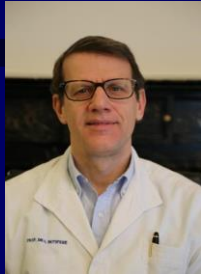


Menopauze

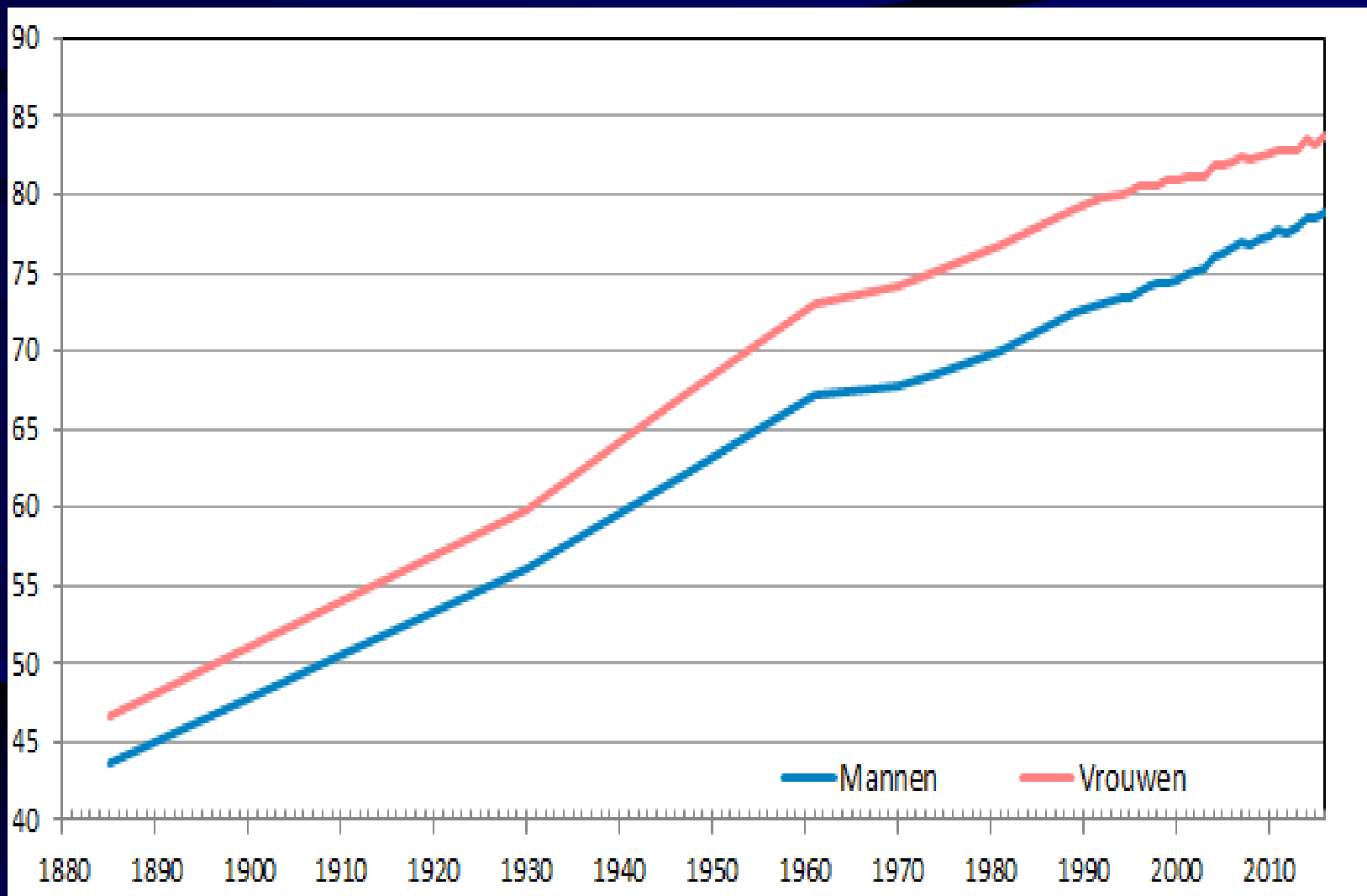
PROF. DR. H. DEPYPERE



Menopauze kliniek: Universitair Ziekenhuis, Gent.

Privaat praktijk: Coupure rechts 4, Gent

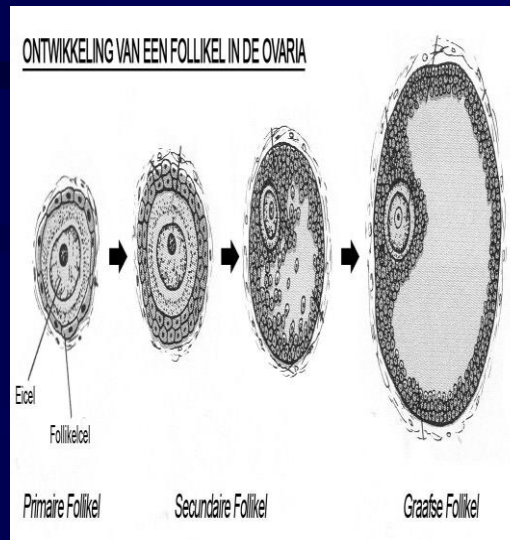




Menopauze – wegvallen van de productie van hormonen (oestrogenen) door de ovaria \pm 51-52 jaar.

In België anno 1888: 46,6 jr; In Nigeria anno 2022: 54 jr.

Bij de geboorte beide meisjes: 700 000 prim follikels.



Biologische discriminatie:

Man ~ testosteron



Vrouw oestrogeen

Hoog FSH en LH en laag oestradiol

Niet mogelijk onder de pil

Wel mogelijk onder Mirena®, Kyleena®

Iedere vrouw (98 %) kende de term menopauze.

61% dacht dat het een **tijdelijke** fase was (17 % dacht dat de menopauze één of twee jaar duurde/44 % dacht dat de menopauze drie tot vijf jaar duurde).

Slechts 39 % beseft dat menopauze definitief is.

Vermoeidheid (66 %), spierpijn en gewrichtsklachten (66 %) waren de belangrijkste klachten.

Nachtelijk transpireren (30%) en warmteopwellingen tijdens de dag 33 % waren aanwezig en waren aanwezig geweest.

46 % van de vrouwen had momenteel slaapproblemen. Bij 17 % hadden slaapproblemen gehad.

30 % hadden een verminderd libido en 25 % hadden last van een vaginaal droogheids gevoel.

12 % kreeg antidepressieva of slaapmedicatie.

