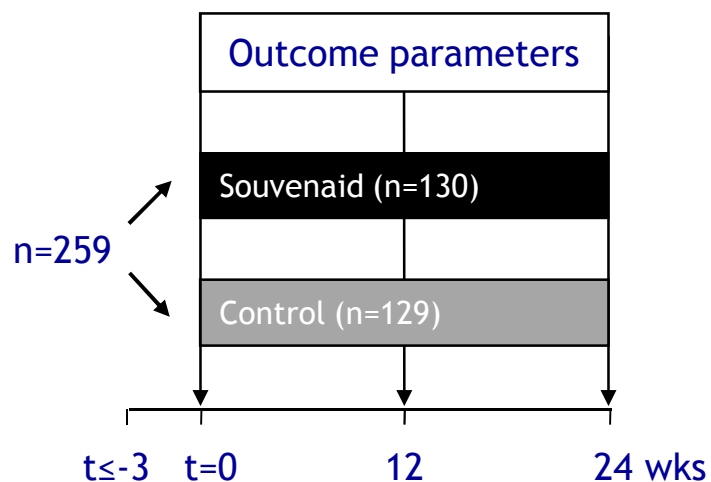
Significantly improved memory (p=0.023)
Memory domain score (z-score) of NTB

Scheltens et al (2012) J Alzheimers Dis

Electrical activity at the synapse – EEG biomarker for functional connectivity
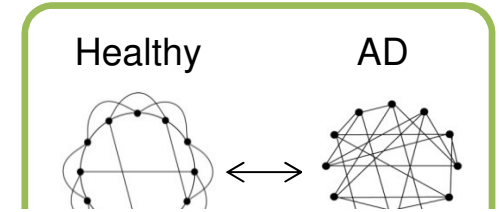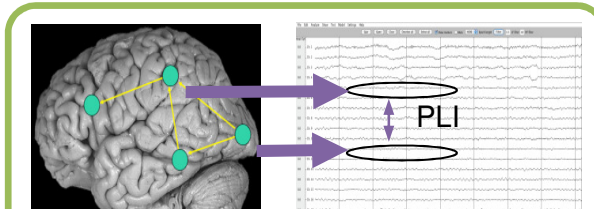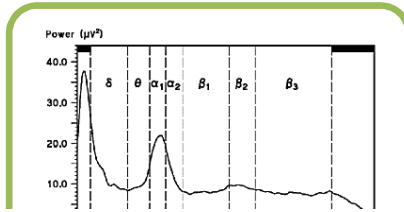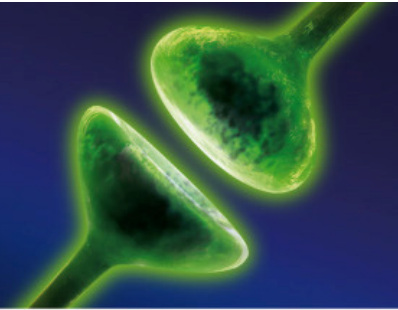
The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer's Disease: A Randomised Controlled Study

Hanneke de Waal[1]*, Cornelis J. Stam[2], Marieke M. Lansbergen[3], Rico L. Wieggers[3], Patrick J. G. H. Kamphuis[3], Philip Scheltens[1], Fernando Maestú[4], Elisabeth C. W. van Straaten[2,3]

1 Alzheimer Center & Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, 2 Department of Clinical Neurophysiology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, 3 Nutricia Research, Utrecht, The Netherlands, 4 Laboratory of Cognitive and Computational Neuroscience, UCM-UPM Center for Biomedical Technology, Madrid, Spain
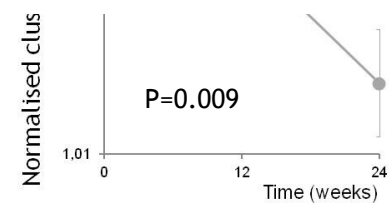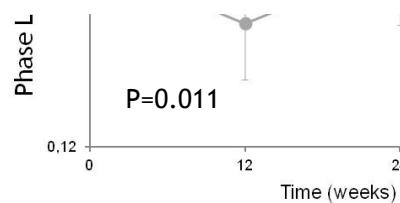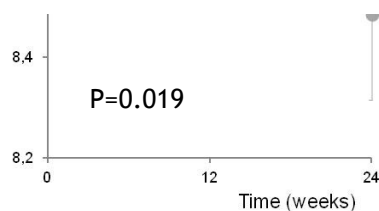
Scheltens et al (2012) J Alzheimers Dis; de Waal et al (2014) PlosOne

