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Demenzen - was können wir tun?

Prim. ao.Univ-Prof. Dr. Christian Lampl
Ärztlicher Direktor
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Ordensklinikum Linz BHS, Seilerstätte Linz, Austria

D E M E N Z E N

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Was können wir tun?
....Irrläufer?

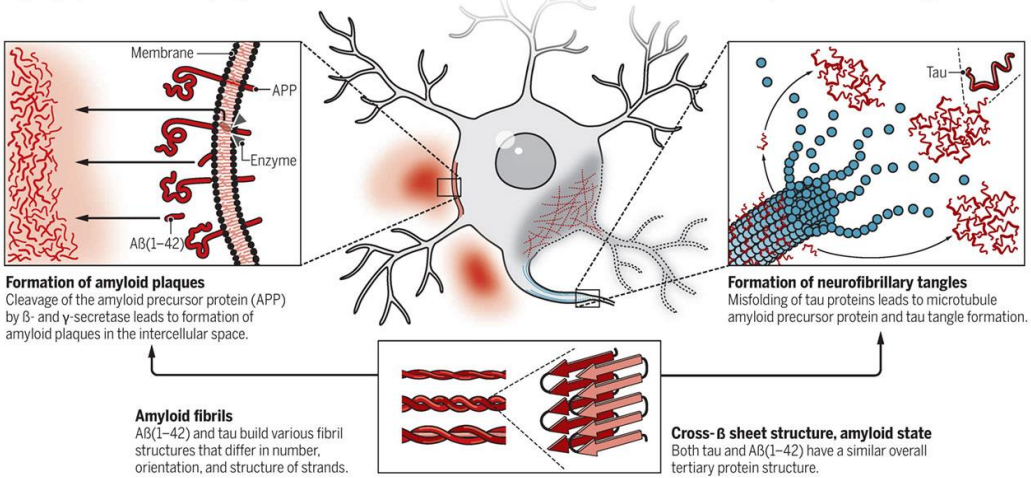
DEMENZ (ein Syndrom) ist ein Verlust der geistigen Fähigkeiten von solcher Schwere, dass der Alltag nicht mehr wie gewohnt bewältigt werden kann.

Die URSACHEN der Demenz (die Krankheiten) sind vielfältig: im Prinzip kann jede schwere Erkrankung des Gehirns und des restlichen Körpers zu einer Demenz führen. Die meisten sind vermeid- oder behandelbar.

Häufigste einzelne Ursache der Demenz ist die ALZHEIMER KRANKHEIT
Häufigste Form der Demenz ist die GEMISCHTE DEMNZ
Hauptrisikofaktor der Demenz ist das ALTER (© Prof. Hans Förstl)

Molecular characteristics of Alzheimer's disease

Amyloid plaques and neurofibrillary tangles that accumulate in an Alzheimer's brain consist of amyloid fibrils with different components but similar tertiary protein structures.

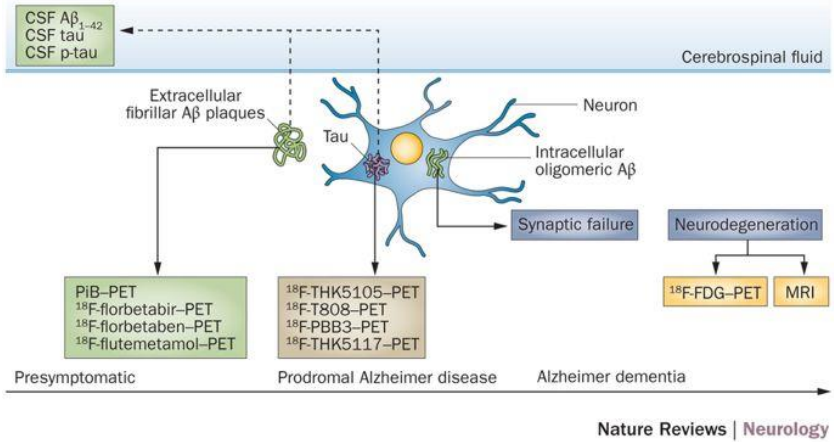


Formation of amyloid plaques
Cleavage of the amyloid precursor protein (APP) by ß- and γ-secretase leads to formation of amyloid plaques in the intercellular space.

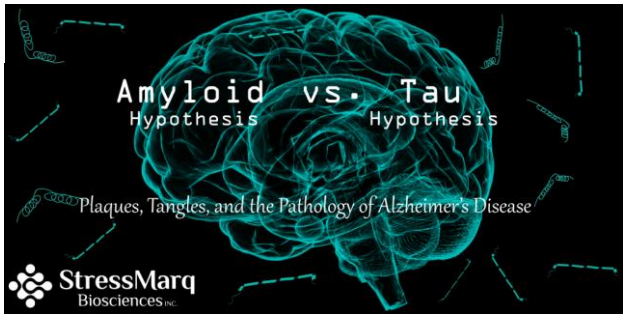
Formation of neurofibrillary tangles
Misfolding of tau proteins leads to microtubule amyloid precursor protein and tau tangle formation.

Amyloid fibrils
Aß(1–42) and tau build various fibril structures that differ in number, orientation, and structure of strands.

Cross-ß sheet structure, amyloid state
Both tau and Aß(1–42) have a similar overall tertiary protein structure.



Nature Reviews | Neurology



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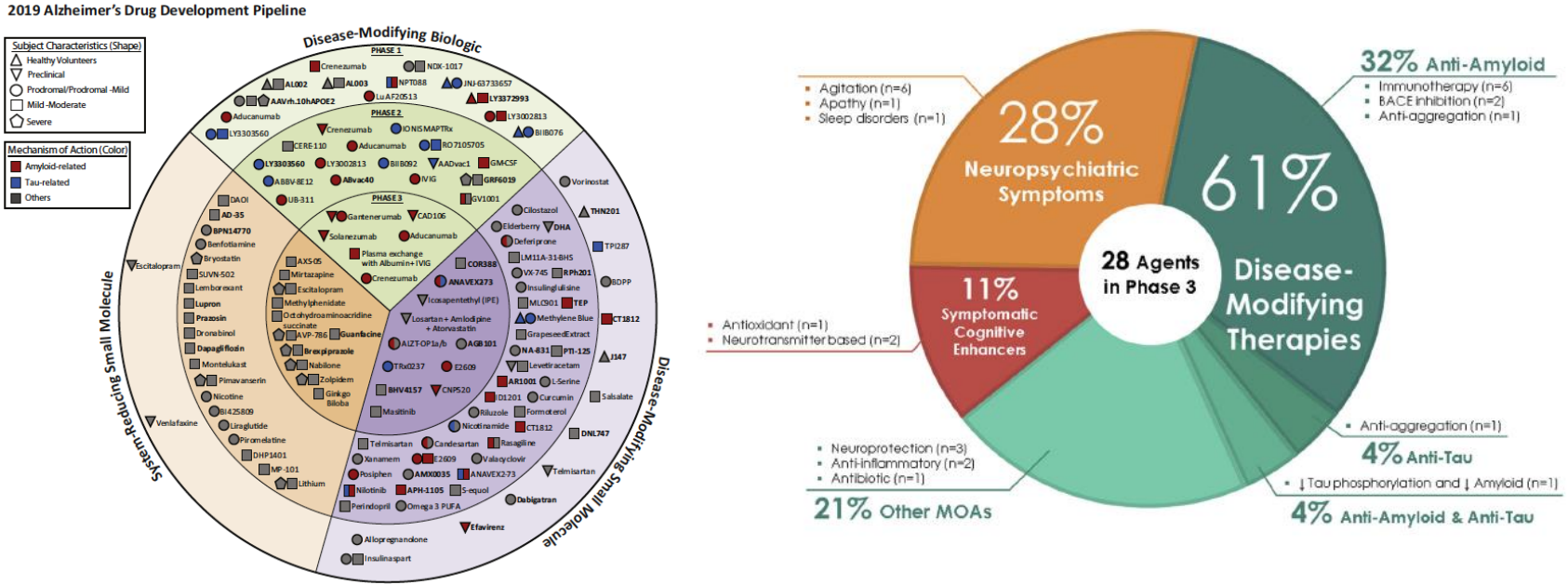
Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019) 272-293