Healthy life years at birth

Women



64.2
years

73.4	Malta
72.0	Sweden
70.4	Ireland
69.1	Norway
68.0	Spain
67.6	Bulgaria
66.9	Italy
66.3	Germany
65.9	Greece
64.5	France
64.3	Poland
	EU-27
63.8	Belgium
63.7	Iceland
63.4	Czechia
62.4	Cyprus
61.8	Hungary
60.8	United Kingdom
59.8	Luxembourg
59.6	Romania
59.5	Switzerland
59.1	Denmark
59.1	Lithuania
58.5	Croatia
57.5	Portugal
57.2	Netherlands
57.0	Austria
56.6	Slovakia
55.7	Finland
55.0	Estonia
54.6	Slovenia
53.7	Latvia

Men



63.7
years

73.7	Sweden
71.9	Malta
71.7	Norway
69.6	Iceland
68.4	Ireland
68.0	Spain
66.8	Italy
65.1	Germany
65.0	Greece
64.0	Bulgaria
	EU-27
63.4	France
63.2	Belgium
62.5	Denmark
62.2	Czechia
62.0	Cyprus
61.5	United Kingdom
61.5	Switzerland
61.4	Luxembourg
61.1	Netherlands
60.5	Poland
60.4	Hungary
59.8	Portugal
59.2	Romania
58.8	Finland
56.8	Austria
56.5	Croatia
56.3	Lithuania
56.3	Slovenia
55.5	Slovakia
52.7	Estonia
51.0	Latvia



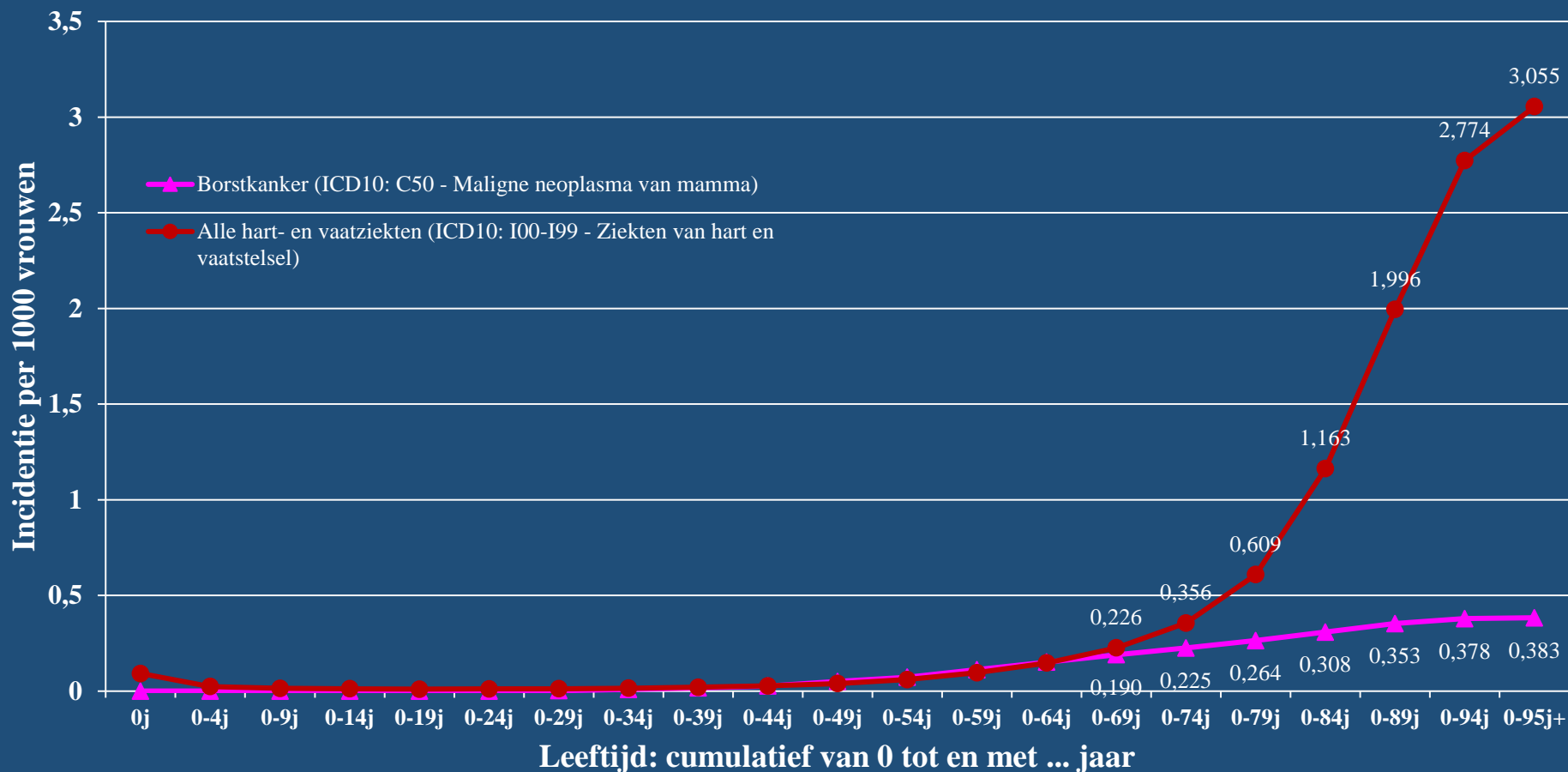
Healthy life years:

the number of years that a person is expected to live without an activity limitation (disability).

Data refer to 2018.

UK, Norway, Iceland and Switzerland: non-EU countries.
Iceland: data from 2016.

Cumulatieve leeftijdsspecifieke incidentie van sterfte bij vrouwen voor enkele geselecteerde oorzaken, Vlaams Gewest, 2015



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/>

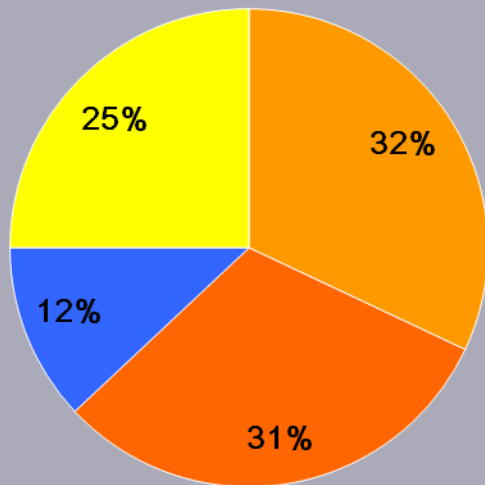
prof Koen Vanherck

Boek *Menopauze alle vragen beantwoord* professor Depypere ISBN 9789089319555

doodsoorzaken 2006

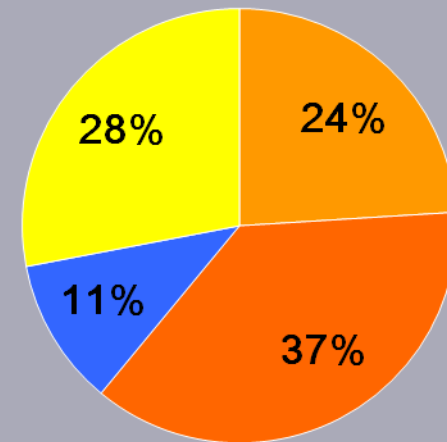
“Vlaams gewest”

