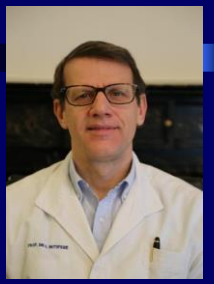
Menopause and dementia and depression

PROF. DR. H. DEPYPERE

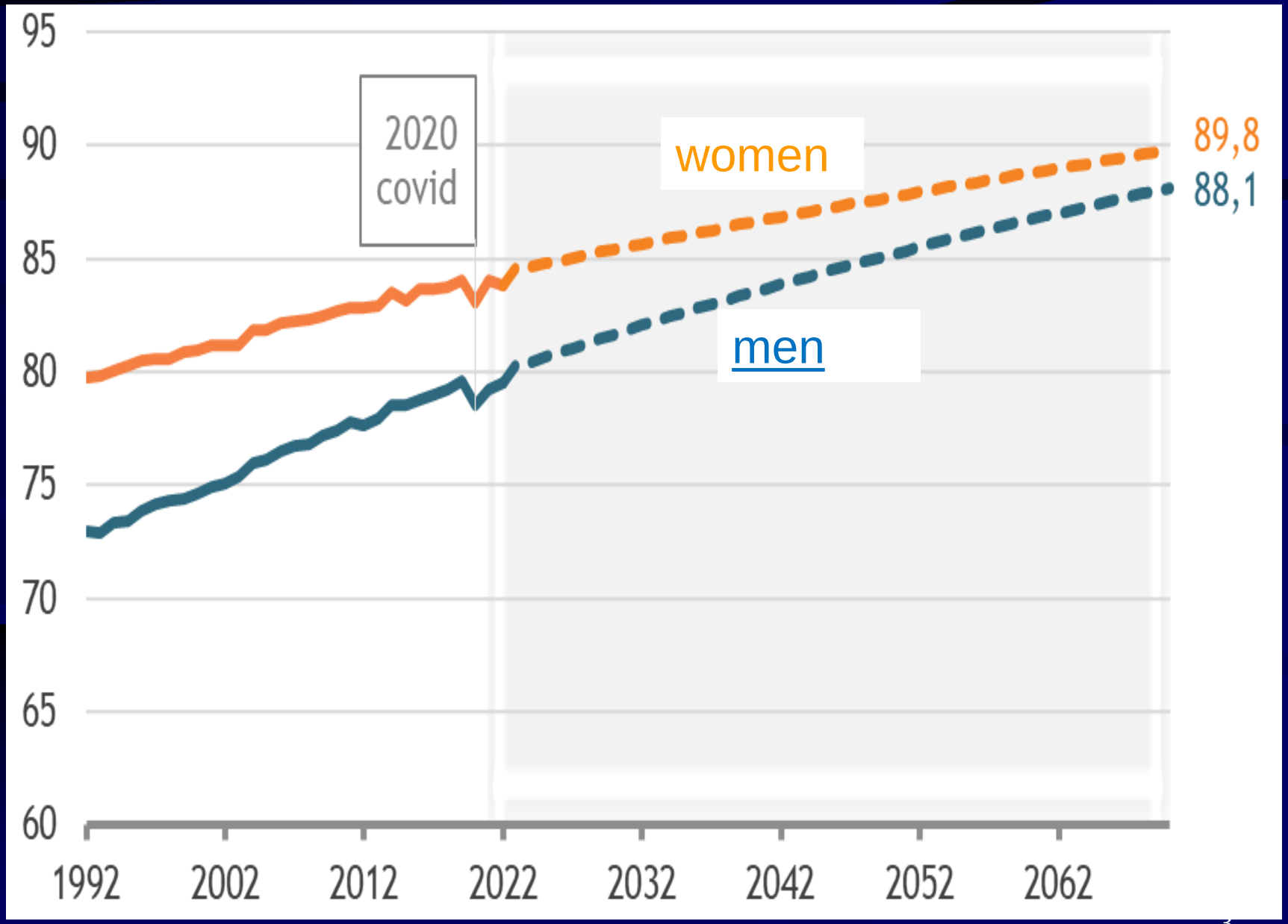


Menopauze and Breast Clinic: University Hospital, Gent, Belgium

Disclosure

Clinical Advisor to OGEDA, BAYER, GEDEON RICHTER, THERAMEX, ASTELLAS

I have no conflict of interest for this talk


95
90
85
80
75
70
65
60
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covid
women
men
89,8
88,1
1992
2002
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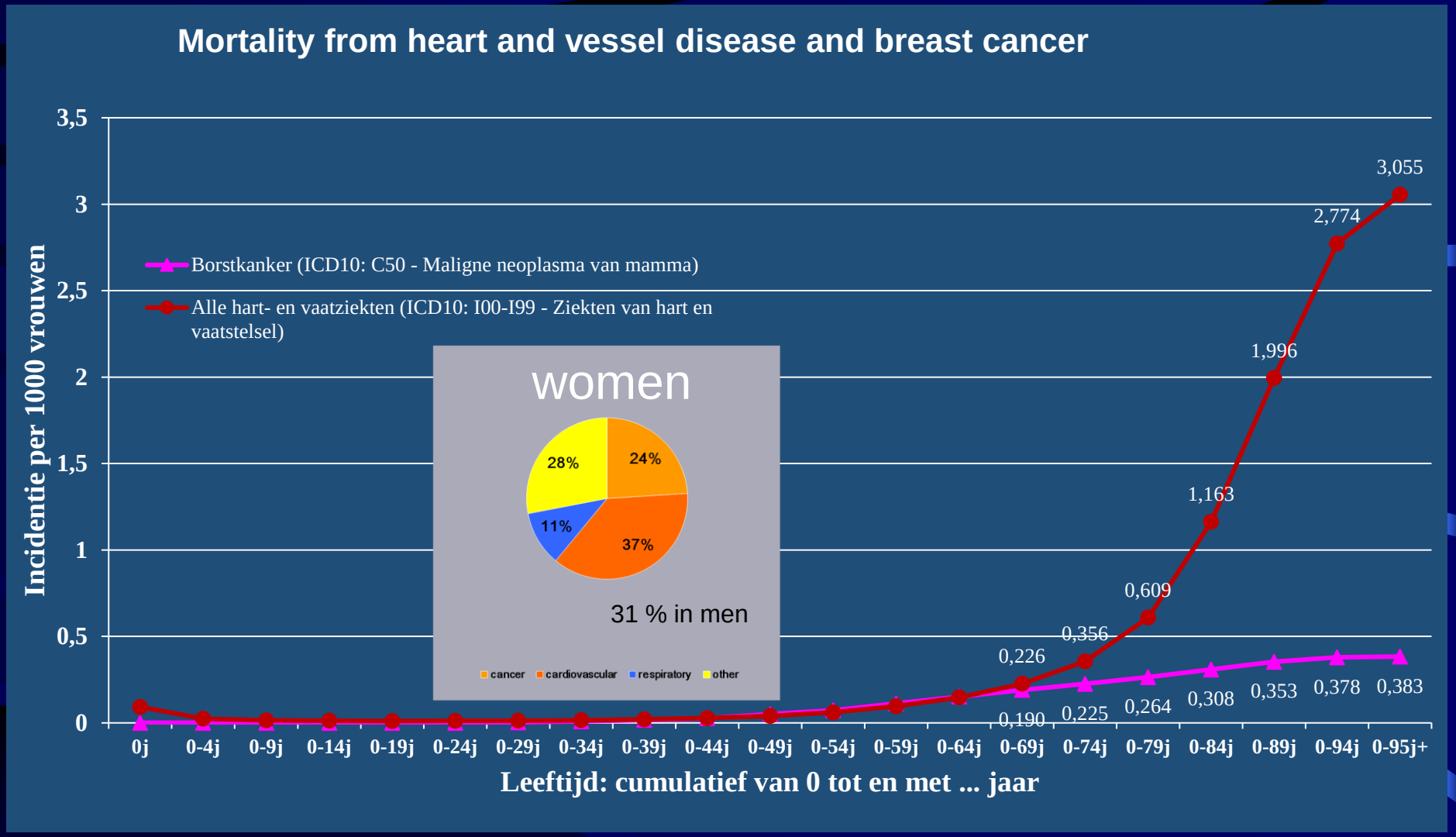


Bron: Agentschap Zorg en Gezondheid. *Cijfers over doodsoorzaken* [Online publicatie]. Brussel, [geraadpleegd op *16/01/2019*].
Beschikbaar op: *http://www.zorg-en-gezondheid.be/cijfers/*

prof Koen Vanherck
Boek Menopauze alle vragen beantwoord professor Depypere ISBN 9789089319555

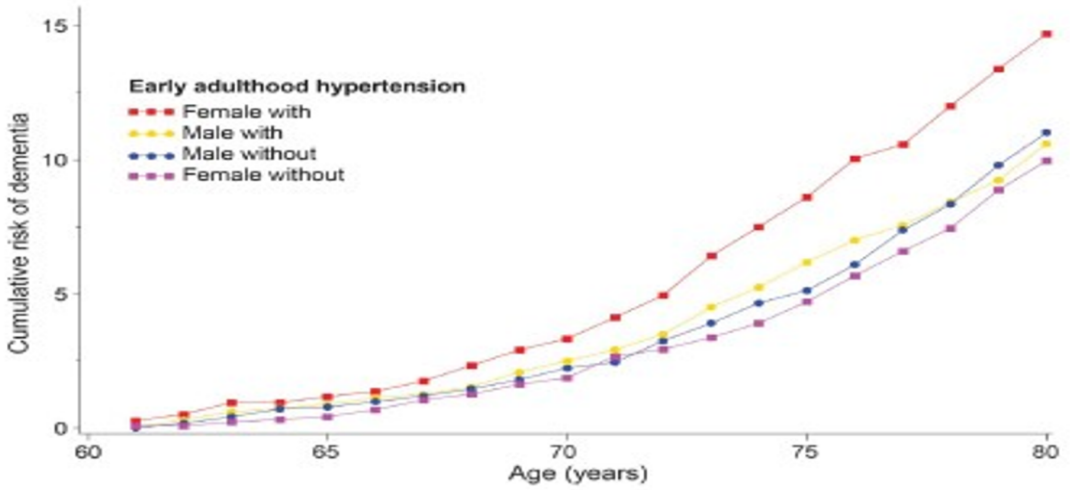
Selectie criteria

RCT cohrane review Boardman, 2015.

Women who started hormone therapy less than 10 years after the menopause had lower mortality (RR 0.70, 95% CI 0.52 to 0.95, moderate quality evidence) and coronary heart disease (composite of death from cardiovascular causes and non-fatal myocardial infarction) (RR 0.52, 95% CI 0.29 to 0.96; moderate quality evidence), though they were still at increased risk of venous thromboembolism (RR 1.74, 95% CI 1.11 to 2.73, high quality evidence) compared to placebo or no treatment.