Featured Article

Alzheimer's disease drug development pipeline: 2019

Jeffrey Cummings[a,b,*], Garam Lee[b], Aaron Ritter[b], Marwan Sabbagh[b], Kate Zhong[c]



www.clinicaltrials.gov. - Phase III Studien

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BACE Inhibitors
CNP 520
Elenbecestat
Lanabecestad

Aß-Antibodies
Crenezumab
Gantenerumab

Active Aß-Immunization
CAD 106

Active Aß-Aggregation:
Na-Oligomannararate

Anti-Agitation
Brexpiprazol
Bupropion
Deudextrometorphan
Dextrometorpahn
Escitalopram
Lumateperone
Mirtazapin vs Carbamazepin

AChE-I:
Donezepil
Octohydroaminoacridin
AChE-I discontinuation

Risik Redution
Angiotensin II Inhibitoren
Lacunar intervention

Antipsychotic:
Pimavanserin

Mast Cells Stabilizer
Cromolyn

Sleep:
Suvorexant
Z-Drugs

Imaging:
Consequences of amyloid imaging
Amyloid PET for CAA

Ginco biloba

MIND diet
Neurostimulation

Anti-Apathy:
Methylphenidate
Pimavanserin

www.clinicaltrials.gov. –
89 „Alzheimer-Studien“, davon therapeutisch.....

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5 immunologische Ansätze

4 Cholinesterase-Hemmer, Memantin

4 andere Neurotransmitter

5 andere pharmakologische Prinzipien (z.B. neuroprotektiv)

5 elektrische (z.B. DBS)

5 andere physikalische Interventionen (z.B. Laser Stimulation, „Photobiomodulation“)

Methodische Probleme

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- Fehldiagnose im Frühstadium (über 20%)
- Variabilität des natürlichen Krankheitsverlaufes
- Unzureichende Erfassung exekutiver Störungen
- Multifaktorielle Krankheitsgrundlagen
- Fehlende Repräsentativität der untersuchten Stichproben
- Veränderung der Prävalenz

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration **Lancet 2013; 382: 1405–12**

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Research Council Cognitive Function and Ageing Study (CFAS)

CFAS I	1989 - 1994;	n=7635
CAFS II	2008 - 2011;	n=7796

Interpretation: This study provides further evidence that a cohort effect exists in dementia prevalence. Later-born populations have a lower risk of prevalent dementia than those born earlier in the past century.

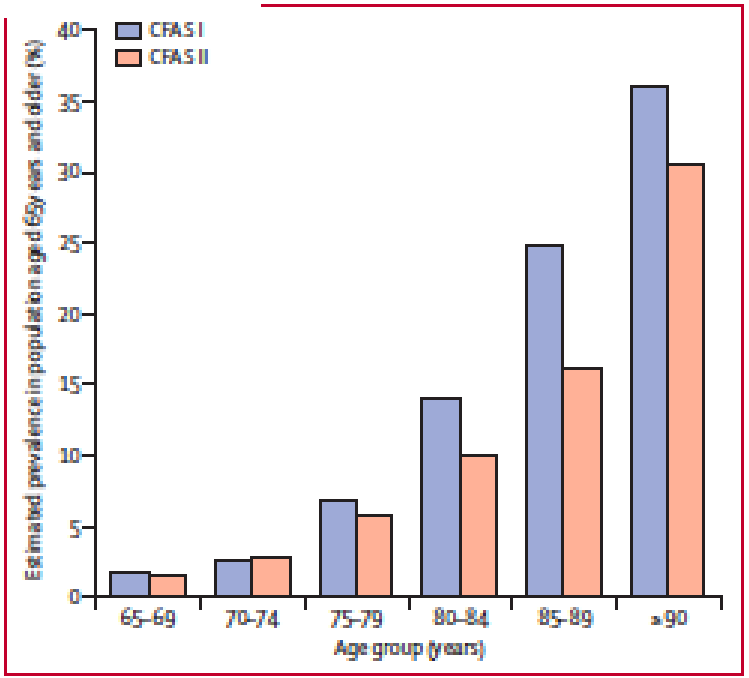

Figure 1: CFAS I and CFAS II age-specific dementia prevalence
CFAS=Cognitive Function and Ageing Study.

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration **Lancet 2013; 382: 1405–12**