man

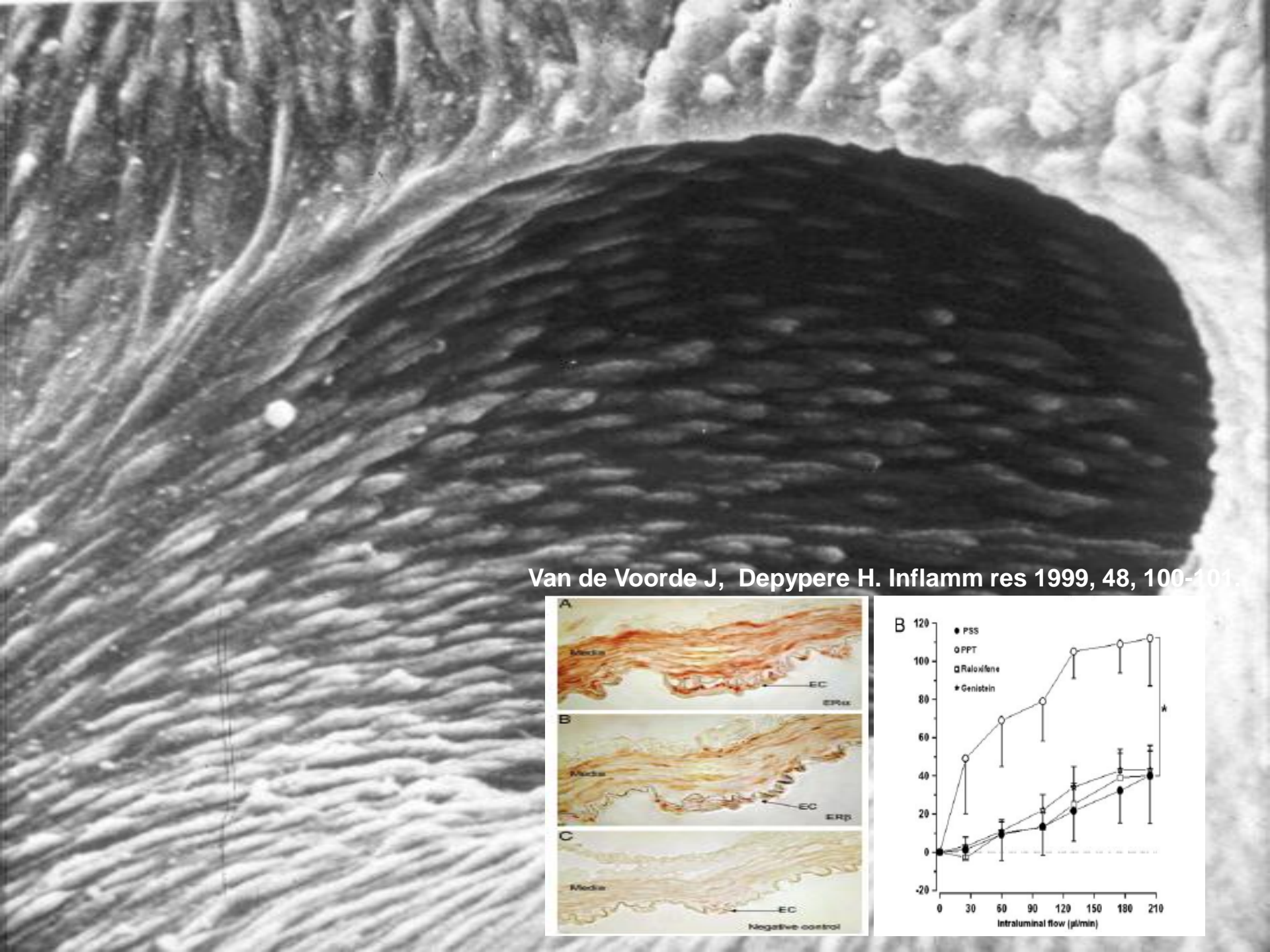


■ Cancer ■ cardiovascular ■ respiratory ■ other

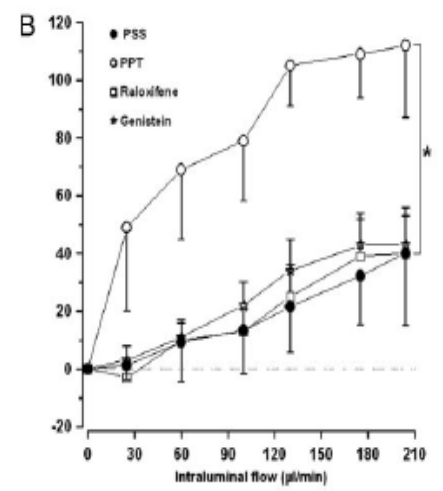
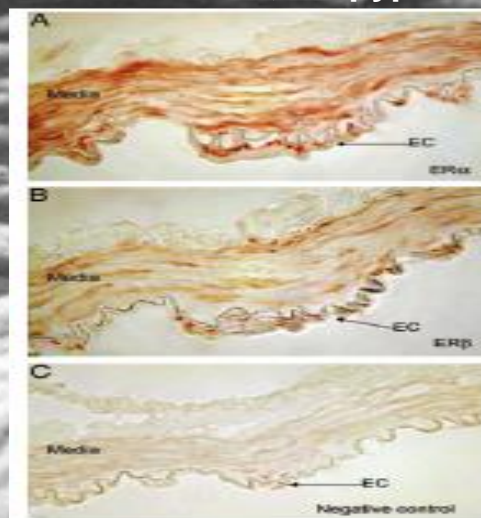
vrouw



■ cancer ■ cardiovascular ■ respiratory ■ other



Van de Voorde J, Depypere H. *Inflamm res* 1999, 48, 100-101.



Invloed van orale vs transdermale toediening van oestrogenen op lipiden en coagulatiefactoren

Table I Differential effects of oral and transdermal estrogens on lipids and coagulation factors

	Oral estrogens	Transdermal estrogens
Total cholesterol	↓	↓
HDL-C	↑	↑
LDL-C	↓	↓
TG	↑	Neutral or ↓
APC activity	↓	Neutral
CRP	↑	Neutral
AT III	↓	Neutral
Fibrinogen	↓	↓
Factor VII activity	Neutral	↓
von Willebrand factor	↑	Neutral or ↓
Prothrombin fragments I and 2	↑	Neutral or ↓

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides; APC, activated protein C; CRP, C-reactive protein; AT III, Antithrombin III.

Nurses health study

Hers study

WHI global study cc

WHI estrogen only

Salpeter

Cohrane: 19 gerandomiseerde studies met 40,410 postmenopauzale vrouwen. Boardman et al. 2015