# Plasma phospholipids identify antecedent memory impairment in older adults

Mark Mapstone[1], Amrita K Cheema[2,3], Massimo S Fiandaca[4,5], Xiaogang Zhong[6], Timothy R Mhyre[5], Linda H MacArthur[5], William J Hall[7], Susan G Fisher[8,14], Derick R Peterson[9], James M Haley[10], Michael D Nazar[11], Steven A Rich[12], Dan J Berlau[13,14], Carrie B Peltz[13], Ming T Tan[6], Claudia H Kawas[13] & Howard J Federoff[4,5]

NATURE MEDICINE

- Mapstone et al. identified a biomarker panel of 10 plasma lipids that can predict conversion from cognitive healthy to MCI/AD within 2-3 years with >90% accuracy

- Changes may reflect the breakdown of neuronal membranes

- Highly publicitized findings
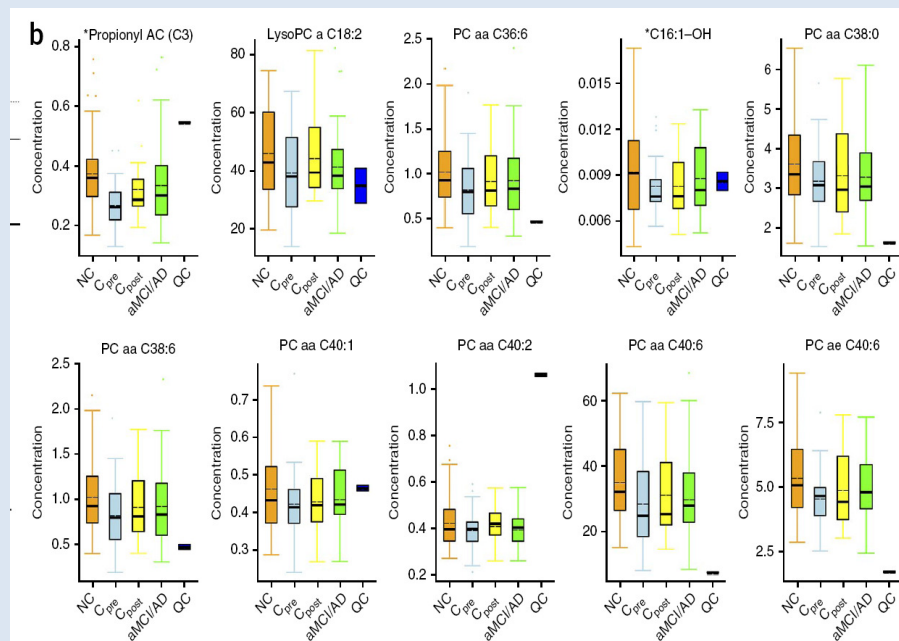
- set of 10 plasma lipids, including 8 phospholipids
- levels are lower in converters and MCI/AD subjects

The Washington Post

**Blood test may predict onset of Alzheimer's and related disease, new study finds**

By Tara Bahrampour, E-mail the writer

Researchers at Georgetown University announced the discovery of a blood test that can predict whether a person will develop Alzheimer's disease or a related condition within three years.