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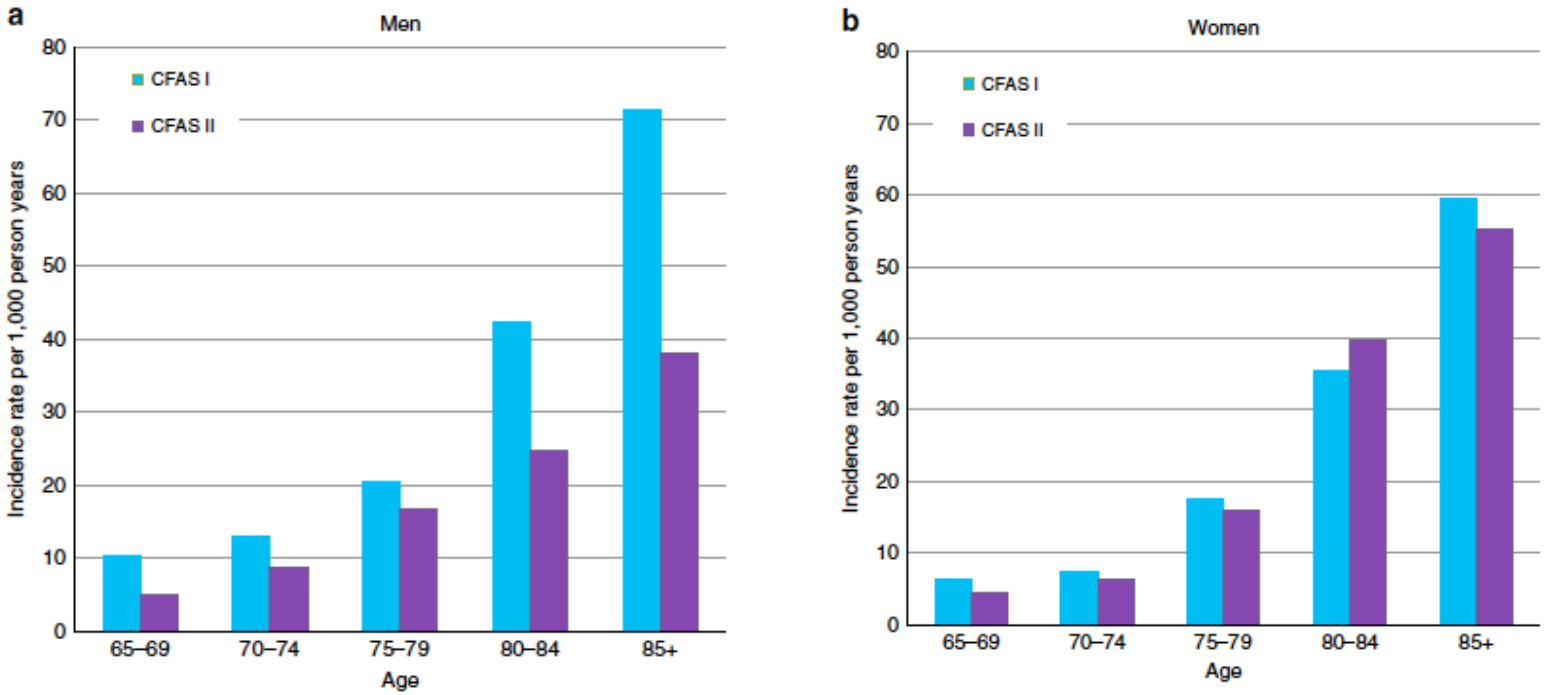
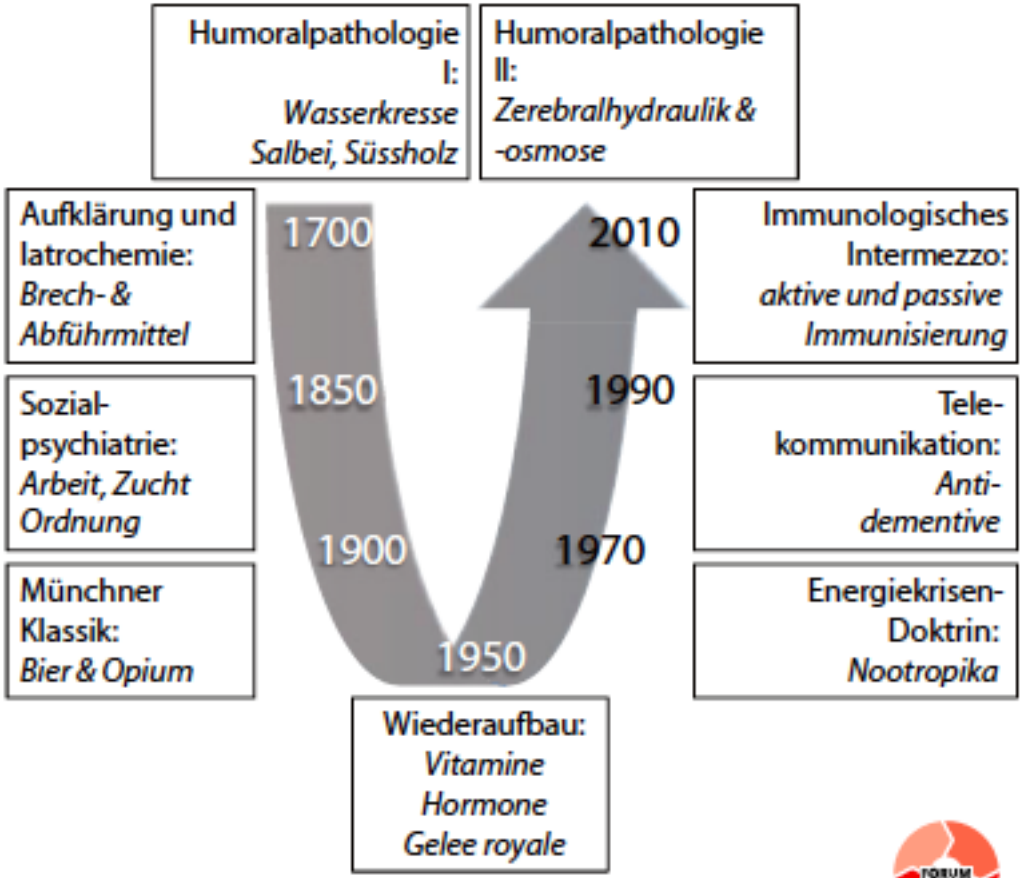


Zeitgeist und Demenzbehandlung



Quelle: Prof. Dr. Hans Förstl

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molecules

MDPI

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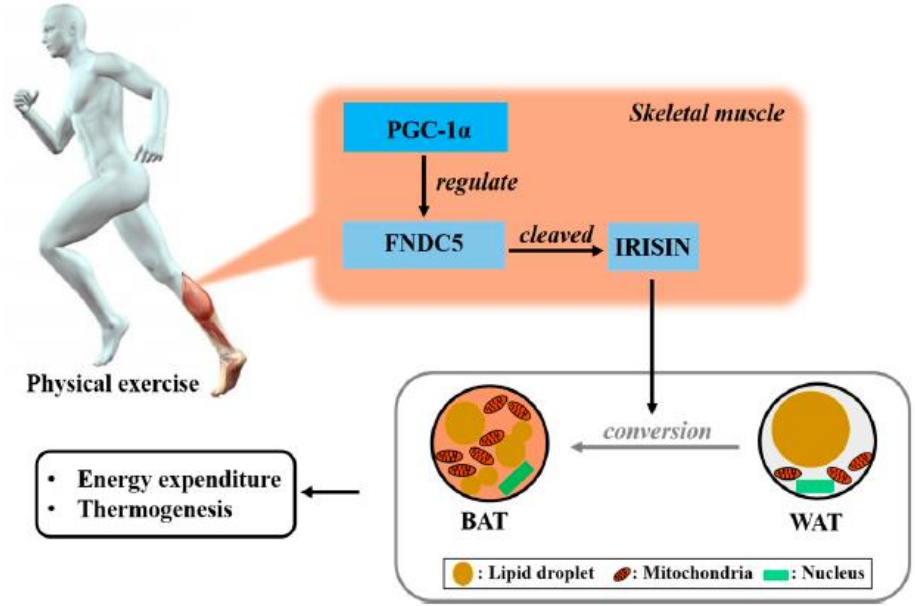
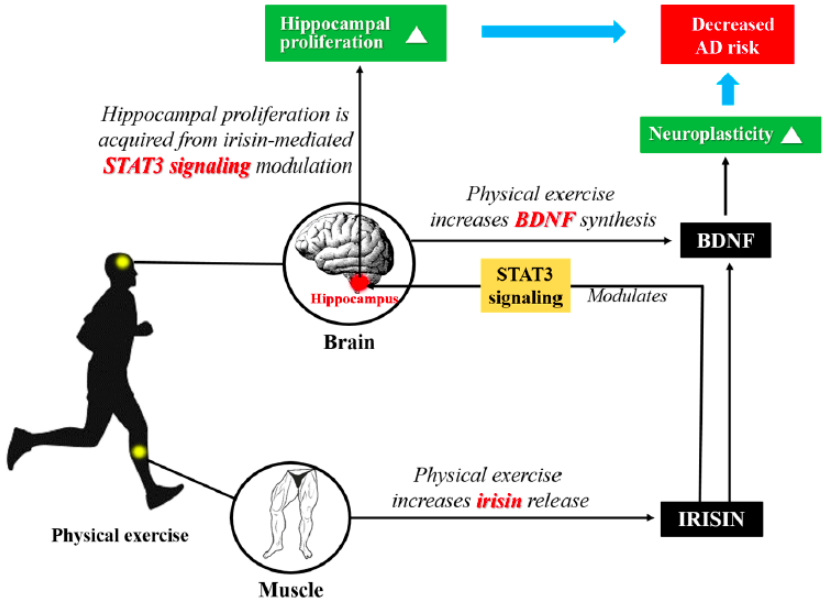
Review