Keeps

Elite

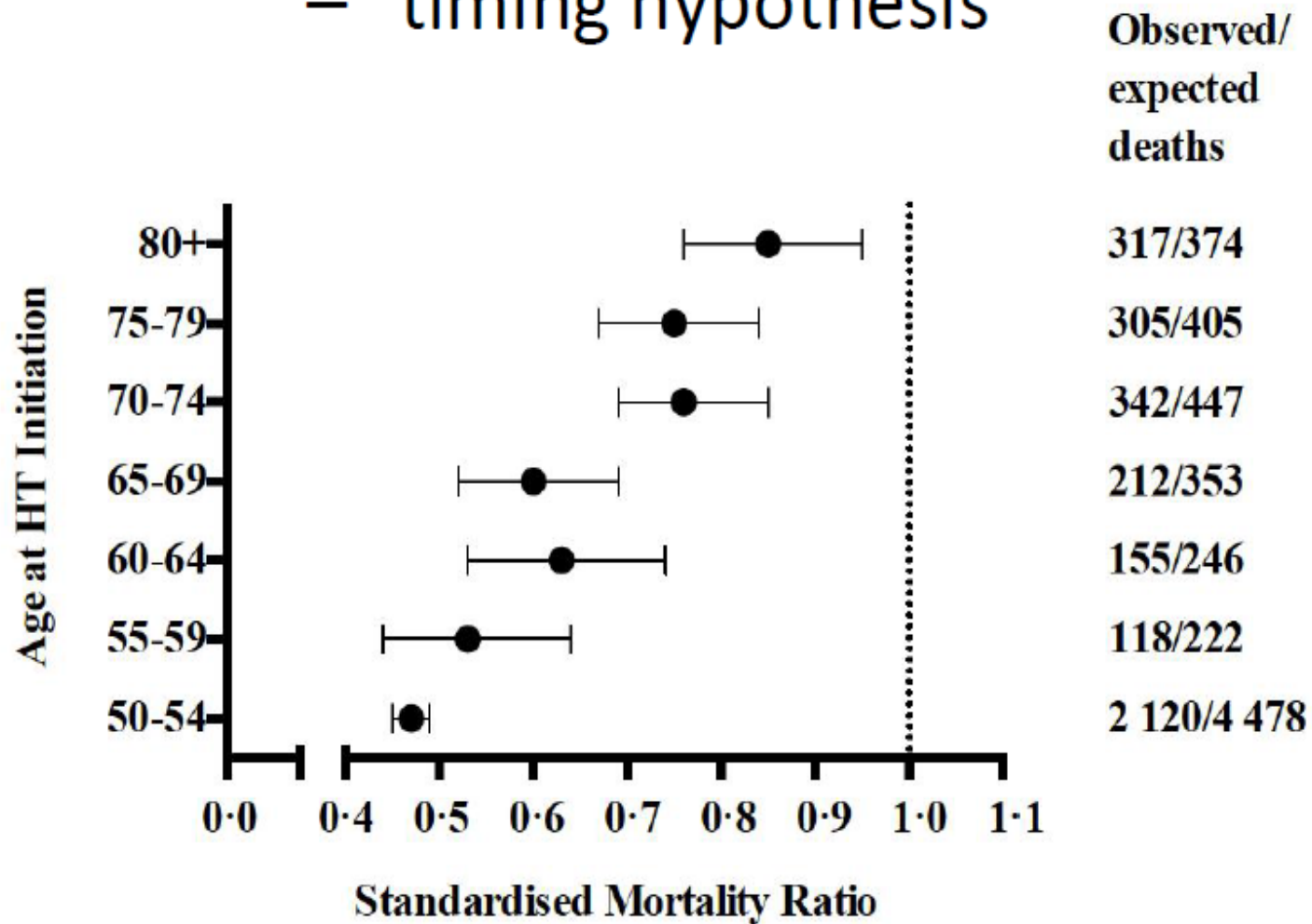
Finse en Deense studies

Selectie criteria

RCTs bij vrouwen bij wie orale HT werd toegediend placebo gecontroleerd en gerandomiseerd.

Those 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.

Risk of cardiac death and the use of HT – “timing hypothesis”



Savolainen-Peltonen et al. JCEM 2016;101:2794-801

Be.stat.bel: women

50-54 jaar: 390 376

55-59 jaar: 398 908

789 284

2 op 100 vrouwen per 10 jaar opvolging zullen niet sterven door inname van HT of 0.2 per jaar.

$789\ 284 / 100 \times 0.2 : 1579$ minder vrouwen die zouden sterven per jaar.

Gebaseerd op 19 gerandomiseerde studies.

Primaire preventie van sterfte door vaatlijden door hormonen in vergelijking met andere producten*

Outcome	Hormonen Therapie, ^{2*}	cholesterol medicatie ³	Aspirine ⁴
CHD	0.68 (0.48-0.96)	0.89 (0.69-1.09)	0.91 (0.80-1.03)
Totale Mortaliteit	0.61 (0.39-0.95)	0.95 (0.62-1.46)	0.95 (0.85-1.06)

*Women <60 years old and/or <10 years since menopause when randomized

*Hodis HN, et al. *Clin Obstet Gynecol* 2008;51:564-586.

¹Salpeter S, et al. *J Gen Intern Med* 2004;19:791-804.

²Salpeter S, et al. *J Gen Intern Med* 2006;21:363-366.


³Walsh JME, et al. *JAMA* 2004;291:363-366.

⁴Ridker PM, et al. *N Engl J Med* 2005;352:1293-1304.



Review Article | Published: 09 July 2018

Sex differences in Alzheimer disease — the gateway to precision medicine

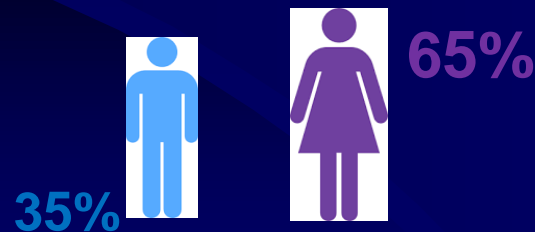
Maria Teresa Ferretti , Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Misoch, Ezio Giacobini, Herman Depypere, Harald Hampel & for the Women's Brain Project and the Alzheimer Precision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

Nature Reviews Neurology **14**, 457–469 (2018) | [Download Citation](#) ↓

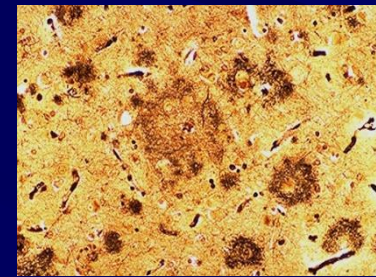
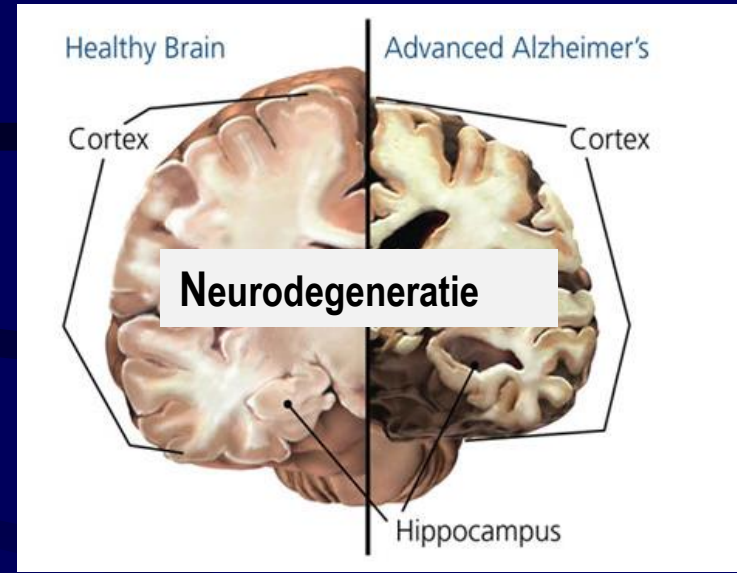
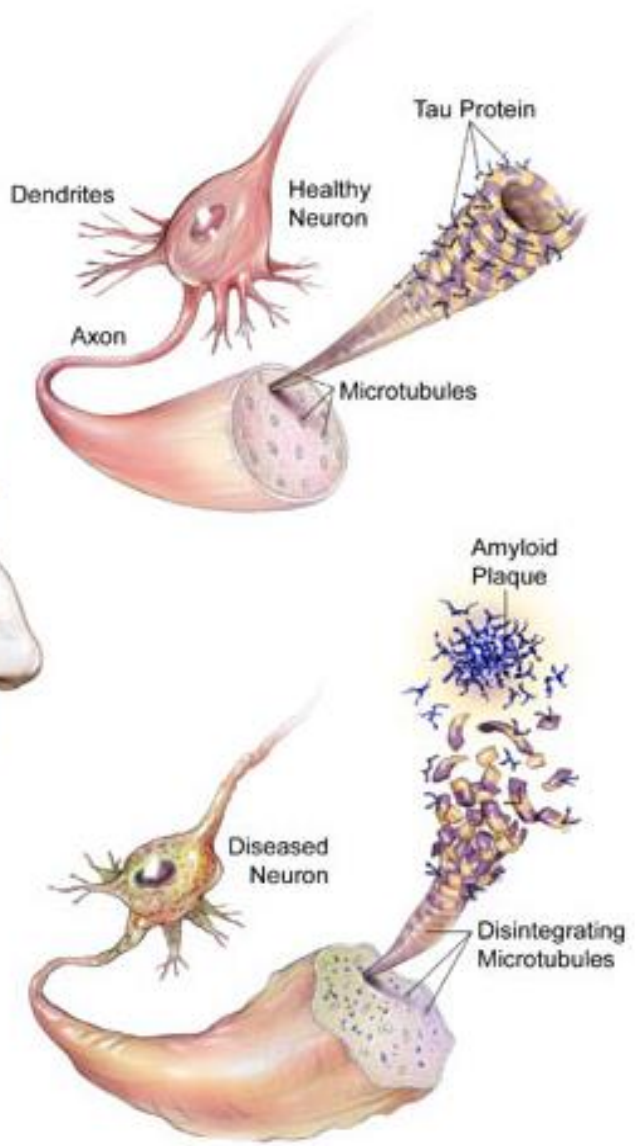
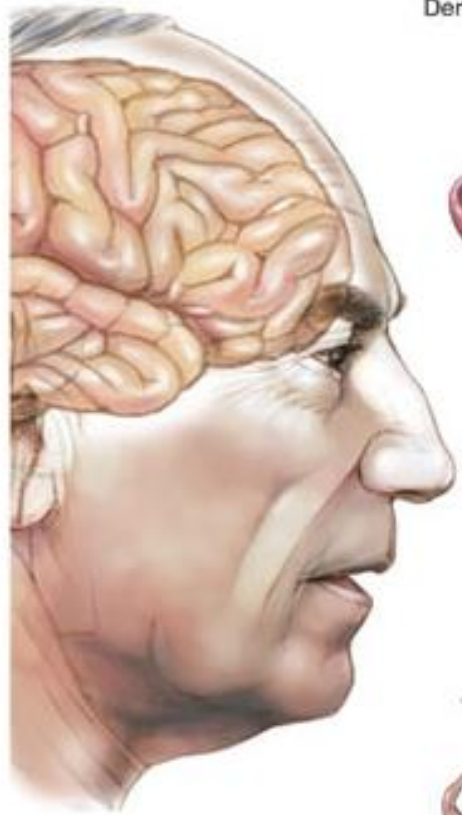
Ziekte van Alzheimer is de belangrijkste oorzaak van dementie, verantwoordelijk voor 60% to 80% tot van patiënten met dementie