BMJ

Blood test can predict Alzheimer's disease, say US scientists
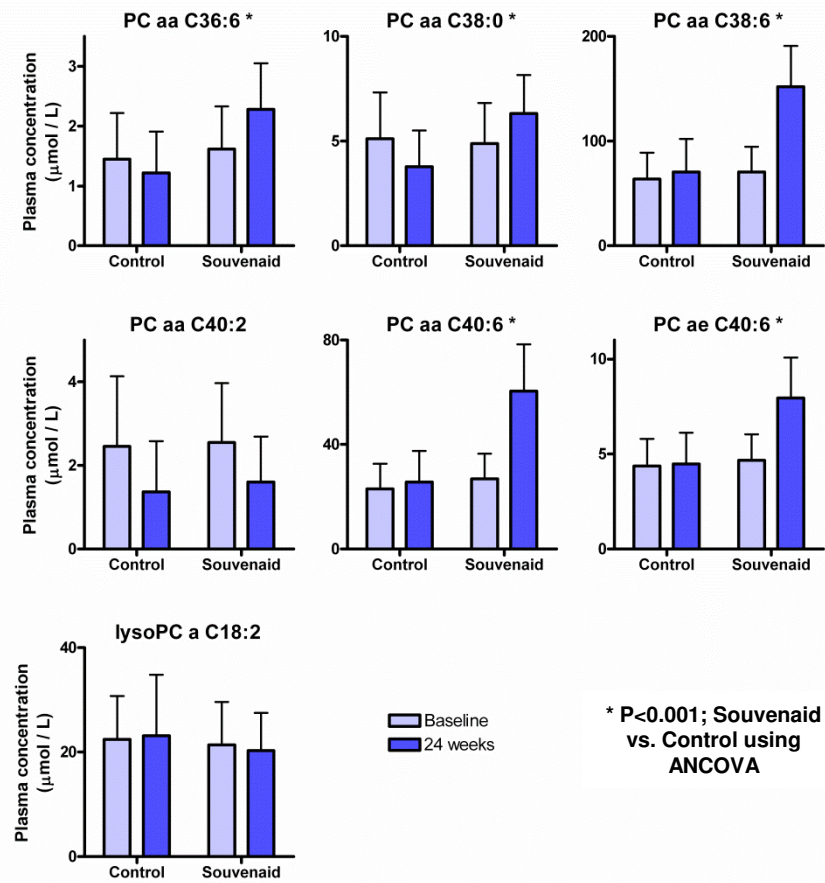
Jacqui Wise