Molecular and Functional Interaction of the Myokine Irisin with Physical Exercise and Alzheimer's Disease

Yunho Jin [1,2,3,†], Dewan Md. Sumsuzzman [1,2,3,†], Jeonghyun Choi [1,2,3], Hyunbon Kang [2,3,4], Sang-Rae Lee [5] and Yonggeun Hong [1,2,3,4,6,*]





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Preventive Medicine
Volume 70, January 2015, Pages 33-38

Relationships between dog ownership and physical activity in postmenopausal women ☆

David O. Garcia [a], Betsy C. Wertheim [b], JoAnn E. Manson [c, d], Rowan T. Chlebowski [e], Stella L. Volpe [f], Barbara V. Howard [g], Marcia L. Stefanick [h], Cynthia A. Thomson [i]

CONCLUSIONS:
Dog ownership is associated with increased physical activity in older women, particularly among women living alone. Health promotion efforts aimed at older adults should highlight the benefits of regular dog walking for both dog owners and non-dog owners

Published in final edited form as:
JAMA Neurol. 2017 May 01; 74(5): 567–573. doi:10.1001/jamaneurol.2016.5778.

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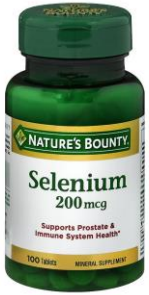
Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE)

Richard J. Kryscio, Ph.D.[1,2,3,4], Erin L. Abner, Ph.D.[1,2,3,5], Allison Caban-Holt, Ph.D.[1,2], Mark Lovell, Ph.D.[1,2,6], Phyllis Goodman, M.S.[7], Amy K. Darke, M.S.[7], Monica Yee, B.A.[8], John Crowley, Ph.D.[8], and Frederick A. Schmitt, Ph.D.[1,2,9]

	ITT		Weighted**	
Treatment	HR (95% CI)	P value	HR (95% CI)	P value
Vitamin E	0.88 (0.64–1.20)	0.41	0.84 (0.61–1.15)	0.27
Selenium	0.83 (0.61–1.13)	0.23	0.80 (0.59–1.09)	0.16
Combined	1.00 (0.74–1.35)	0.98	0.99 (0.74–1.32)	0.93



* All HR estimates are vs. Placebo;

** weighted analysis is missing 50 participants

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 12, 1596–1602
doi:10.1093/gerona/glw078
Advance Access publication September 27, 2016

OXFORD

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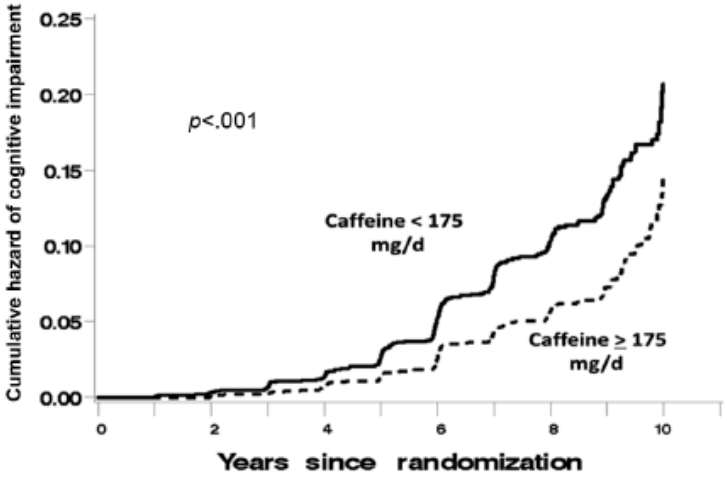
Research Article

Relationships Between Caffeine Intake and Risk for Probable Dementia or Global Cognitive Impairment: The Women's Health Initiative Memory Study

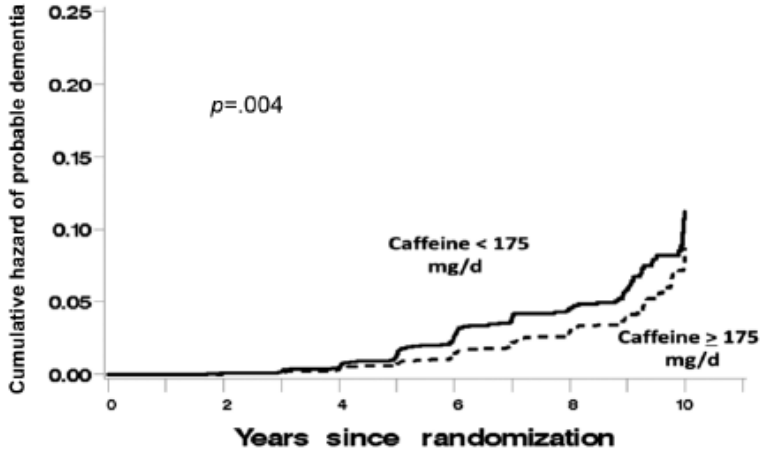
Ira Driscoll,[1] Sally A. Shumaker,[2] Beverly M. Snively,[3] Karen L. Margolis,[4] JoAnn E. Manson,[5] Mara Z. Vitolins,[6] Rebecca C. Rossom,[4] and Mark A. Espeland[3]

1 Tasse Kaffee ist ca. 50 mg Coffein

MCI



Dementia



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Coffee Consumption Habits and the Risk of Mild Cognitive Impairment: The Italian Longitudinal Study on Aging

Vincenzo Solfrizzi[a,1,*], Francesco Panza[b,c,d,1,*], Bruno P. Imbimbo[e], Alessia D'Introno[a]

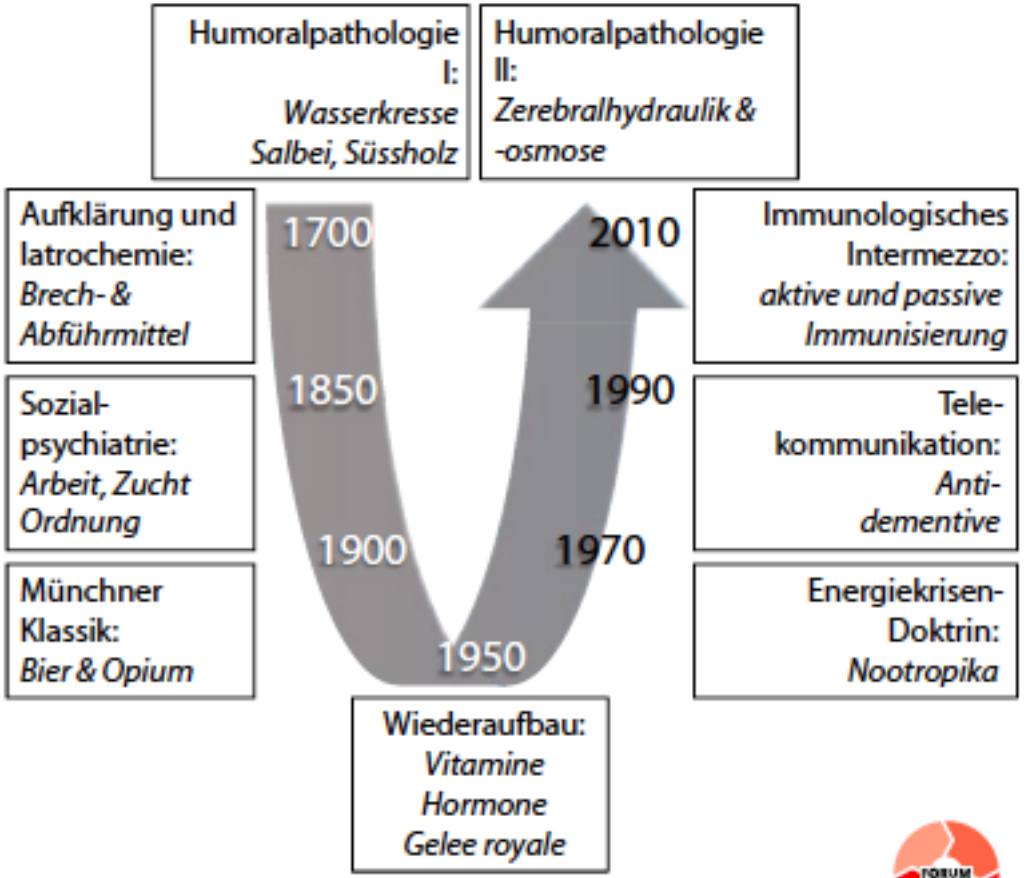
Journal of Alzheimer's Disease 47 (2015) 889–899