EARLY-ADULTHOOD HYPERTENSION IS ASSOCIATED WITH 65% INCREASED DEMENTIA RISK AMONG WOMEN BUT NOT MEN

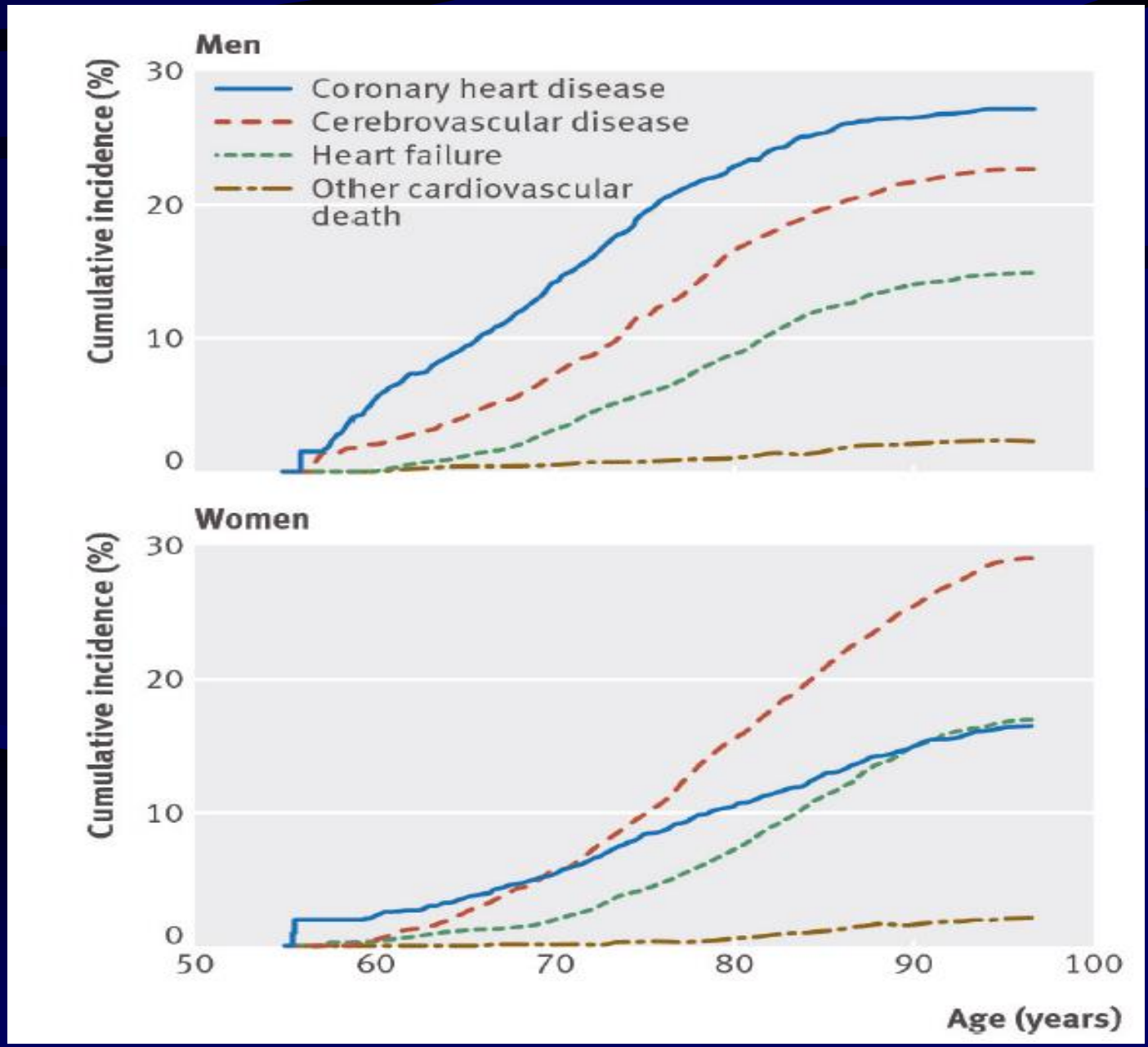
5,646 members of an integrated health care delivery system who participated in the Multiphasic Health Checkups (MHC)



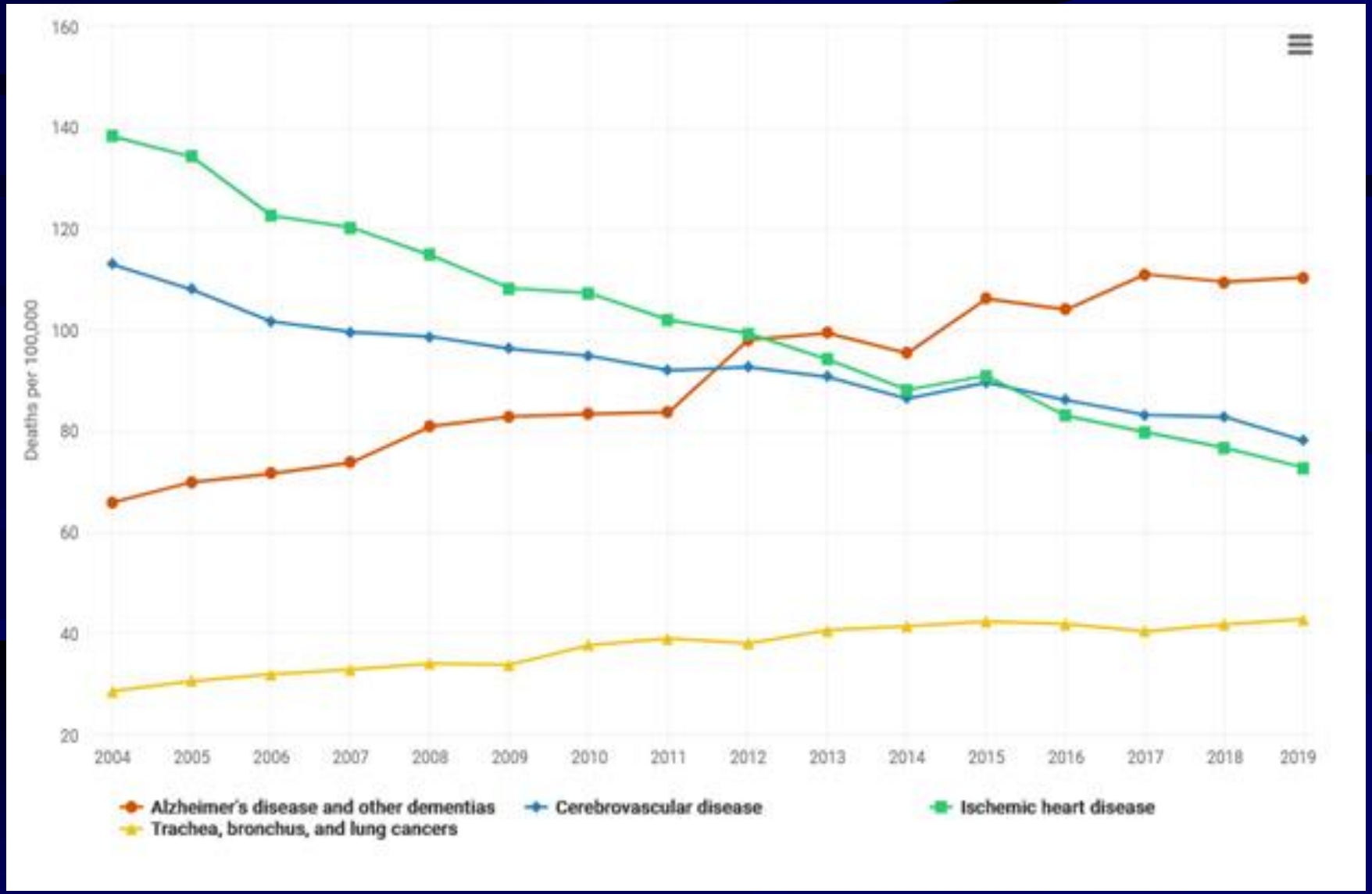
Gilsanz P. et al. (2017) Neurology

12

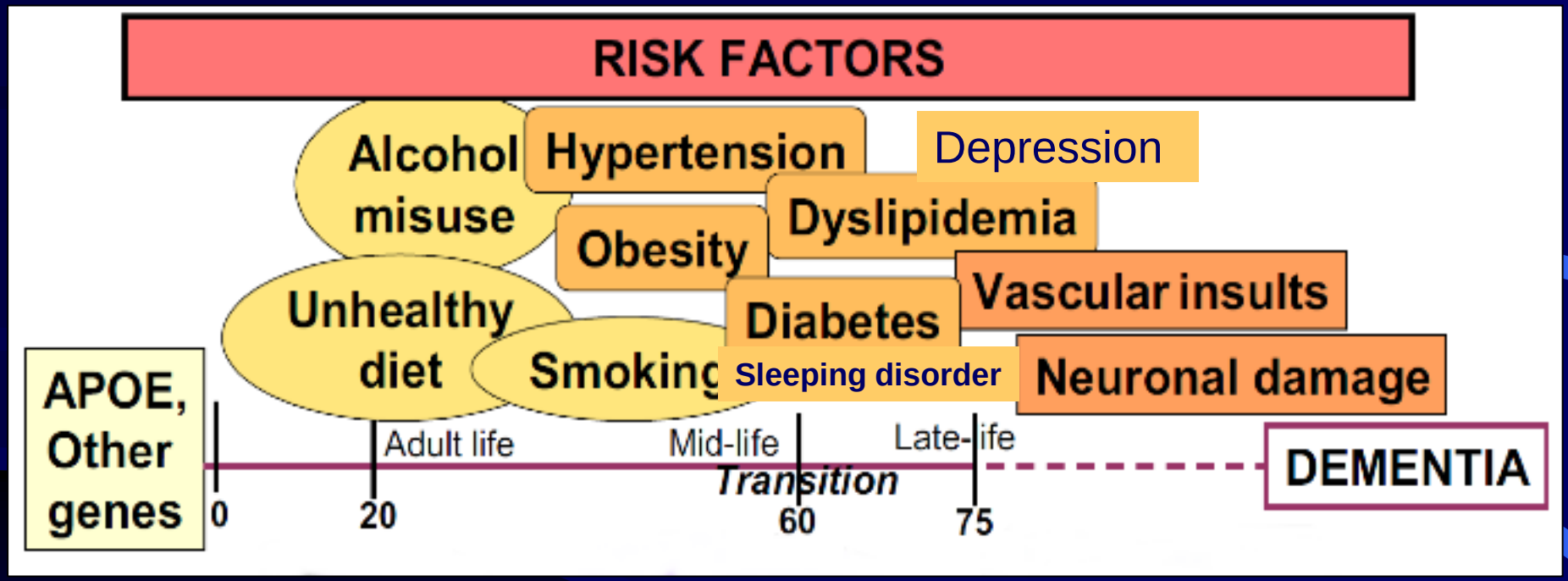
Mid-adulthood hypertension was associated with 65%(95%confidence interval [CI] 1.25–2.18) increased dementia risk among women but not men. Onset of hypertension in mid-adulthood predicted 73% higher dementia risk in women (95% CI 1.24–2.40) compared to stable normotensive. There was no evidence that hypertension or changes in hypertension increased dementia risk among men. Conclusions: Though midlife hypertension was more common in men, it was only associated with dementia risk in women. Sex differences in the timing of dementia risk factors have important implications for brain health and hypertension management.