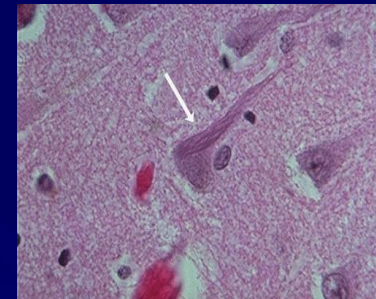
AD patients worldwide



KENMERKEN VAN DE ZIEKTE VAN ALZHEIMER



Amyloid Plaques



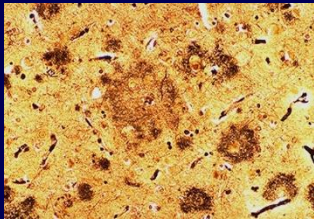
Neurofibrillaire kluwenvorming

ZIEKTE VAN ALZHEIMER

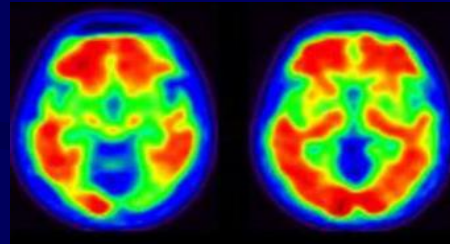
IN VIVO DETECTIE

SURROGAAT MERKERS

Amyloid Plaques



Amyloid PET



CSF/Plasma A β 1-42

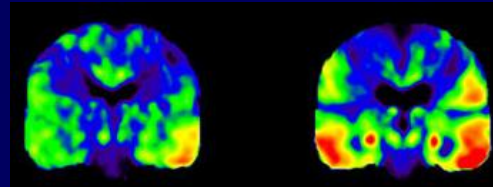
of



Neurofibrillaire kluwen



Tau PET

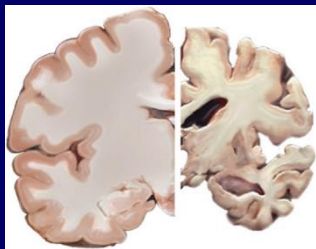


CSF/Plasma T-tau P-tau

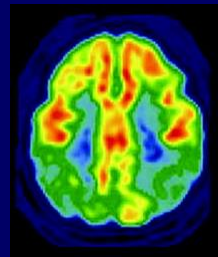
of



Neurodegeneratie

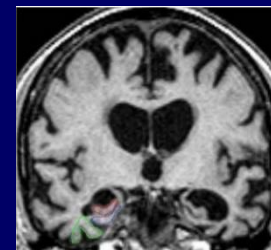


18-FDG PET



or

Brain Atrophy (MRI)