Coffee, tea, or caffeine consumption may be protective against cognitive impairment and dementia (MCI).
We evaluated 1,445 individuals, aged 65–84 year old, with a 3.5-year median follow-up.

Regular:	1 cup/day	HR 0.47
	1-2 cups/day	HR: 0.31
Increase	>1 cup of coffee/day	HR: 1.8

Conclusion: In conclusion, cognitively normal older individuals who increased their coffee consumption had a higher rate of developing MCI, while a constant in time moderate coffee consumption was associated to a reduced rate of the incidence of MCI.

Zeitgeist und Demenzbehandlung



Quelle: Prof. Dr. Hans Förstl

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Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease

Robert Howard, M.D., Rupert McShane, F.R.C.Psych., James Lindesay, D.M.,

N ENGL J MED 366;10 NEJM.ORG MARCH 8, 2012

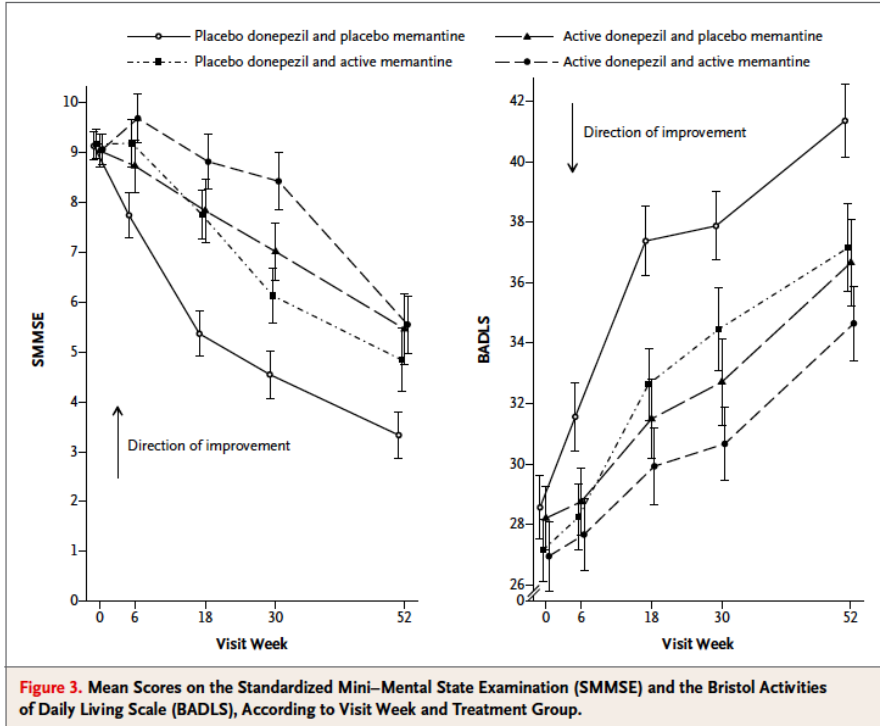

Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Conclusions:

In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months.

Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease

Lawrence S. Honig, M.D., Ph.D., Bruno Vellas, M.D., Michael Woodward, M.D., Mercè Boada, M.D., Ph.D.,

N ENGL J MED 378;4 NEJM.ORG JANUARY 25, 2018

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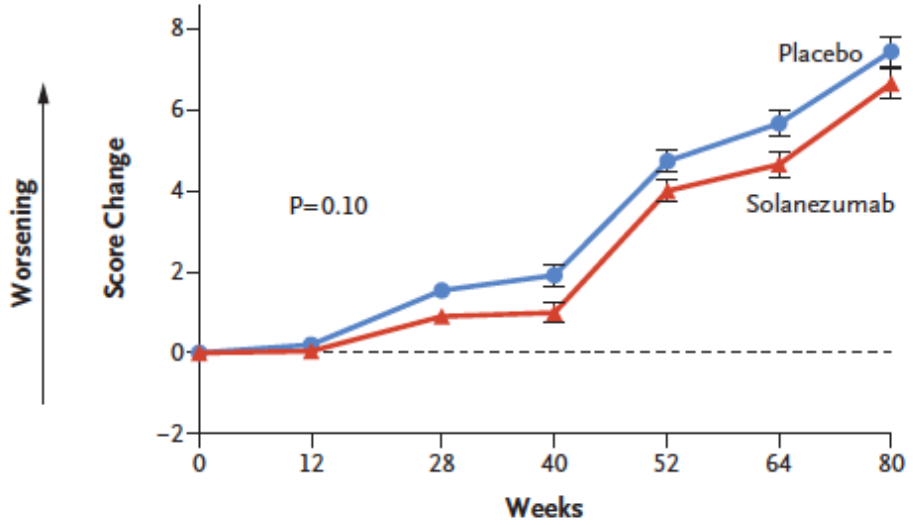
A Change in Alzheimer's Disease Assessment Scale–Cognitive Subscale Score



No. at Risk							
Placebo	1067	—	—	—	—	—	893
Solanezumab	1053	—	—	—	—	—	908

Solanezumab is a humanized monoclonal antibody solanezumab was designed to increase the clearance from the brain of soluble Aβ

ARTICLE

doi:10.1038/nature19323

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The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1],