Leening MJGL et al., (2014) BMJ


Deaths per 100,000
160
140
120
100
80
60
40
20
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Alzheimer's disease and other dementias
Cerebrovascular disease
Ischemic heart disease
Trachea, bronchus, and lung cancers

Alzheimer's dementia: risk factors



Adapted from Kivipelto et al. (2013) Alzheimer's & Dementia

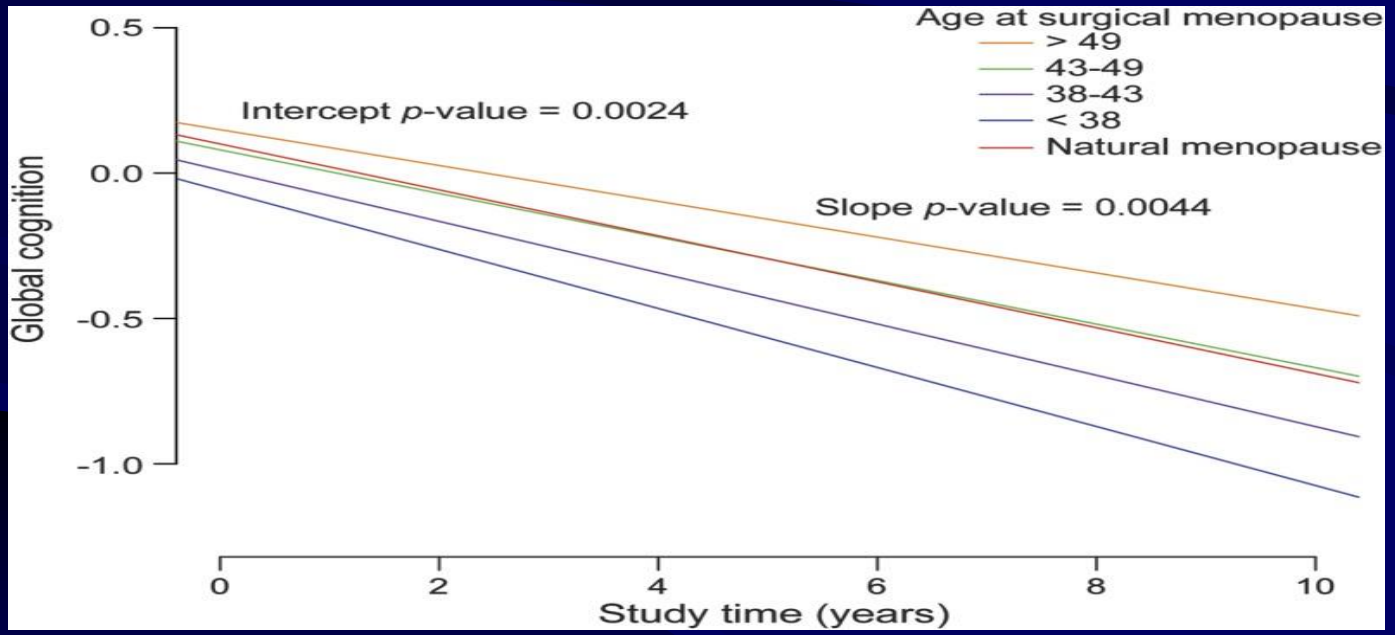
WHIMS, mean age was 68 years of age: increase of dementia. Reviewed by Prof Maki, in climacteric in 2012.

JA Manson et al. JAMA 2017, 318 (10): 927-938 - 18 years follow-up WHI			
AD or dementia mortality – 18 year follow-up			
CEE/MPA		0,93	(0,77- 1,11)
CEE alone		0,74	(0,59- 0,94)
Pooled data		0,85	(0,74- 0,98)
All cause mortality during trial (50-59 years)			
CEE/MPA		0,67	(0,43- 1,04)
CEE alone		0,71	(0,46- 1,09)
Pooled data		0,69	(0,51- 0,94)

Mayo clinic study Rocca et al. 2007

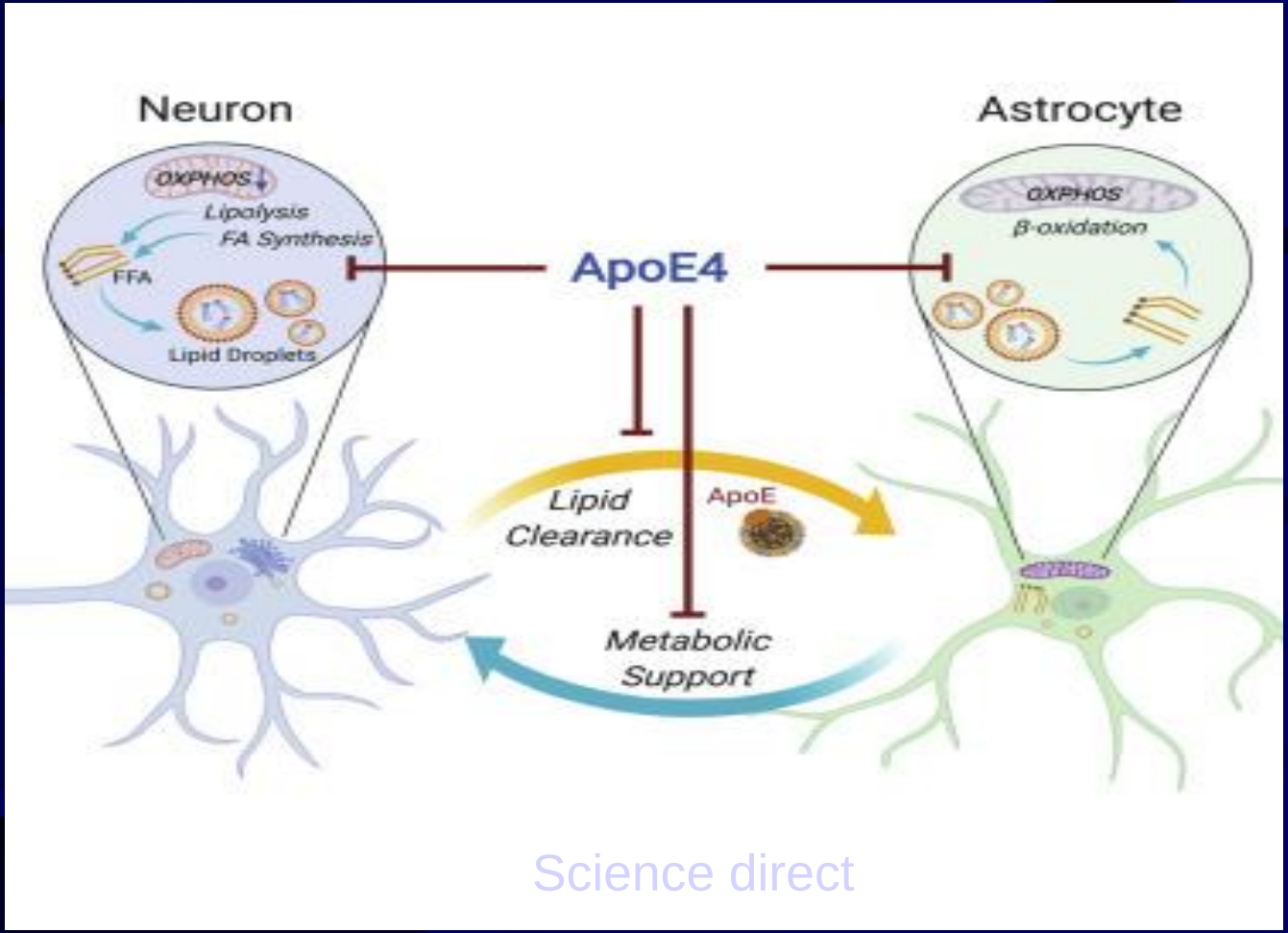
Danish cohort study. Phung et al. 2010.

Religious order and Rush memory and aging Project. Bove et al. 2014



Direct effect of estrogen		Indirect effect of estrogen
Synaptic plasticity	**Estrogen stimulates an increase of dendritic spines and synapses in hippocampal CA1 pyramidal cells**.	There is evidence that cardiovascular problems induce not only vascular dementia but also AD. Several cardiovascular risk factors are also risk factors for AD. These include arterial hypertension, elevated LDL cholesterol, low HDL cholesterol and diabetes. The pathways of this association have not yet been elucidated.
Free radicals	**Estrogen provides neuroprotection** against oxidative stress via an antioxidant effect.	
Cholinergic neurotransmitter system	**Estrogen stimulates the choline acetyltransferase, an enzyme that produces acetylcholine** (a neuro-transmitter important for memory functions and whose levels are reduced in Alzheimer's disease).	
Cellular maintenance and survival	**Estrogen enhances the survival of neurons** via modulation of the neurotrophins, which are growth factors responsible for survival and maintenance of neurons. In addition, estrogen also has anti-apoptotic effects.	
Amyloid-β protein	**Estrogen decreases the formation of amyloid- β plaques**, stimulates the degradation of amyloid-β and protects against cell death induced by amyloid-β.	
Tau protein	**Estrogen prevents hyperphosphorylation of the tau protein causing a decreased formation of neurofibrillary tangles**.	