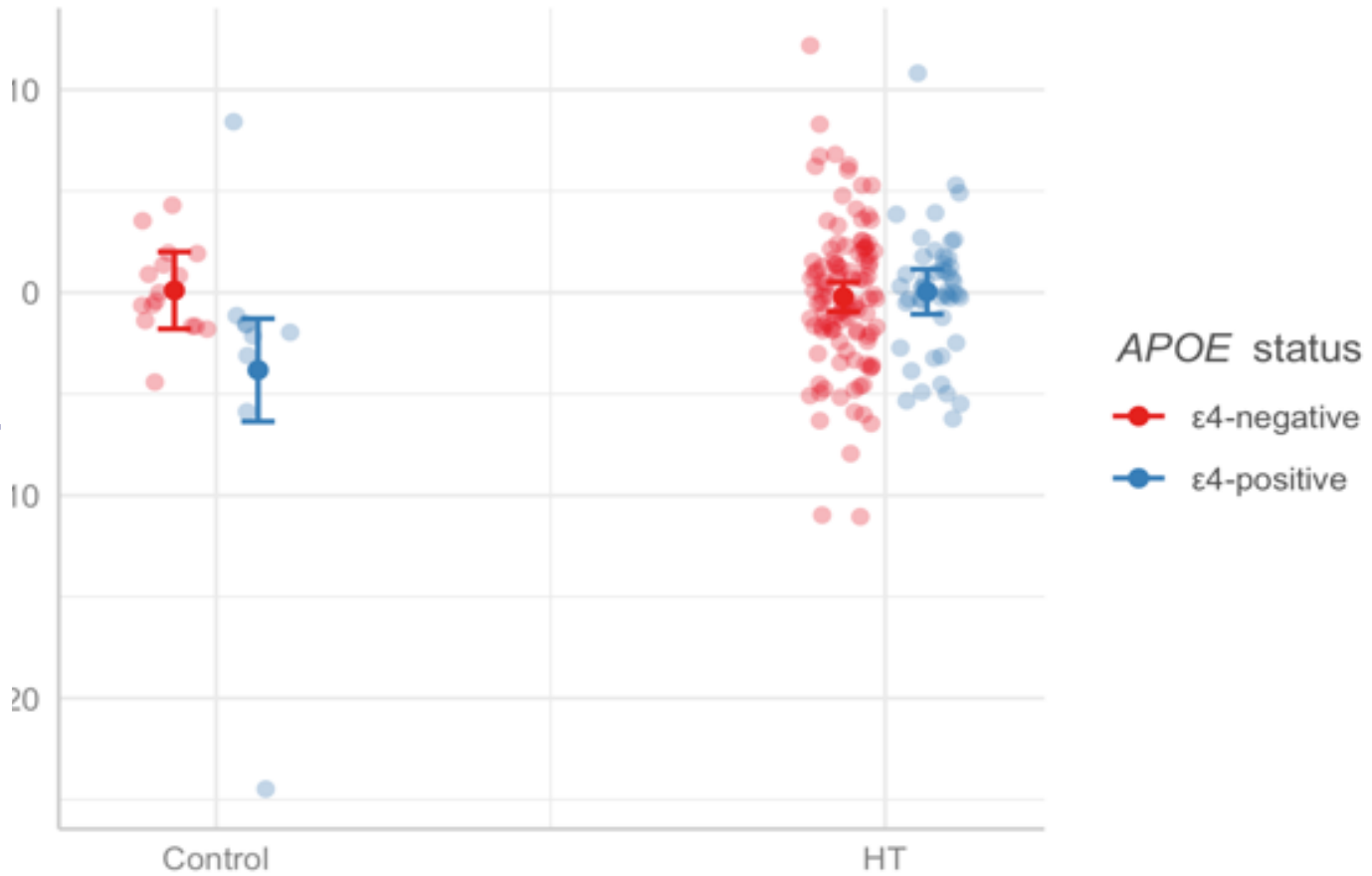


Depypere H¹, Vergallo A^{2*}, Lemercier P^{2*}, Lista S², Benedet AL³ Ashton NJ^{3,4,5,6}, Cavedo E, Zetterberg H^{3, 7, 8, 9, 10}, Blennow K^{3,7}, Vanmechelen E¹¹, Hampel H²; the Neurodegeneration Precision Medicine Initiative (NPMI).

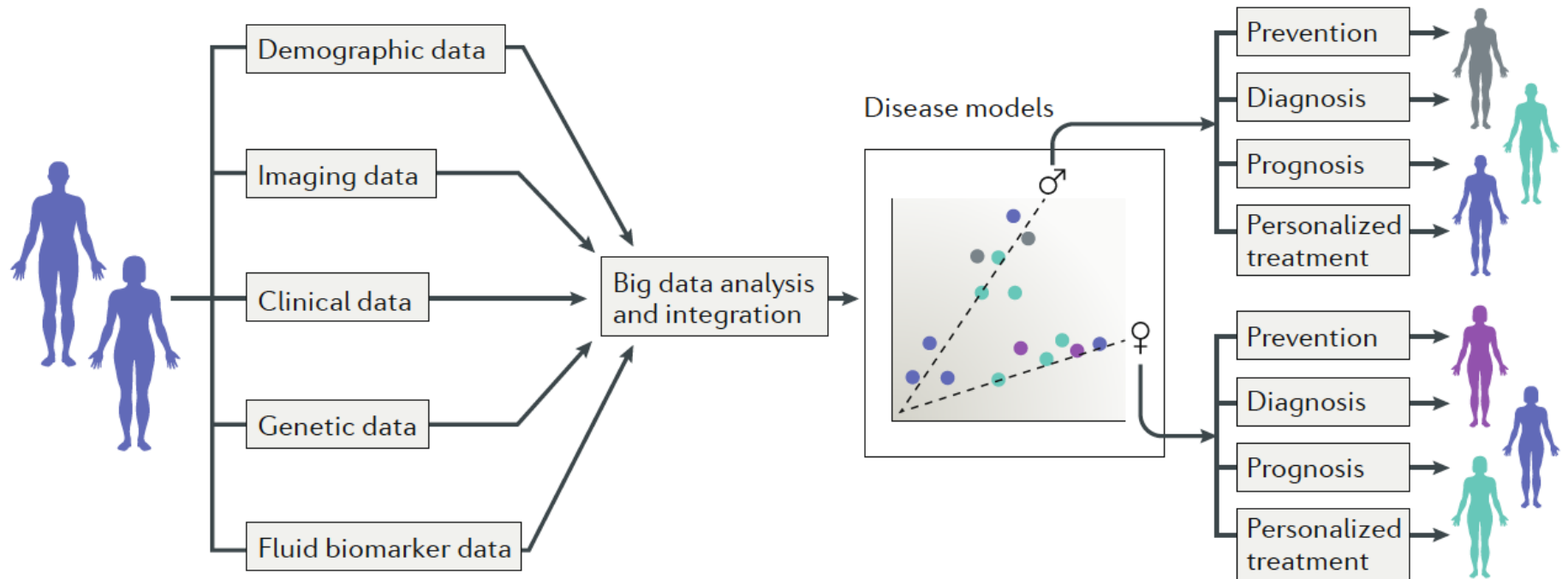
Menopause Hormone Therapy significantly alters Pathophysiological Biomarkers of Alzheimer's Disease

Alzheimer's and dementia: 2022 sept


Neurale serum parameters



Meer gepersonaliseerde precisie geneeskunde



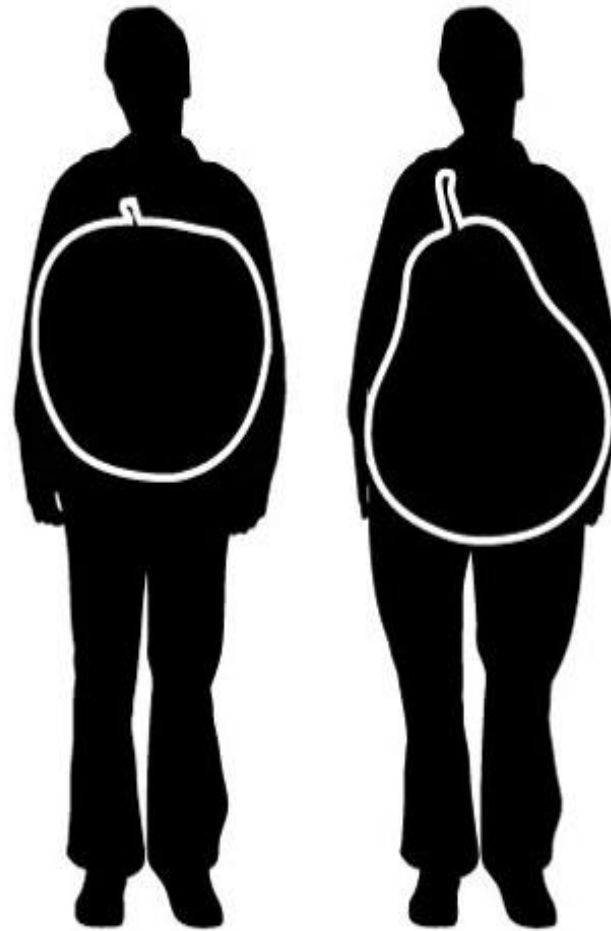
Sex differences in Alzheimer disease — the gateway to precision medicine

Maria Teresa Ferretti , Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santucci Chadha, Francesca Baracchi, H el ene Girouard, Sabina Misoch, Ezio Giacobini, Herman Depypere, Harald Hampel & for the Women’s Brain Project and the Alzheimer Precision Medicine Initiative