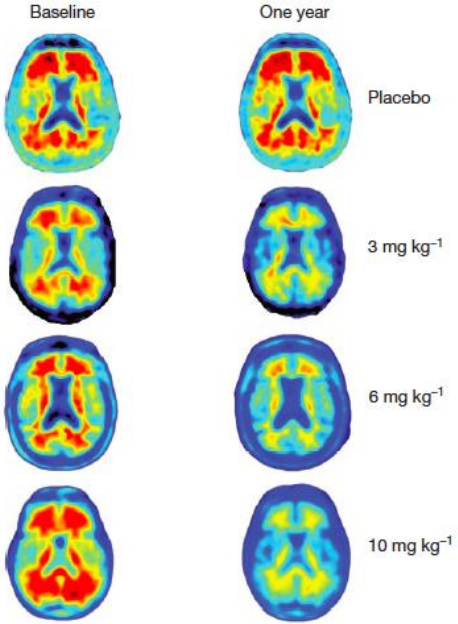
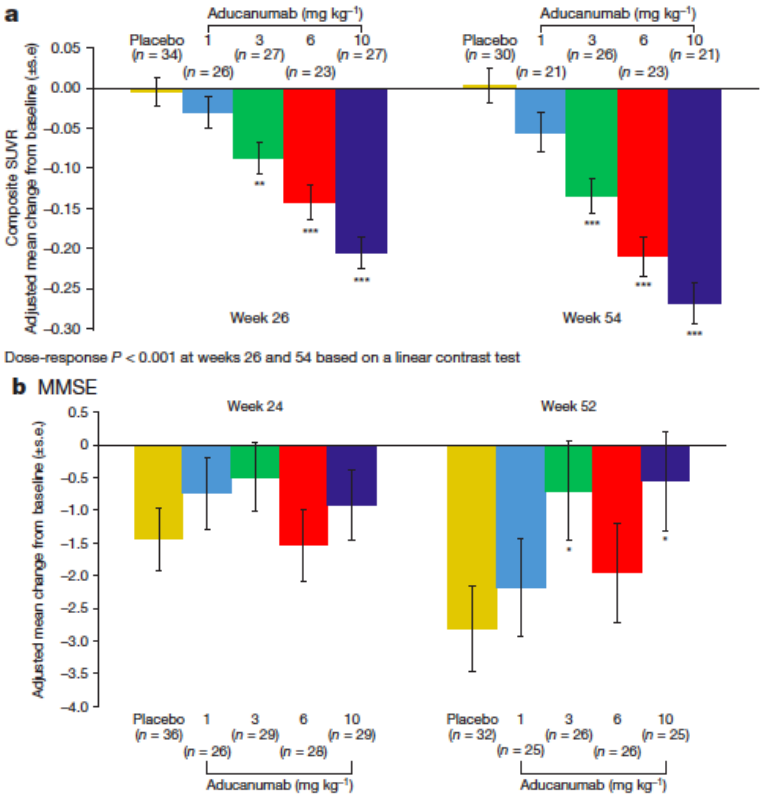


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen



Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease

Michael F. Egan, M.D., James Kost, Ph.D., Pierre N. Tariot, M.D.,

N Engl J Med 2018;378:1691-703.

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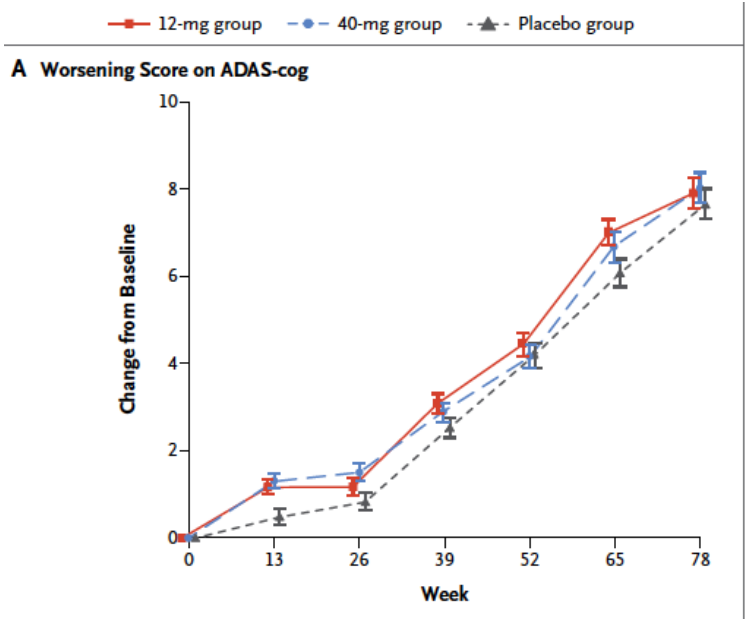
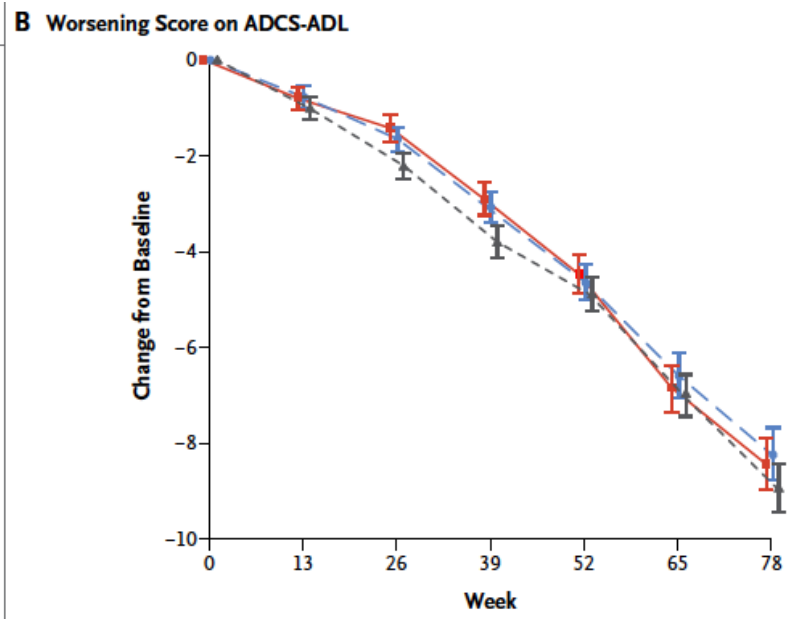
Verubecestat (MK-8931) is an experimental drug for the treatment of Alzheimer´s disease. It is an inhibitor of beta-secretase 1.





CONCLUSIONS

Verubecestat did not reduce cognitive or functional decline in patients with mild-to-moderate Alzheimer's disease and was associated with treatment-related adverse events.

The New York Times

Will We Ever Cure Alzheimer's?

Few drugs have been approved for treatment of this dementia, and none works very well. It has become one of the most intractable problems in medicine.

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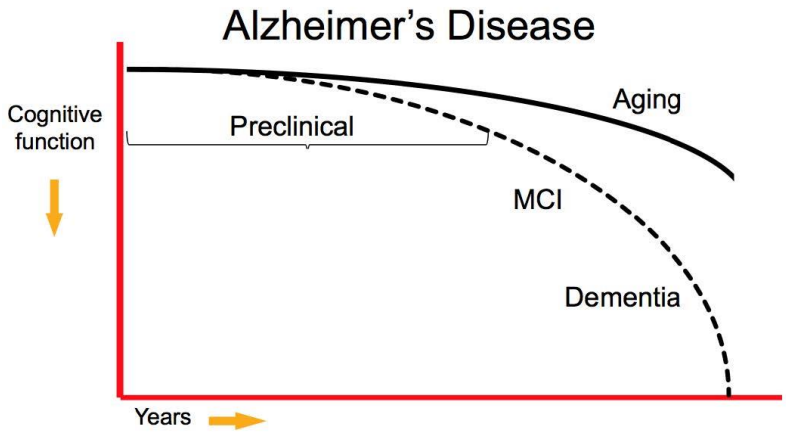

