Mood changes, depression and memory concerns

PROF. DR. H. DEPYPERE

Menopauze and Breast Clinic: University Hospital, Gent, Belgium









Review Article | Published: 09 July 2018

Sex differences in Alzheimer disease — the gateway to precision medicine

Maria Teresa Ferretti A, 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 🚽



DEMENTIA: RISK FACTORS



CMC

UZ 🟛 GENT GENT



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

Mortality from heart and vessel disease and breast cancer



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

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.

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Leening MJGL et al., (2014) BMJ

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



urce - "Dementia: a public health priority" report, World Health Organization and Alzheimer's Disease International

AD patients worldwide



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

KENMERKEN VAN DE ZIEKTE VAN ALZHEIMER









CMC





Amyloid Plaques

Neurofibrillar tangles



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

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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	
Free radicals	Estrogen provides neuroprotection against oxidative stress via an antioxidant effect.	cardiovascular risk factors are also risk factors for AD. These include arterial hypertension, elevated LDL cholesterol,	
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).	low HDL cholesterol and diabetes. The pathways of this association have not yet been elucidated.	
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

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



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)				

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 E4- women on ERT. The E4+ women had no positive effect of ERT. They had no better results than E4- 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 E4- women but not among E4+ women.
Rippon 2006	1498 postmenopausal women mean age:Dementia present: 73.3 yearsDementia absent: 62.4 yearsApoE4 allele present in 736 women	Observational: Cross-sectional	Single administration of neuropsychological tests.	Compared with E4- women who had no history of ERT, E4- women who took ERT had an 80% reduction in AD risk. E4+ women without a history of ERT had a two-fold increased risk of AD, while E4+ 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 E4+ women, but this hypothesis did not reached statistical significance because of the small numbers available.
Tang 1996	1124 non-demented womenMean age: 74,2 years156 estrogen usersAPOE 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 E4+ women. An evaluation for the homozygote E4+ 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 E4+ 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 ϵ 4- women (n=32) - estrogen users: 73.18 ± 4.22 - non-users: 73.77 ± 2.43 ϵ 4+ 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 $\mathcal{E}4+$ women who may be in the early stages of AD. The ERT users who are $\mathcal{E}4+$ 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 $\mathcal{E}4-$ 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 £4 status was found: for £4- there was no difference in decline between women using ERT and those not using it; for £4+, 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 Depypere H e	No influence on cognition was seen. t 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

572 www.thelancet.com Vol 404 August 10, 2024

Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad^{*}, Naaheed Mukadam^{*}

Lancet 2024; 404: 572-628

599 references

Herman Depypere a,*, Lisa Mosconib, Roberta Diaz Brintonc, Harald Hampeld

a Menopause and Breast Clinic, Gent University Hospital, Corneel Heymanslaan 10, 9000 Ghent, Belgium

b The Alzheimer's Prevention Program and Women's Brain Initiative, Departments of Neuroscience, Neurology and Radiology, Weill Cornell Medicine, 402 East 70th Street, New York, NY 10021, USA

c Department of Pharmacology, Neuroscience and Neurology, University of Arizona, College of Medicine, 1230 N. Cherry Avenue, Room 470, Tucson, AZ 85724-5126, USA

d Sorbonne University, Alzheimer Precision Medicine, HP Salpêtrière Hospital, Boulevard de l'hopital, [^]F-75013 Paris, France

* Corresponding author.



https://doi.org/10.1016/j.maturitas.2025.108217 Received 22 January 2025; Received in revised form 9 February 2025; Accepted 12 February 2025 Maturitas The selected negative studies in the Lancet Commission report exhibit limitations. For instance, in both [5] and [7], only a small percentage of women were diagnosed with AD.

Pourhadi et al. [7] specifically report that "only 26% of our cases were Alzheimer's disease compared with an expected proportion of 70%," and "we were not able to isolate vascular dementia from other types of dementia due to the low validity of vascular dementia diagnosis."

Further, [6] and [7] primarily assessed oral estrogens combined with synthetic progestins, such as norethisterone, rather than micronized progesterone.

Oral estrogen and progestin preparations administered later in life can increase the risk of thrombosis [10]. This is very relevant since women are more vulnerable to stroke than men [11]. This risk might be mitigated by opting for transdermal routes [10]. Moreover, high-dose oral hormone preparations can destabilize existing plaques and induce plaque rupture by stimulating metalloproteinases [12], among other pathways.

Finally, it seems biologically implausible that a relatively short duration of MHT use, as reported in [6,7], could result in neuronal loss sufficient to trigger clinical symptoms of AD dementia

ZIEKTE VAN ALZHEIMER IN VIVO DETECTIE

SURROGATE MARKERS





Depypere H¹, Vergallo A^{2*}, Lemercier P^{2*}, Lista S², Benedet AL³ Ashton NJ^{3,4,5,6}, Cavedo E, Zetterberg H^{3, 7, 8, 9, 10}, Blennow K^{3,7}, Vanmechelen E¹¹, Hampel H²; 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 R association® Alzheimer's & Dementia*

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.



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

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





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



p<0.001

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'.

https://doi.org/10.1038/s41591-025-03564-3 Nature medicine, March 2025

Vorige bijlage



Changes to the female brain during menopause, together with social and cultural factors, might affect disease risk. **By Sofia Moutinho**

It is important to study ways to reduce the important rise in the prevalence of AD, cardiovascular disease, osteoporosis in women.



REVIEWS NEUROLOGY

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Alzheimer disease seen through the lens of sex and gender" by Laura Castro-Aldrete, Melanie Einsiedler, Julie Novakova Martinkova, Herman Depypere, Ting Fang Alvin Ang, Michelle Mielke, Shireen Sindi, Harris A. Eye, Rhoda Au, Anne Marie Schumacher Dimech, Anna Dé, Cassandra Szoeke, Maria Carmela Tartaglia, and Antonella Santuccione Chadha [NRNEUROL-23-239V2D], has been Accepted for publication in Nature Reviews Neurology