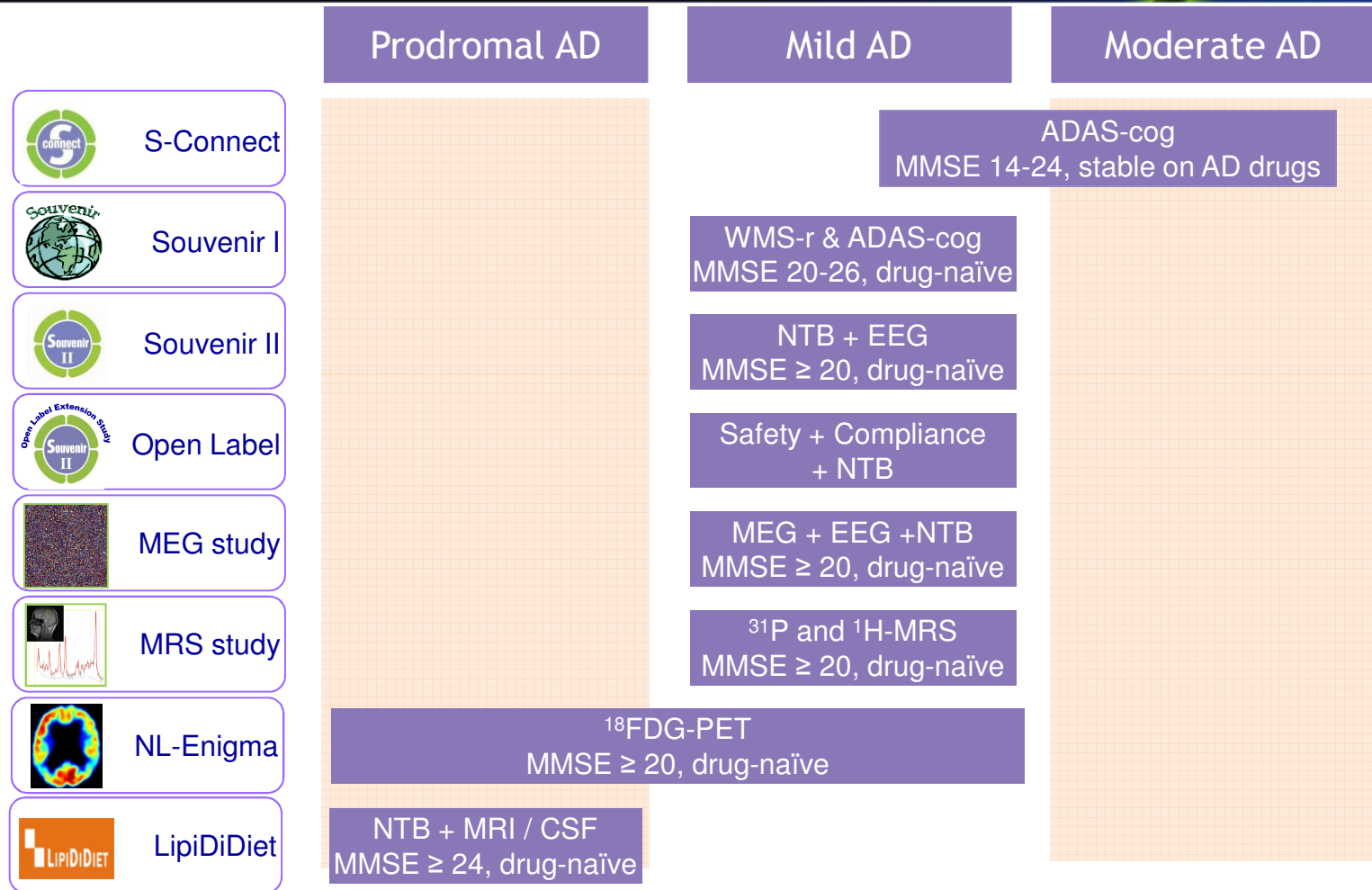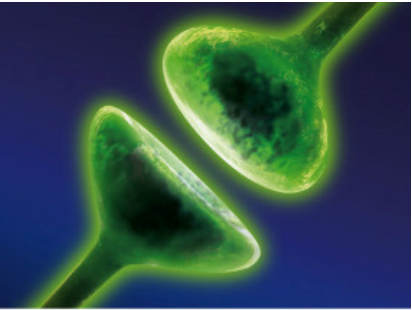# Souvenaid increases levels of the biomarker phospholipids
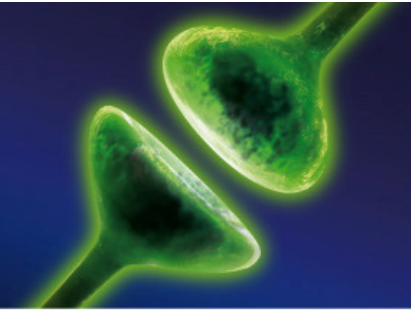
- Baseline and 24-week plasma samples from the Souvenir II study
- Drug-naïve patients with very mild AD
- Polar lipid profile

- By providing nutrients which normally rate-limit phospholipid synthesis Souvenaid can:
  - modify a biomarker profile reflecting disturbed phospholipid metabolism
  - be useful in asymptomatic subjects with plasma lipid biomarker profiles predictive for conversion to AD

5 / 7 measured phospholipids reported by Mapstone significantly increased by Souvenaid

Souvenaid Clinical Development

	Prodromal AD	Mild AD	Moderate AD
S-Connect			ADAS-cog MMSE 14-24, stable on AD drugs
Souvenir I		WMS-r & ADAS-cog MMSE 20-26, drug-naïve	
Souvenir II		NTB + EEG MMSE ≥ 20, drug-naïve	
Open Label		Safety + Compliance + NTB	
MEG study		MEG + EEG +NTB MMSE ≥ 20, drug-naïve	
MRS study		^{31}P and ^{1}H-MRS MMSE ≥ 20, drug-naïve	
NL-Enigma	^{18}FDG-PET MMSE ≥ 20, drug-naïve		
LipiDiDiet	NTB + MRI / CSF MMSE ≥ 24, drug-naïve		

Souvenir I received funding from NL STW
Souvenir II receives funding from the NL Food & Nutrition Delta project, FND N°10003
LipiDiDiet is funded by the EU FP7 project LipiDiDiet, Grant Agreement   N° 211696
NL-Enigma funded by NWO NIHC project, N°057-13-003.

Thank you!