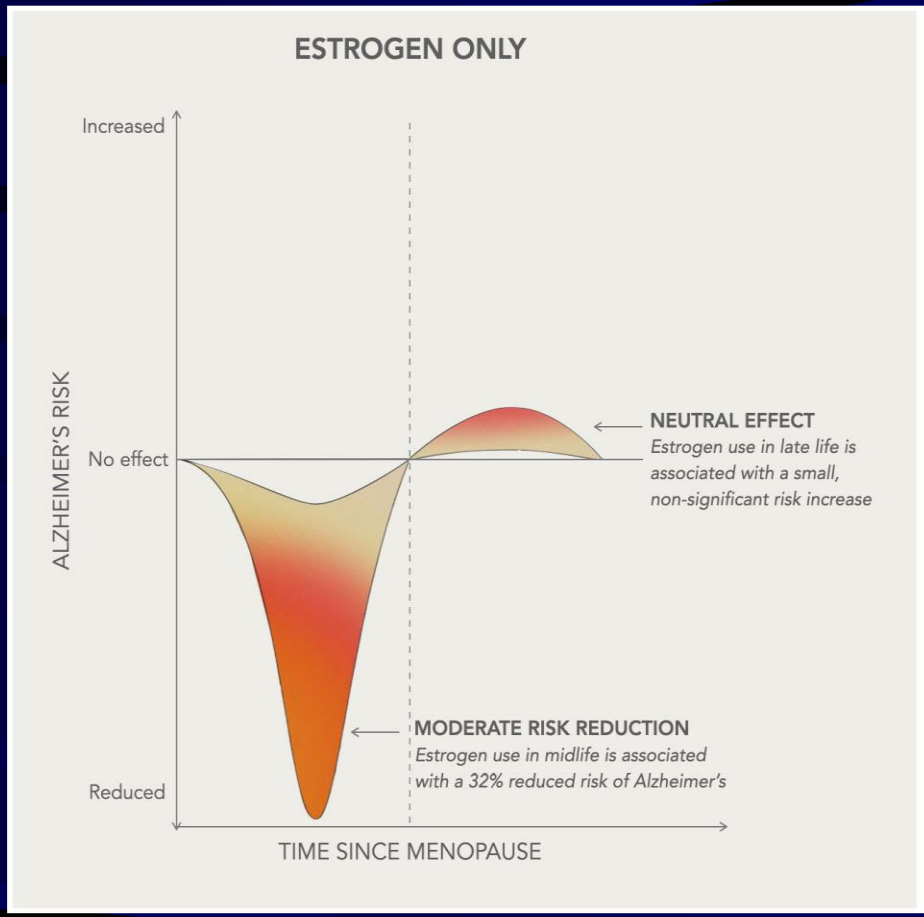
Depypere H et al, Maturitas 2016

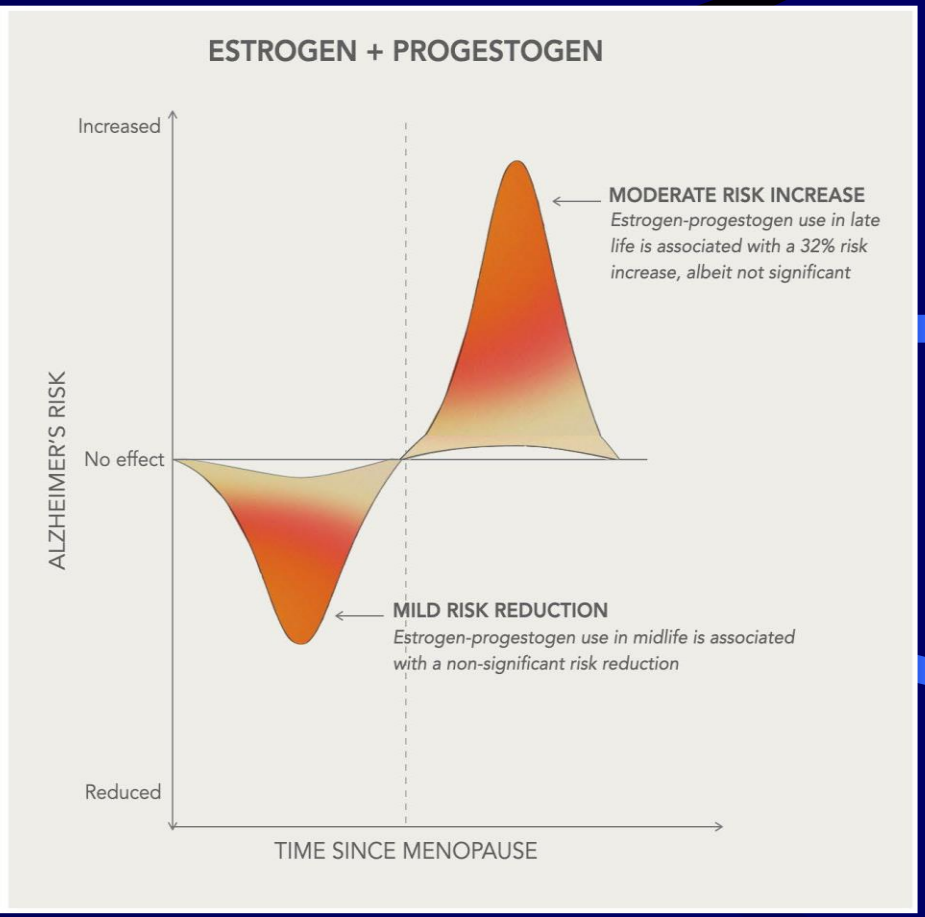


Possible isoforms of ApoE: E2E2, E2E3, E2E3, E2E4, E3E4, E4E4.

Article	Study population	Type of study	Follow-up	Outcome
Burkhardt 2004	181 postmenopausal women Mean age: - Estrogen users: 65.40 +/- 6.34 - Non-users: 67.03 +/- 6.80 ApoE4 allele present in 64 women	Observational: Cross-sectional	Single administration of the California Verbal Learning Test.	The women with the best performance were the Ɛ4- women on ERT. The Ɛ4+ women had no positive effect of ERT. They had no better results than Ɛ4- women without ERT.
Yaffe 2000	2716 postmenopausal women ≥65 years ApoE4 allele present in 677 women	Observational: Prospective cohort	The MMSE was administered annually for 6 years.	Estrogen use was associated with less cognitive decline among Ɛ4- women but not among Ɛ4+ women.
Rippon 2006	1498 postmenopausal women mean age: - Dementia present: 73.3 years - Dementia absent: 62.4 years ApoE4 allele present in 736 women	Observational: Cross-sectional	Single administration of neuropsychological tests.	Compared with Ɛ4- women who had no history of ERT, Ɛ4- women who took ERT had an 80% reduction in AD risk. Ɛ4+ women without a history of ERT had a two-fold increased risk of AD, while Ɛ4+ women with a history of ERT had no increased risk.
Ryan 2009 **(the 3C city study)**	3130 postmenopausal women ≥65 years ApoE4 allele present in 597 women	Observational: Prospective cohort	Testing of general cognition, verbal fluency, verbal and visual memory, psychomotor speed and executive functions was done 3 times in 6 years	Current use of ERT was associated with better performance in certain cognitive domains, and this association was stronger the longer the duration of ERT. Current use of ERT may decrease AD risk associated with the presence of ApoE4+.
Zandi 2002 **(the cache county study)**	1889 women Mean age: - Estrogen users: 76.2 +/- 7.0 - Non-users: 73.1 +/- 5,8 ApoE4 allele present in 569 women	Observational: Prospective cohort	Screening at the beginning of the study and after 3 years with the modified MMSE. A clinical assessment was done in case of a positive screening.	ERT users had a reduced risk of AD compared with non-users. This effect appeared to be stronger for Ɛ4+ women, but this hypothesis did not reached statistical significance because of the small numbers available.
Tang 1996	1124 non-demented women Mean age: 74,2 years 156 estrogen users APOE genotypes were available for 53·7% of the women	Observational: Prospective cohort	Standard annual clinical assessments and criterion-based diagnoses were used in follow-up (range 1–5 years)	The age at onset of Alzheimer's disease was significantly later and the relative risk of AD was significantly reduced in ERT users in comparison with the non-users. ERT use was associated with a reduction in the risk of AD for the heterozygote Ɛ4+ women. An evaluation for the homozygote Ɛ4+ women was not possible.
Yue 2007	182 postmenopausal women Mean age - Estrogen users: 66,3 +/- 8,3 - Non-users: 67,1 +/- 7,6 ApoE4 allele present in 32 women	Observational: Cross-sectional	Measuring of the volume of the brain hippocampus with MRI. Single administration of 6 cognitive tests.	The volume of the hippocampus of the Ɛ4+ women was significantly larger in the HRT group in comparison with the control group. The cognitive tests showed no significant improvement of cognitive function in ERT users when compared to non-users.
Sundermann 2008	51 postmenopausal women age Ɛ4- women (n=32) - estrogen users: 73.18 ± 4.22 - non-users: 73.77 ± 2.43 Ɛ4+ women (n=19) - estrogen users: 70.41 ± 4.22 - non-users: 69.70 ± 3.60	Observational: Cross-sectional	Single testing of the odour threshold	ERT use may offer protection against loss of olfactory function in Ɛ4+ women who may be in the early stages of AD. The ERT users who are Ɛ4+ had a significantly higher odour threshold sensitivity in comparison with the non-users. No significant differences were seen between the ERT users and non-users of the Ɛ4- women.
Kang and grodstein (2012)	3697 postmenopausal women Mean age 72 years ApoE4 allele present in 948 women	Observational: Prospective cohort	Telephonic testing of cognitive functions was done 3 times in 6 years	Compared with 'never users', past or current ERT users showed modest but statistically significant worse rates of decline in the cognitive function. A suggestive interaction with Ɛ4 status was found: for Ɛ4- there was no difference in decline between women using ERT and those not using it; for Ɛ4+, women using ERT experienced a decline in cognitive function.
Gleason 2015 Keeps	693 young healthy menopausal women - 220 allocated to o-CEE low dose + m-P - 211 allocated to t-E2 + m-P - 262 allocated to placeboApoE4 present 25.9 %//Duration : 4 years	Randomized, double-blinded, placebo-controlled clinical trial	Different cognition and mood tests	No influence on cognition was seen.

Depypere H et al, Maturitas 2016





A systematic of 6 RCT reports (21,065 treated and 20,997 placebo participants) and 45 observational reports (768,866 patient cases and 5.5 million controls). We used fixed and random effect meta-analysis to derive pooled relative risk (RR) and 95% confidence intervals (C.I.) from these studies.