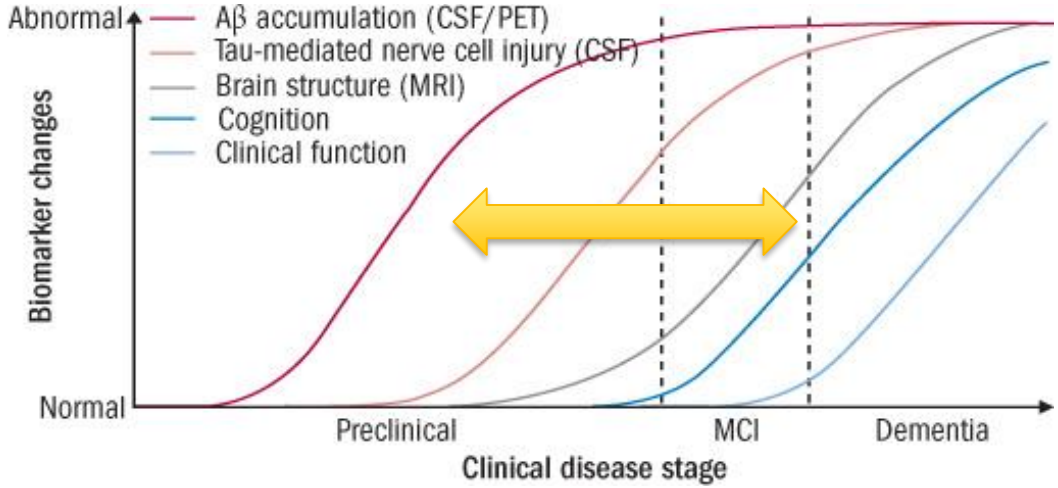

Sleep disturbances and the risk of dementia

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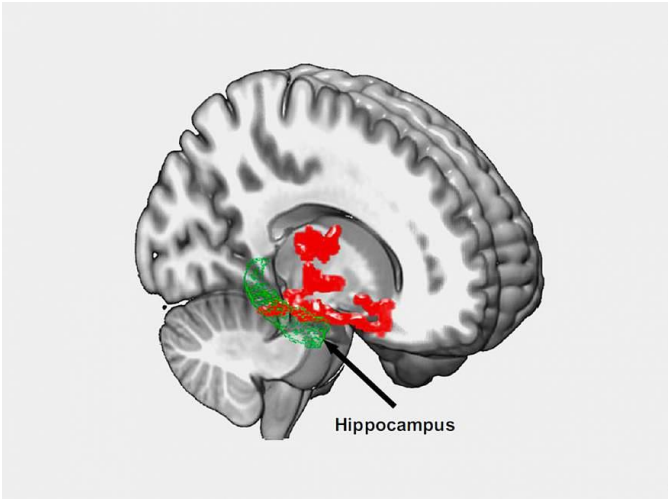
NEWS RELEASES

Friday, April 13, 2018

Lack of sleep may be linked to risk factor for Alzheimer's disease

Preliminary NIH study shows increased levels of beta-amyloid.



Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia

Neurology® 2017;88:1172-1179

Andrew J. Westwood, MD
Alexa Beiser, PhD
Nikita Jain
Jayandra J. Himali, PhD
Charles DeCarli, MD
Sanford H. Auerbach, MD
Matthew P. Pase, PhD*
Sudha Seshadri, MD*

Table 2 Self-reported sleep duration and the adjusted risk of incident dementia

	All-cause dementia			Alzheimer disease		
Event	No. events/total n	HR (95% CI)	p Value	No. events/total n	HR (95% CI)	p Value
Sleep duration at baseline, h			0.01[a]			0.07[a]
<6	24/209	0.90 (0.58–1.38)	0.62	16/209	0.71 (0.42–1.20)	0.20
6–9	191/2,152	Reference		152/2,152	Reference	
>9	19/96	2.01 (1.24–3.26)	0.005	13/96	1.71 (0.96–3.05)	0.07
Sleep duration at baseline, h						
≤9	215/2,361	Reference		168/2,361	Reference	
>9	19/96	2.04 (1.26–3.30)	0.004	13/96	1.77 (1.00–3.16)	0.05
Former sleep duration (13 years before baseline), h						
≤9	207/2,255	Reference		159/2,255	Reference	
>9	14/84	1.25 (0.72–2.16)	0.43	10/84	1.10 (0.57–2.10)	0.79
Change in sleep between former and baseline time points			0.01[a]			0.11[a]
≤9 h at former and baseline time points	191/2,180	Reference		148/2,180	Reference	
>9 h at former and baseline time points	3/16	1.34 (0.42–4.26)	0.62	2/16	1.02 (0.25–4.20)	0.98
Change from >9 to ≤9 h	11/68	1.30 (0.70–2.41)	0.41	8/68	1.17 (0.57–2.41)	0.67
Change from ≤9 to >9 h	16/75	2.43 (1.44–4.11)	0.001	11/75	2.20 (1.17–4.13)	0.01

Abbreviations: CI = confidence interval; HR = hazard ratio.
Models are adjusted for age, sex, education, *APOE* ε4 allele status, and homocysteine.
[a]p Value for overall model.

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Science News *from research organizations*

Detecting Alzheimer's disease before it's too late

Intervention long before the first signs of memory issues may be required to slow disease progression

Date: April 23, 2018

Source: Society for Neuroscience

Summary: The rate at which the protein beta-amyloid accumulates into the sticky plaques associated with Alzheimer's disease (AD) is already slowing by the time a patient would be considered to have preclinical AD, according to a longitudinal study of healthy adults.

How early can we diagnose Alzheimer disease (and is it sufficient)?

Ronald C. Petersen, PhD, MD

Neurology® 2018;91:395-402.