Nerrattini M. Frontiers in neuroscience, 2023

nature REVIEWS NEUROLOGY

Review Article | Published: 09 July 2018

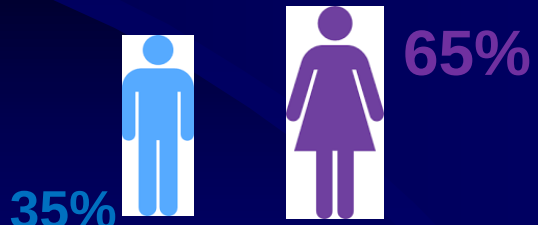
Sex differences in Alzheimer disease — the gateway to precision medicine

Maria Teresa Ferretti ✉, Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Misoch, Ezio Giacobini, Herman Depypere, Harald Hampel & for the Women's Brain Project and the Alzheimer Precision Medicine Initiative

Nature Reviews Neurology **14**, 457–469 (2018) | Download Citation ⬇

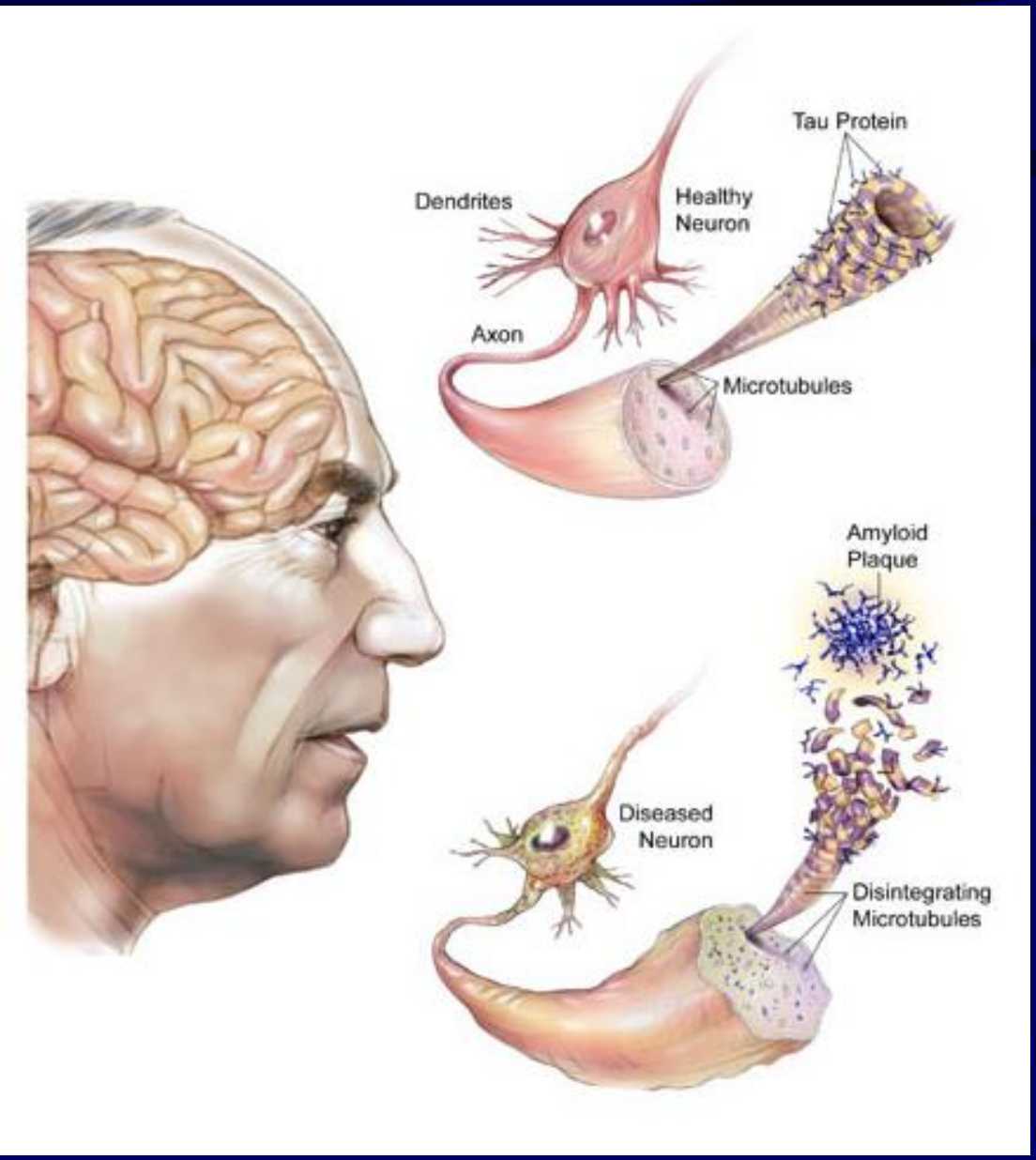
Alzheimer's disease is the most important cause of dementia in women, responsable for 60 to 80 % of dementia in women..

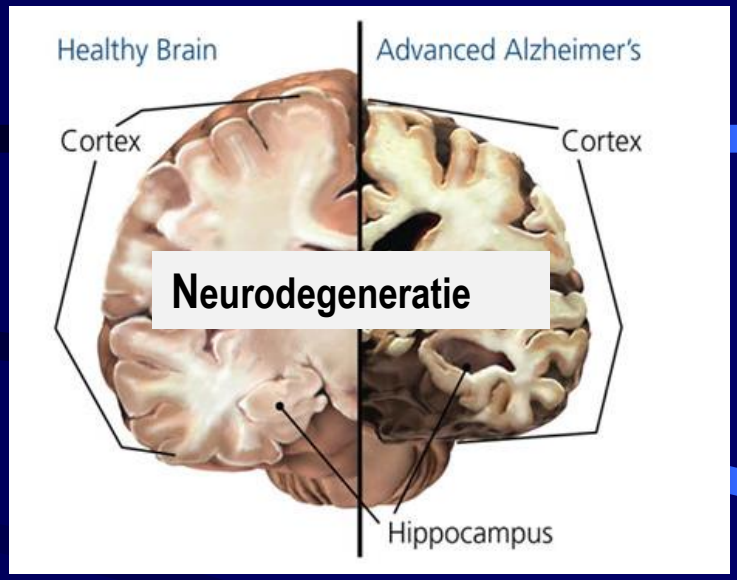
AD patients worldwide

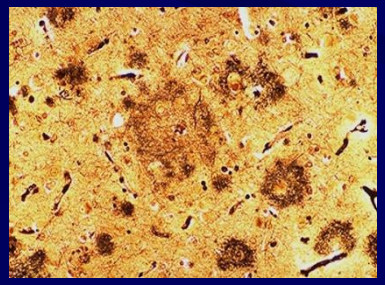


Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia 2018

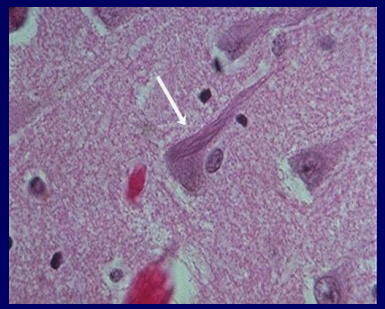
KENMERKEN VAN DE ZIEKTE VAN ALZHEIMER







Amyloid Plaques



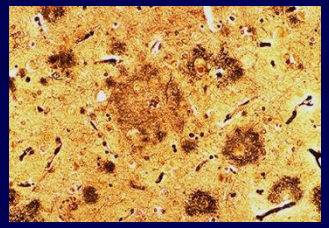
Neurofibrillar tangles

Ziekte van Alzheimer

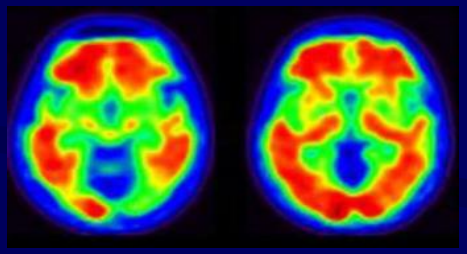
In vivo Detectie

SURROGATE MARKERS

Amyloid Plaques



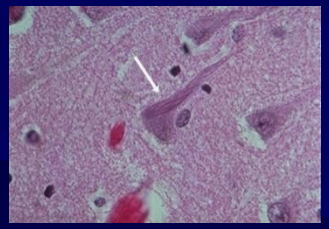
Amyloid PET



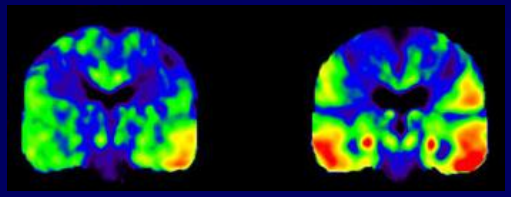
of

CSF/Plasma Aβ1-42

Neurofibrillar Tangles



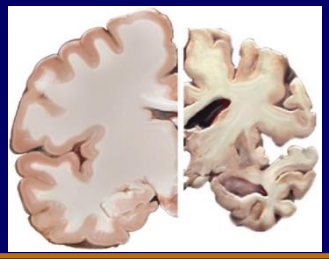
Tau PET



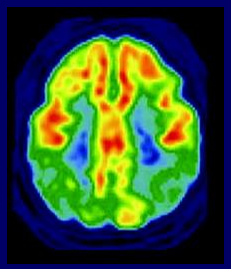
of

CSF/Plasma T-tau P-tau

Neurodegeneration

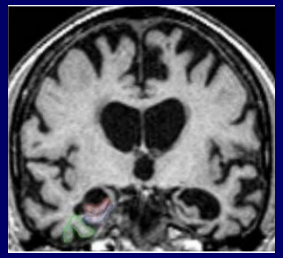


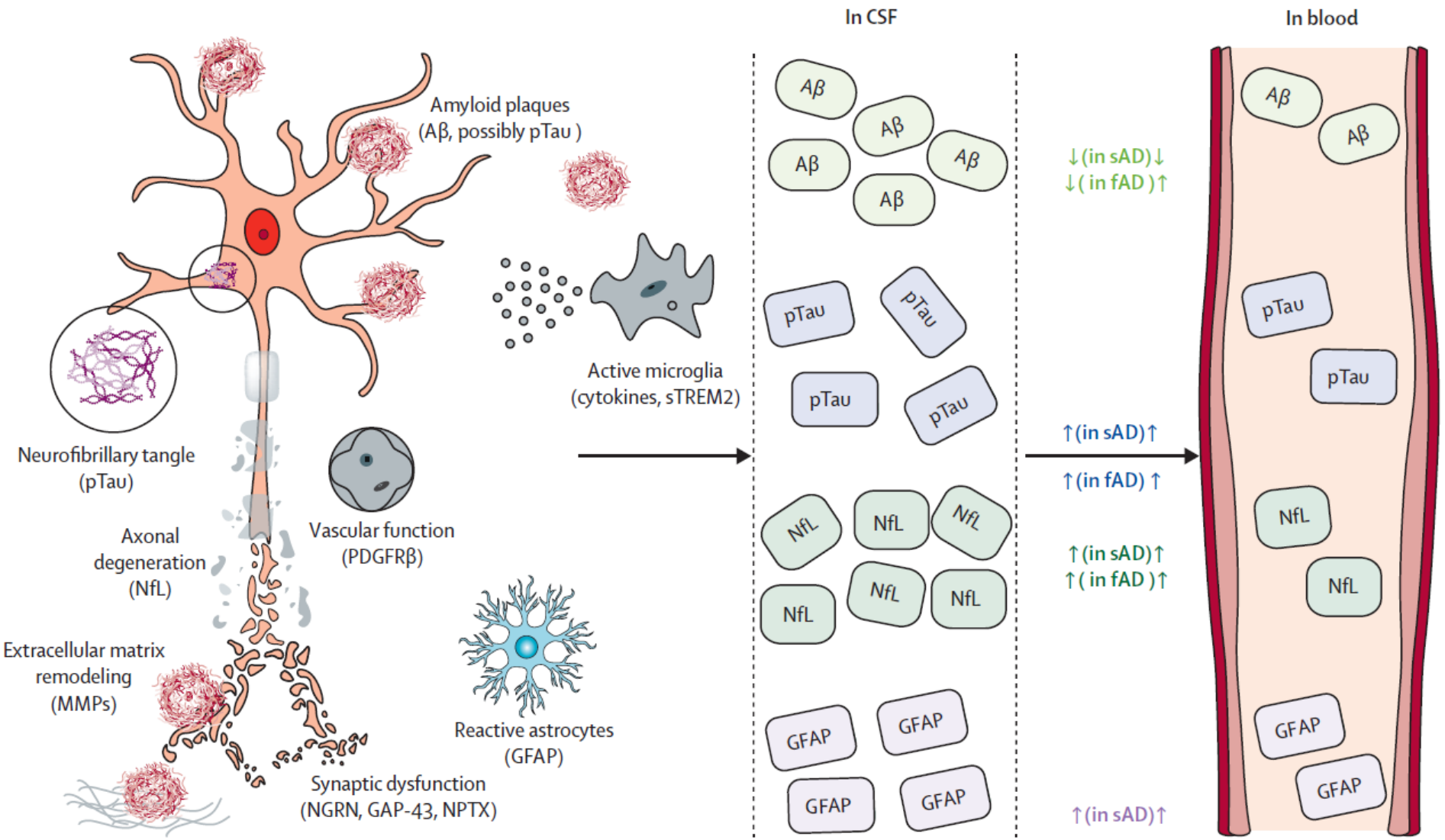
18-FDG PET



or

Brain Atrophy (MRI)




In CSF
In blood
Amyloid plaques
(Aβ, possibly pTau)
Active microglia
(cytokines, sTREM2)
Neurofibrillary tangle
(pTau)
Vascular function
(PDGFRβ)
Axonal
degeneration
(NfL)
Extracellular matrix
remodeling
(MMPs)
Reactive astrocytes
(GFAP)
Synaptic dysfunction
(NGRN, GAP-43, NPTX)
Aβ
pTau
NfL
GFAP
↓(in sAD)↓
↓(in fAD)↑
↑(in sAD)↑
↑(in fAD) ↑
↑(in sAD)↑
↑(in fAD)↑
↑(in sAD)↑

Depypere H[1], Vergallo A[2*], Lemercier P[2*], Lista S[2], Benedet AL[3] Ashton NJ[3,4,5,6], Cavedo E, Zetterberg H[3, 7, 8, 9, 10], Blennow K[3,7], Vanmechelen E[11], Hampel H[2]; the Neurodegeneration Precision Medicine Initiative (NPMI).

Menopause Hormone Therapy significantly alters Pathophysiological Biomarkers of Alzheimer's Disease

Alzheimer's and dementia: 2022 sept

alzheimer's association® | Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

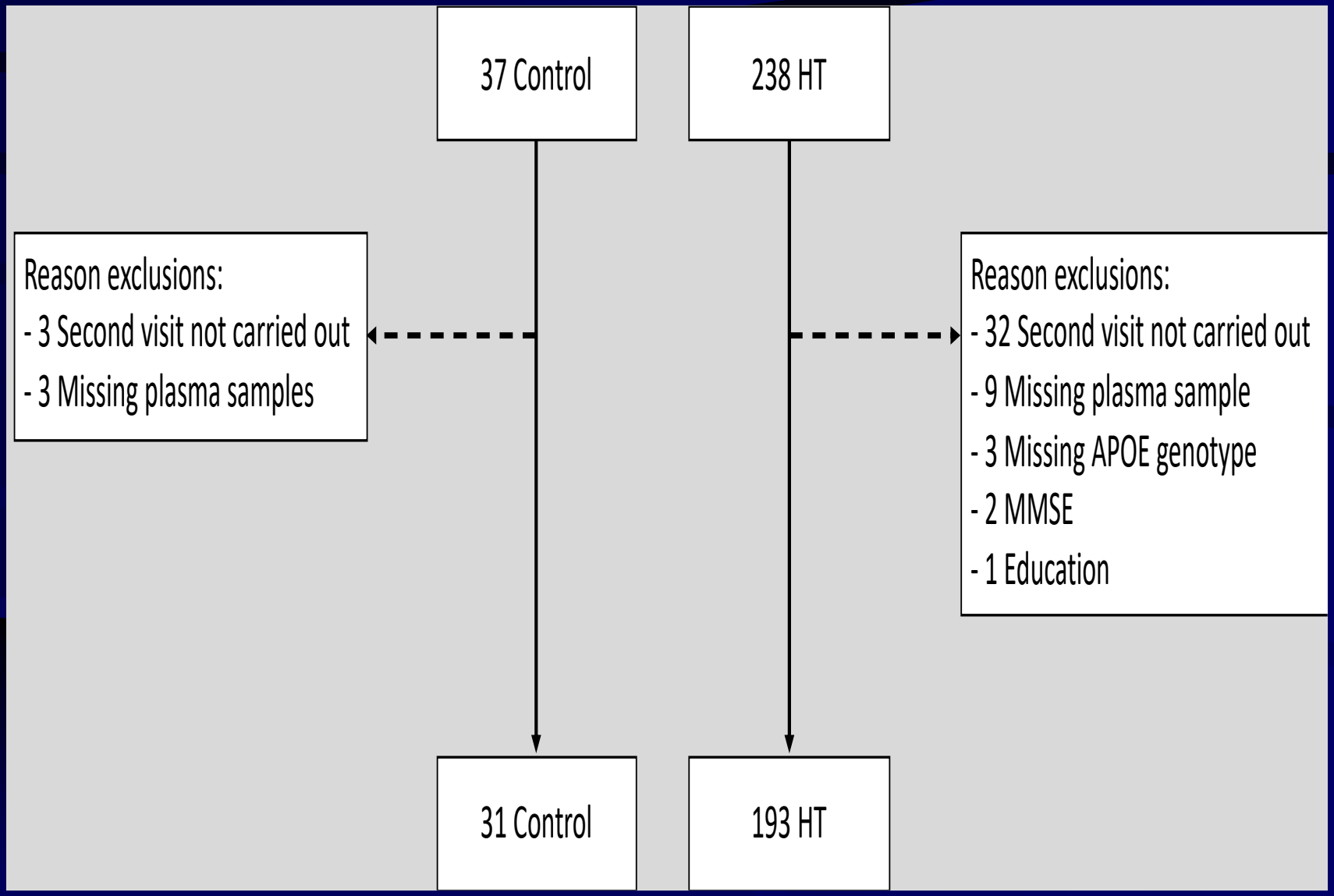
Pilot study including only ‘healthy’ recently menopausal women, with normal tension, normal cholesterol serum levels, no thyroid disfunction,… without any medication.

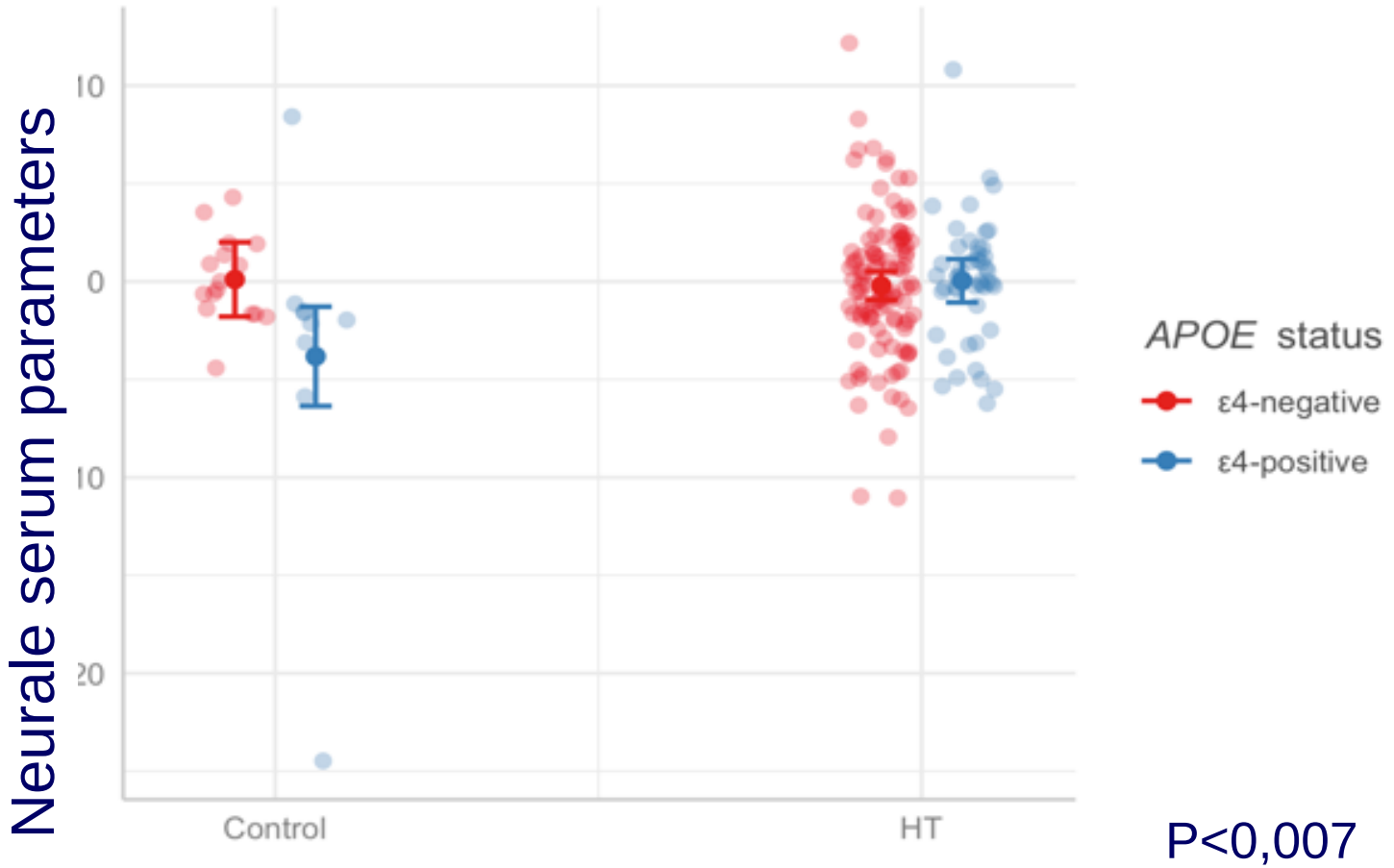
After extensive counselling and deciding to take or not to take hormones women were asked to participate in this prospective trial.