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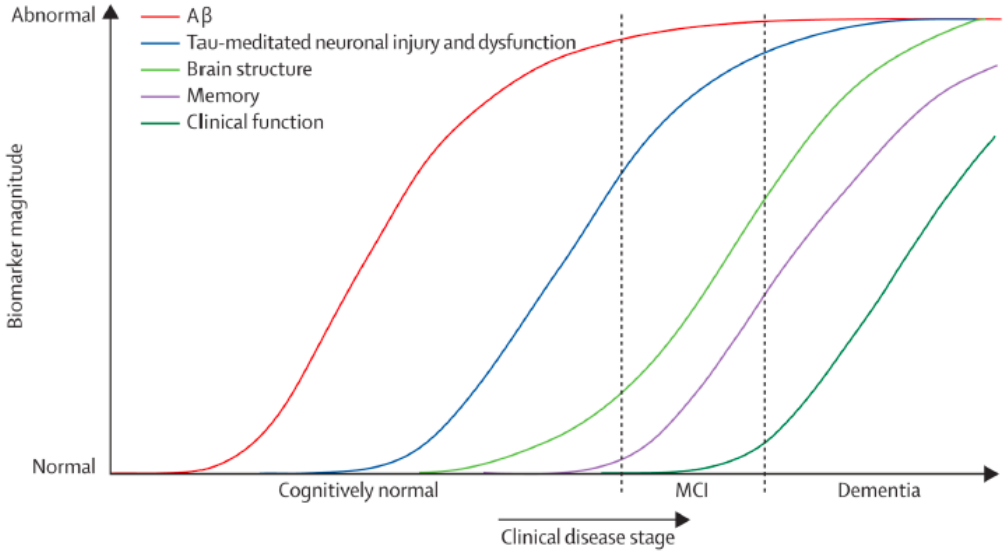
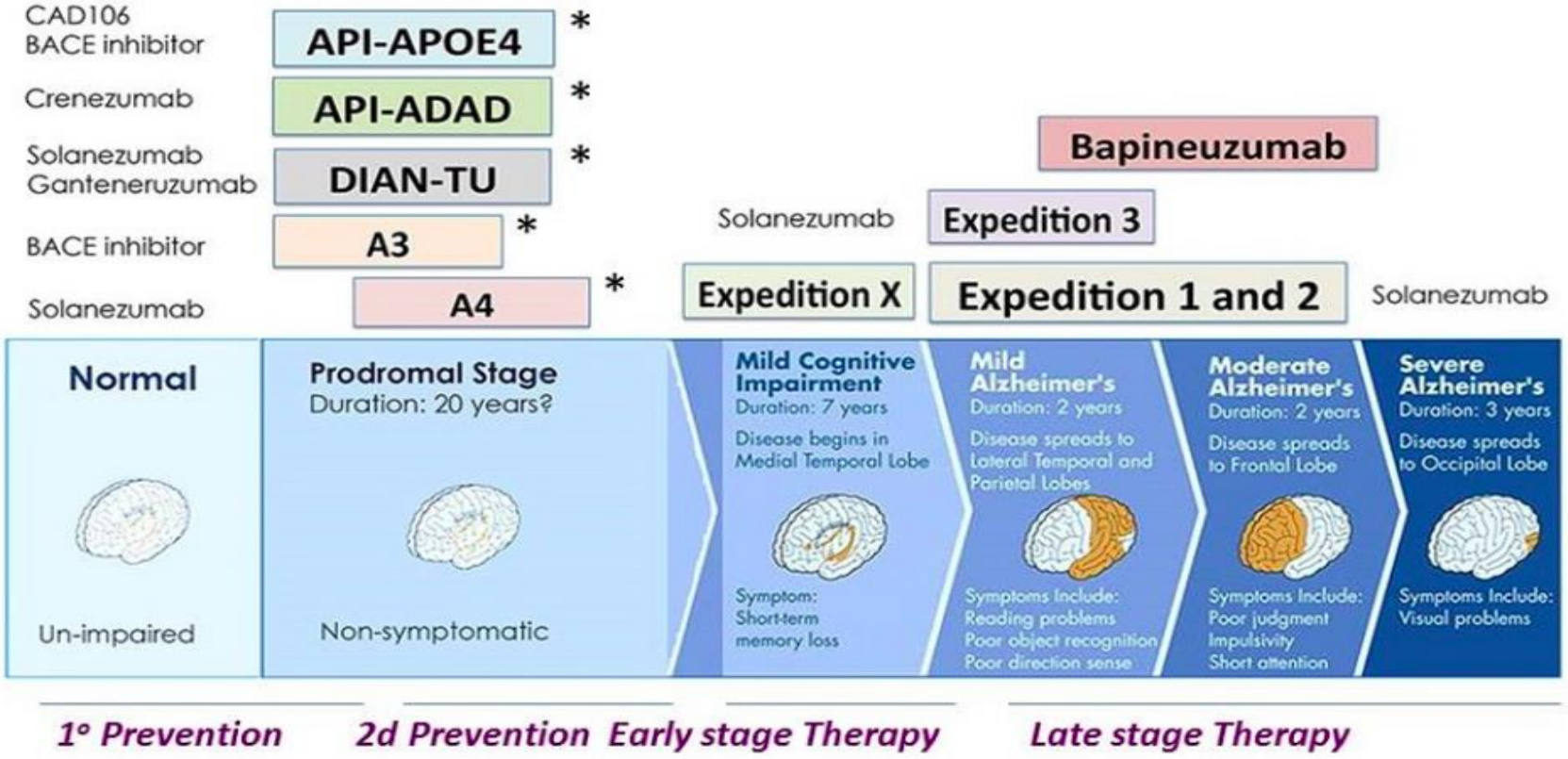
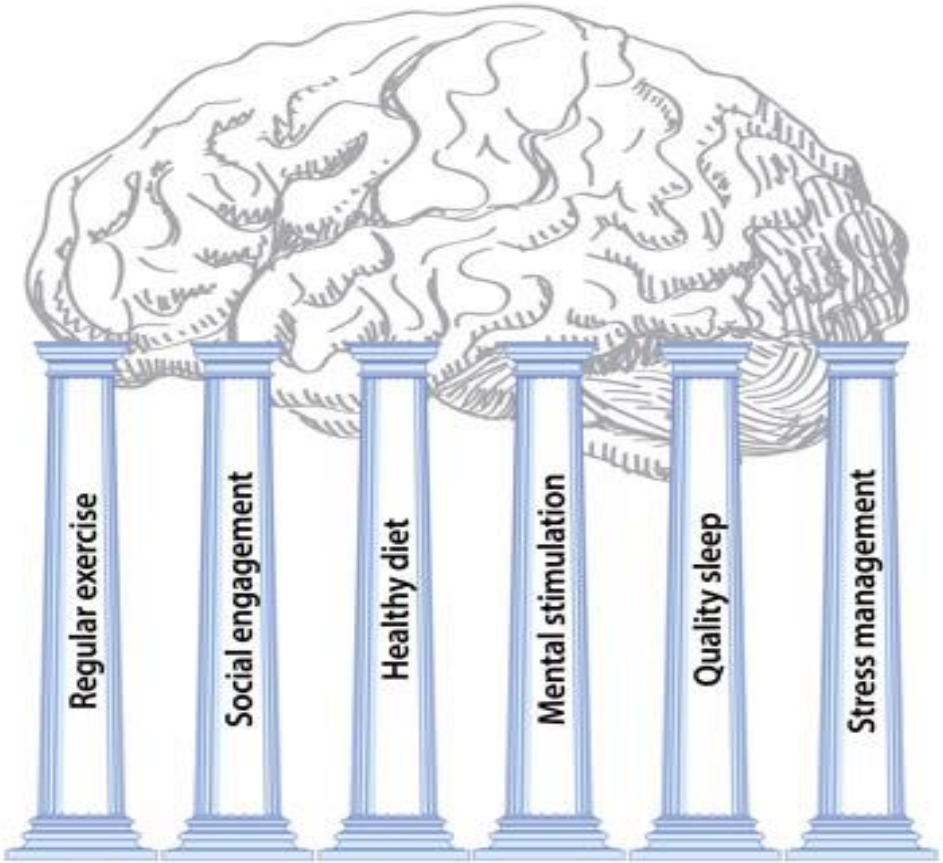


Prävention


CAD106
BACE inhibitor
API-APOE4
*
Crenezumab
API-ADAD
*
Solanezumab
Ganteneruzumab
DIAN-TU
*
BACE inhibitor
A3
*
Solanezumab
A4
*
Bapineuzumab
Solanezumab
Expedition 3
Expedition X
Expedition 1 and 2
Solanezumab
Normal
Un-impaired
Prodromal Stage
Duration: 20 years?
Non-symptomatic
Mild Cognitive Impairment
Duration: 7 years
Disease begins in Medial Temporal Lobe
Symptom: Short-term memory loss
Mild Alzheimer's
Duration: 2 years
Disease spreads to Lateral Temporal and Parietal Lobes
Symptoms Include: Reading problems Poor object recognition Poor direction sense
Moderate Alzheimer's
Duration: 2 years
Disease spreads to Frontal Lobe
Symptoms Include: Poor judgment Impulsivity Short attention
Severe Alzheimer's
Duration: 3 years
Disease spreads to Occipital Lobe
Symptoms Include: Visual problems
1° Prevention
2d Prevention
Early stage Therapy
Late stage Therapy

The 6 Pillars of Alzheimer's Prevention



Ordens klinikum Linz
Barmherzige Schwestern Elisabethinen