Groups comprised: no hormone intake, oral or transdermal hormone intake (with of without natural progesterone/LNG IUS).

All women had blood drawn, with immediate centrifugation and storage in special aliquots at -80°C, at the beginning and after six months of the study.

Genotesting for ApoE was done at the beginning.

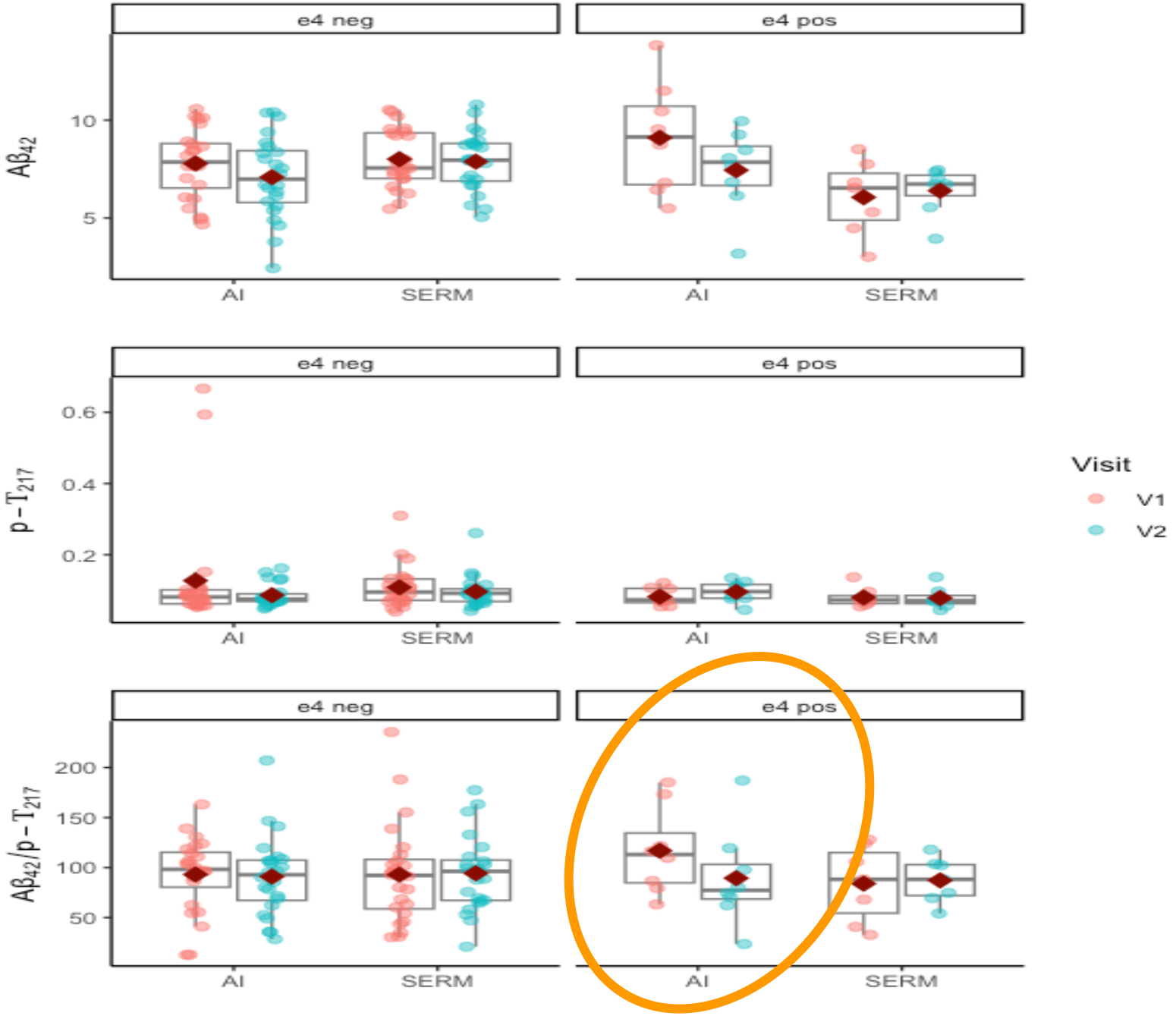

37 Control
238 HT
Reason exclusions:
- 3 Second visit not carried out
- 3 Missing plasma samples
Reason exclusions:
- 32 Second visit not carried out
- 9 Missing plasma sample
- 3 Missing APOE genotype
- 2 MMSE
- 1 Education
31 Control
193 HT


Neurale serum parameters
10
0
10
20
Control
HT
APOE status
ε4-negative
ε4-positive

P<0,007

If hormones are protective, what about serms, TSEC, aromatase inhibitors

Duavive® (35 women)
Tamoxifen (31 women)
Aromatase inhibitors (33 women)


e4 neg
e4 pos
Aβ42
10
5
AI
SERM
p-T217
0.6
0.4
0.2
Aβ42/p-T217
200
150
100
50
Visit
V1
V2

Position paper of the North American Menopause Society.

Women appear to be particularly vulnerable to depression during perimenopause years and the years immediately after menopause.

Women have a double rate of depression during that period.

Women at greatest risk are those with a history of depressed mood earlier in life.

Feeling stressed or blue or clinically depressed.

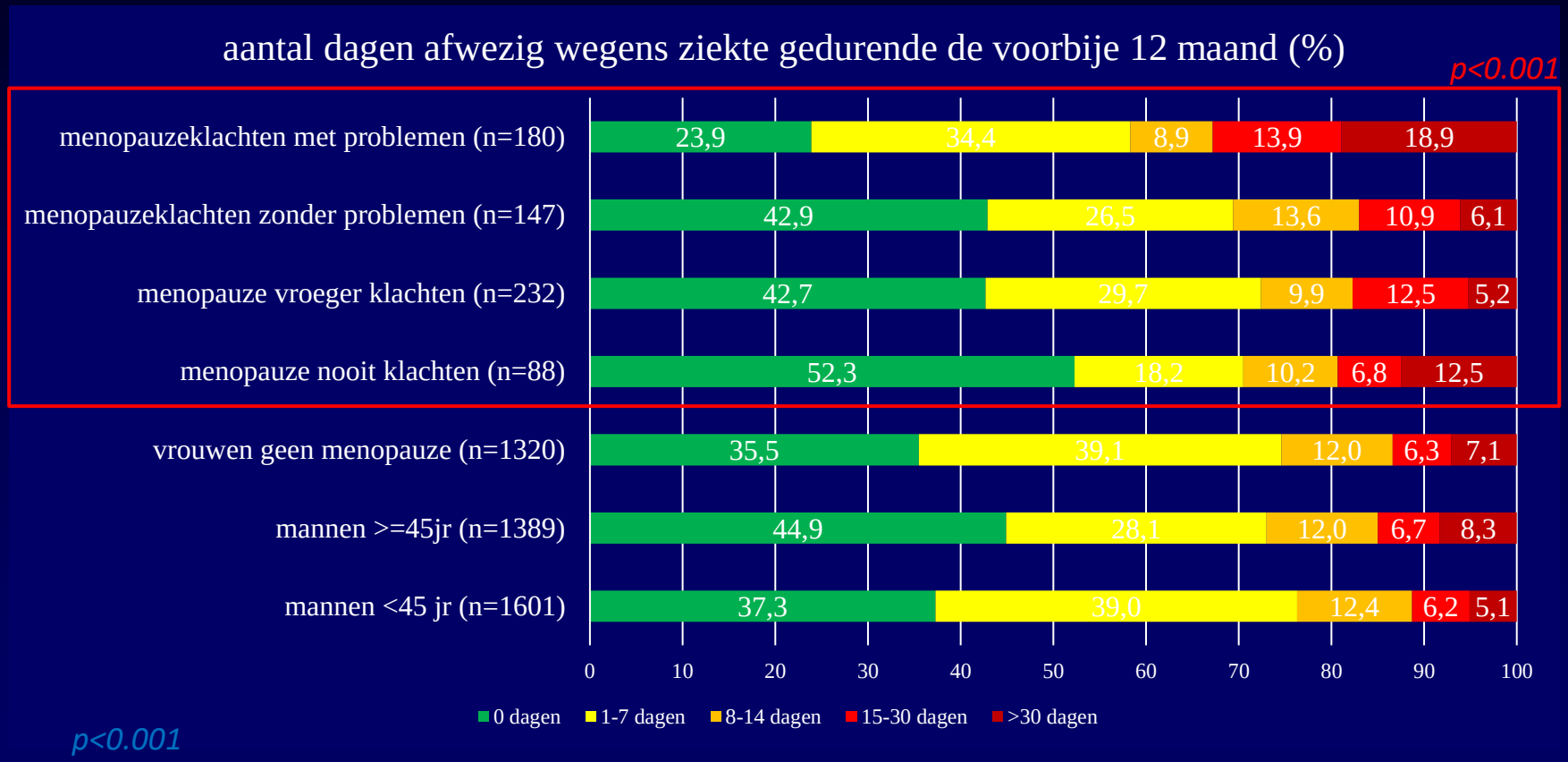
Major depression is a condition associated with a chemical imbalance in the brain and changing hormones during perimenopause may be associated with that imbalance.

Symptoms are prolonged tiredness, low energy, loss of interest in normal activities, sadness, irritability, sleep disturbances , weight changes, agitation, decreased sex drive and this during more than 2 weeks.

Treatment: antidepressants and/or cognitive behavior psychotherapy.

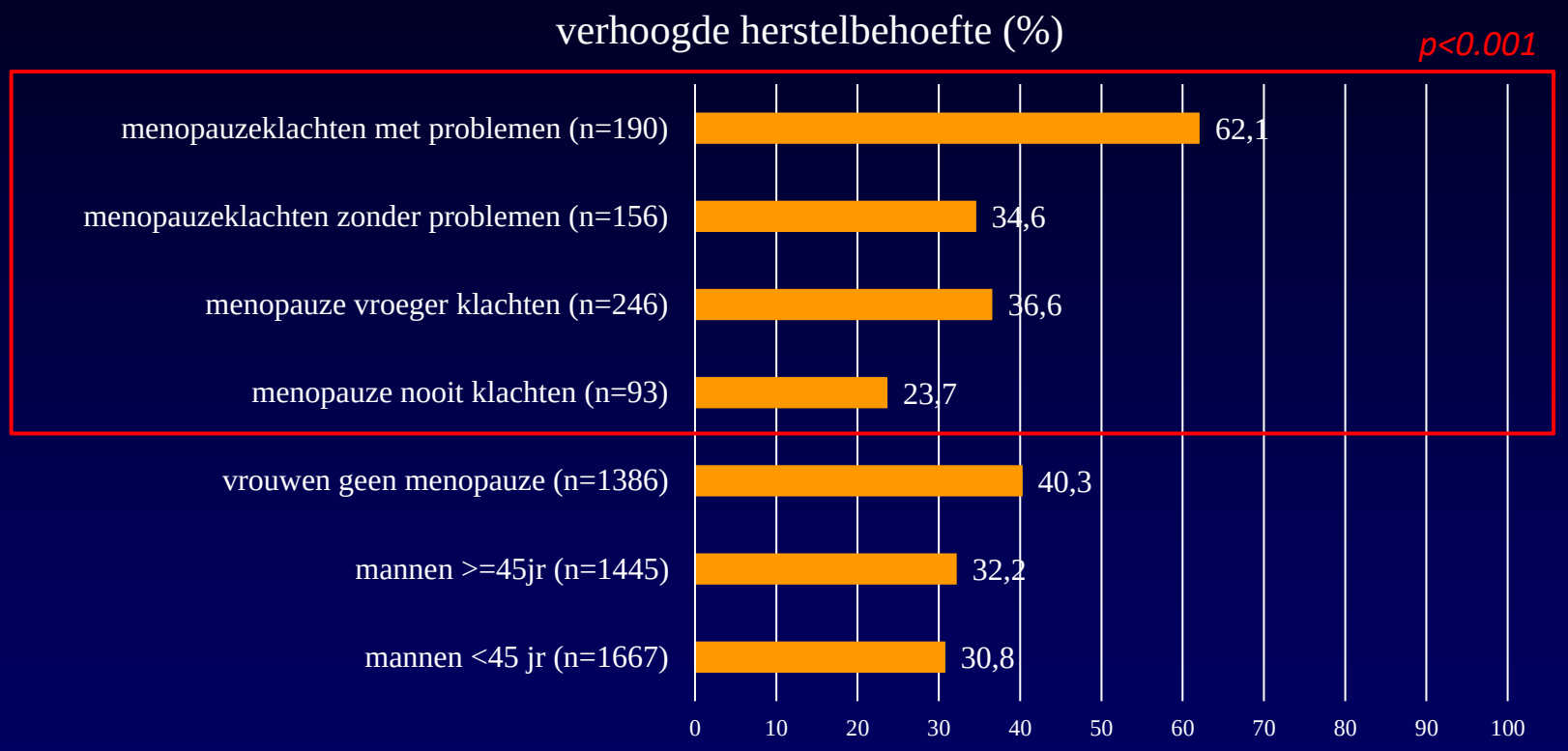
Estrogen also has been shown to significantly improve mood. A healthcare provider may recommend a trial of systemic estrogen therapy for women with symptoms of depression.

Menopause complaints and number days absence at work



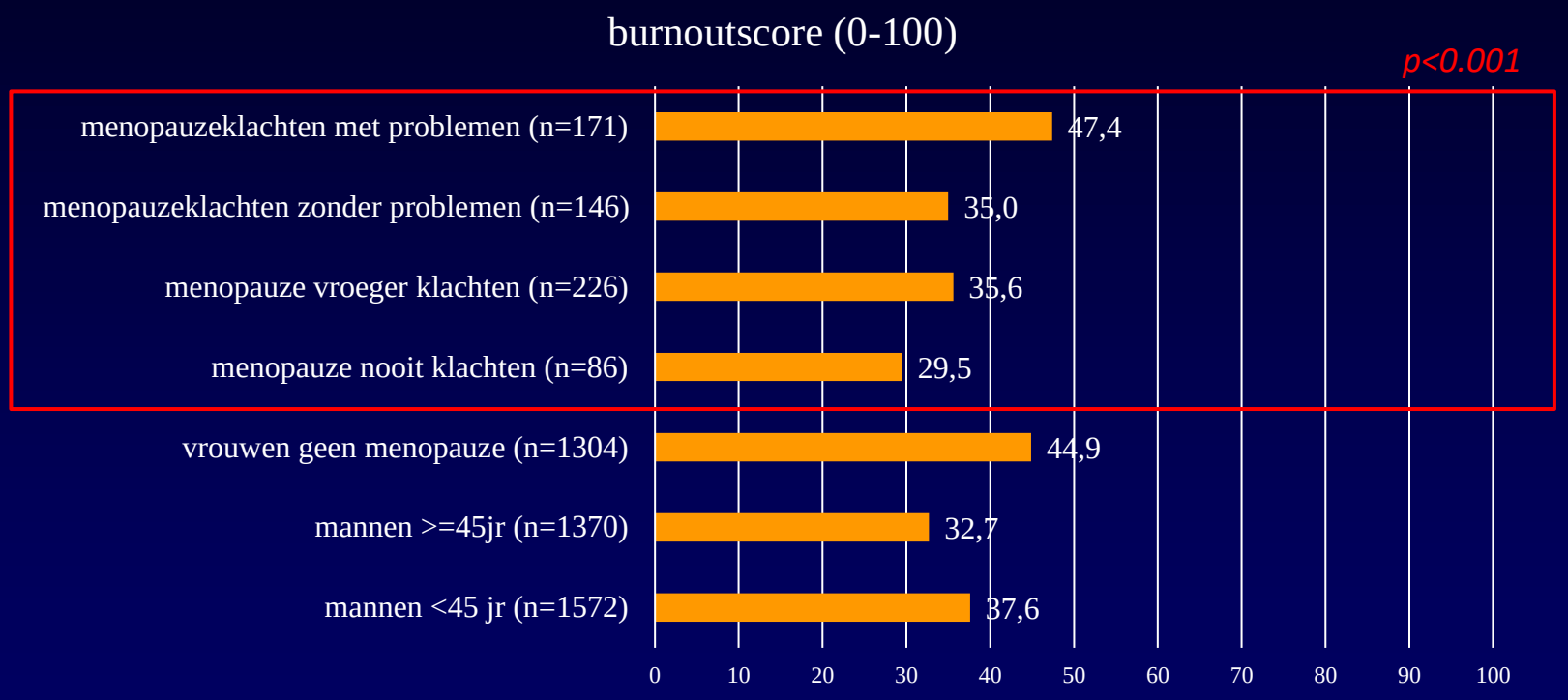
Kiss P, Depypere H, Demeester M, Maturitas, accepted for publication

Menopause complaints and increased time to recover



p<0.001

Menopausecomplaints and burnout



p<0.05

*JoAnn Pinkerton (executive director of the North American Menopause Society): ‘*An entire generation of women has not received effective (hormonal) treatment for menopausal complaints due to poor or incorrect communication about hormone use’.

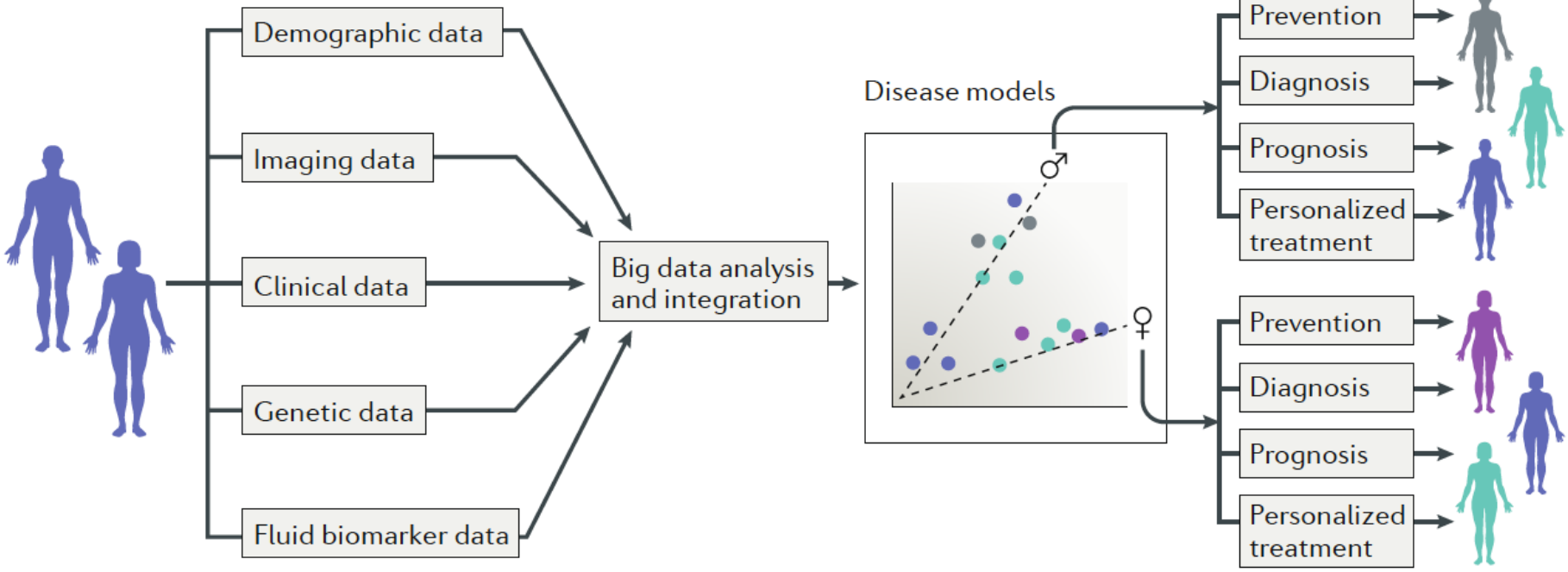
Cynthia Stuenkel (University of California): 'Many young doctors stopped training about hormone use during menopause after the publication of the WHI study in 2002.'

*JoAnn Manson (professor Harvard University, US): ‘*More than 50 million American women will be older than 51 by 2020.” Nevertheless, it is difficult for many women today to find a doctor with sufficient experience to prescribe hormones, let alone adequately treat menopausal symptoms’.

It is time to reactivate our interest of hormone therapy for the prevention of heart and vessel disease, osteoporosis*, dementia, breast cancer,…

***The Women's Health Initiative Randomized Trials and Clinical Practice**A Review JoAnn E. Manson, et al online May 1, 2024. doi:10.1001/jama.2024.6542

Meer gepersonaliseerde precisie geneeskunde



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Sex differences in Alzheimer disease — the gateway to precision medicine

Maria Teresa Ferretti ✉, Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Misoch, Ezio Giacobini, Herman Depypere, Harald Hampel & for the Women's Brain Project and the Alzheimer Precision Medicine Initiative

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