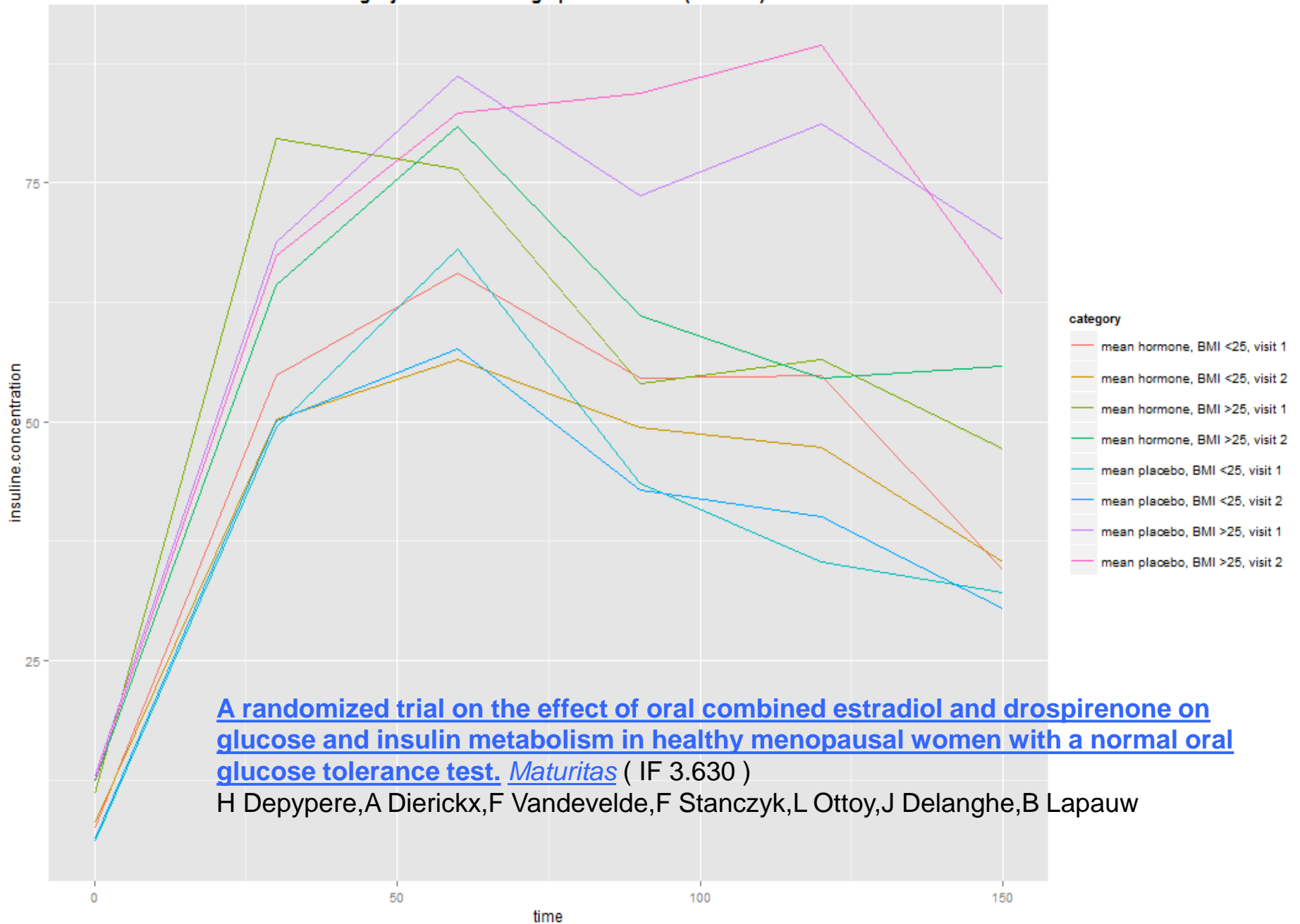
THE APPLE, by definition, is round. You have the body people want to cycle up to. But is it easy to dress? No, it's not. That's why you think it so much safer to cover yourself with yards of fabric, making absolutely sure not one centimeter of flesh can peep out.

Sometimes the thickened waist of the Apple maddens with the meropause. At the earlier end of the scale is a little puggy fit. Of all our shapes, the Apple tends to be the least confident. If, despite of your beautiful, soft, pillow-soft breasts and divinely sculpted ankles, you really don't like your body, but can't dispute either of a wonderful cleavage that can be enhanced with low tops and fitted jackets. Your body is easy to redefine with the right clothes.



Appelvorm – metabool syndroom

Vergelijken behandeling op visite 1 en 2 (insuline)



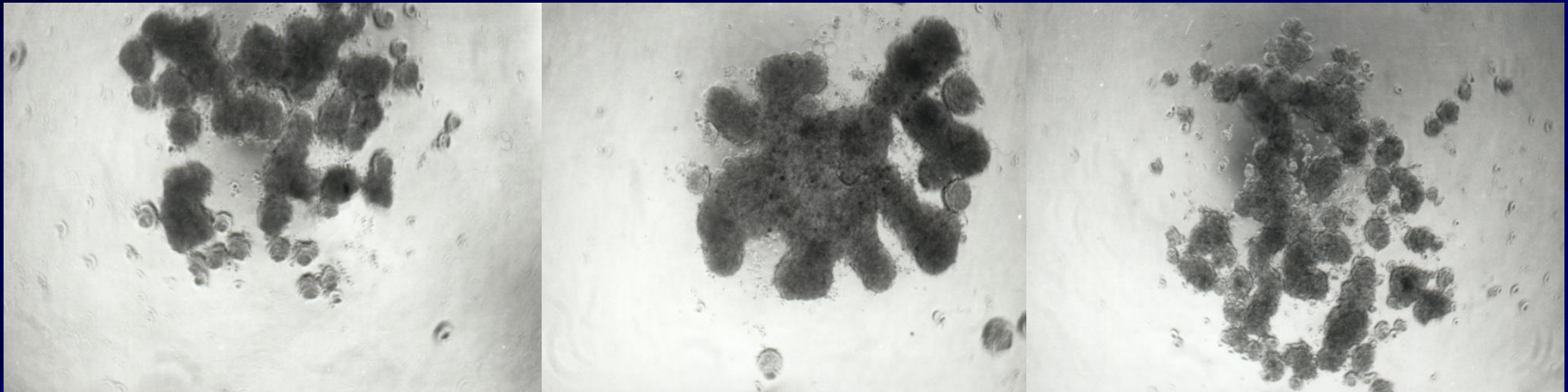
[A randomized trial on the effect of oral combined estradiol and drospirenone on glucose and insulin metabolism in healthy menopausal women with a normal oral glucose tolerance test. *Maturitas* \(IF 3.630 \)](#)

H Depypere, A Dierickx, F Vandeveld, F Stanczyk, L Ottoy, J Delanghe, B Lapauw

Hyperinsulinemie:

Nefast voor borstkanker

Proliferation and cell cell adhesion SLOW AGGREGATION ASSAY



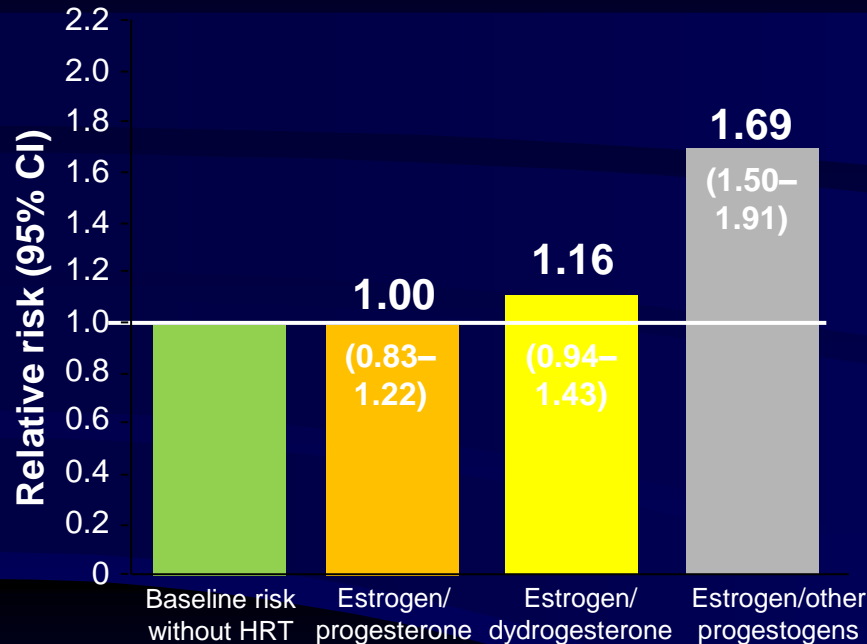
Nefast voor diabetes

Nefast voor hart - en vaatlijden

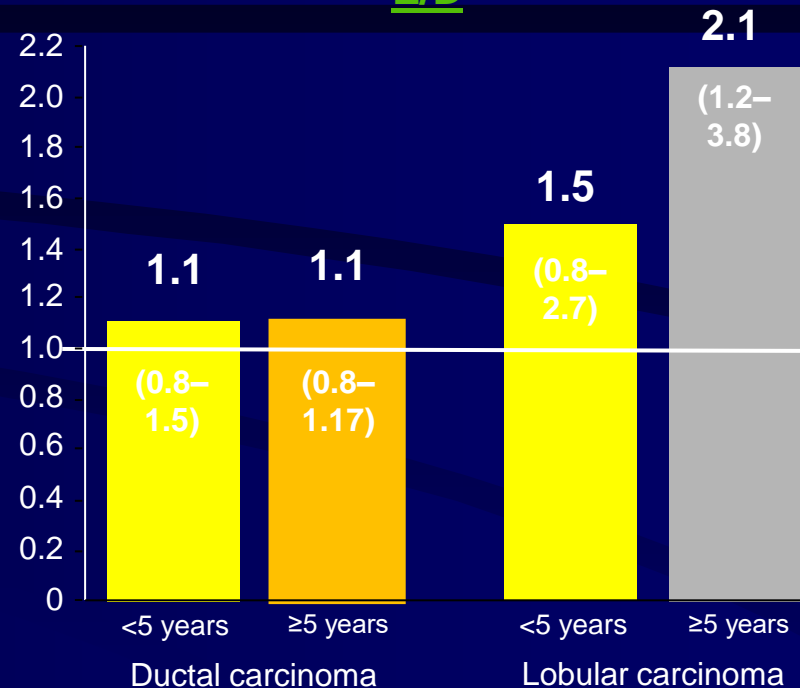
Nefast voor dementie

Choice of Progestogen and Breast Cancer Risk: E3N French Cohort Study

Risk of all breast cancer



Risk of breast cancer subtypes with E/D



- Not statistically significantly different from risk without HRT
- Significantly different from the risk without HRT

N = 80,377 women, for an average treatment duration of 8.1 years

Risk elevation may not be uniform for all progestogens

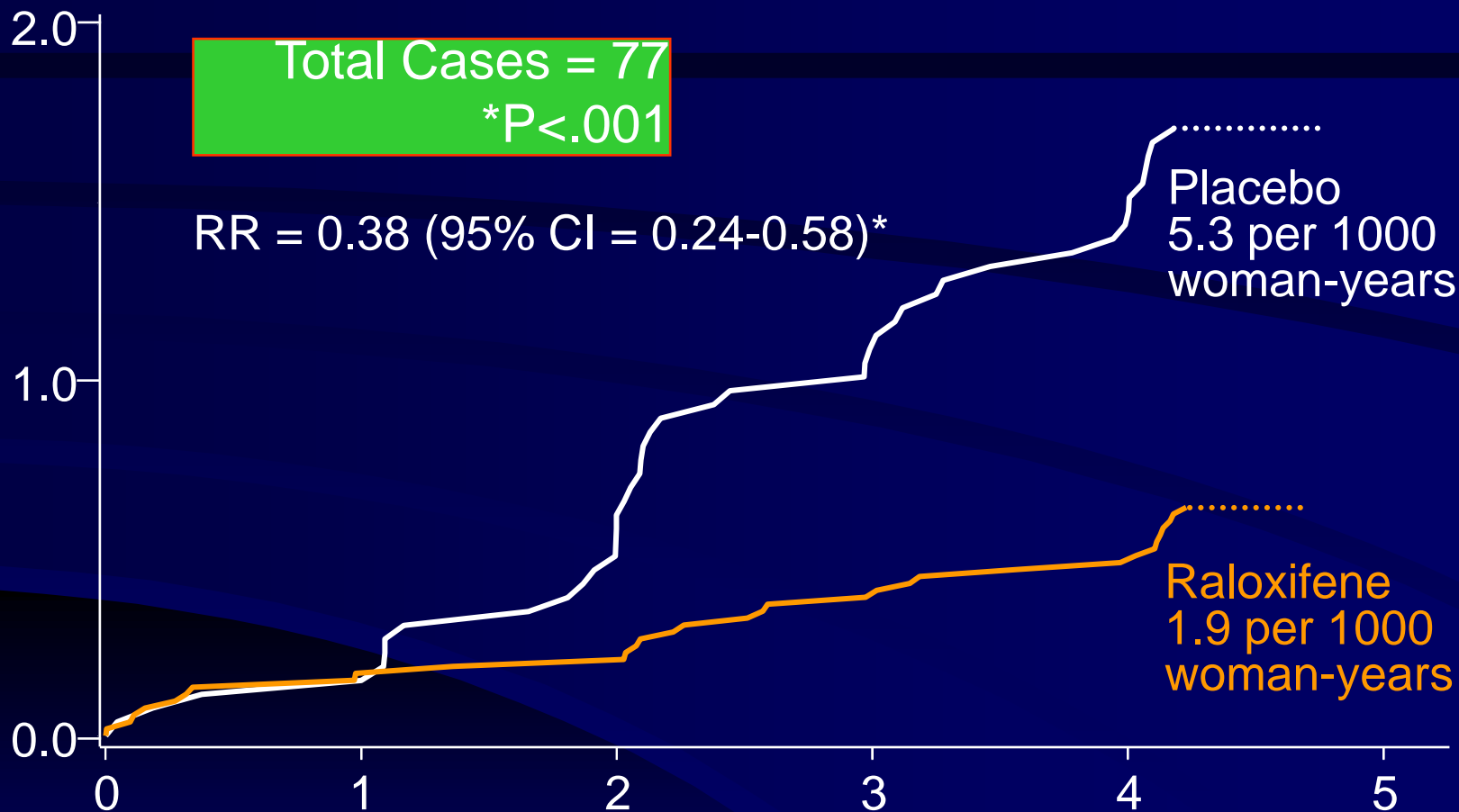
Outcome by Age 50-60 years of age at inclusion

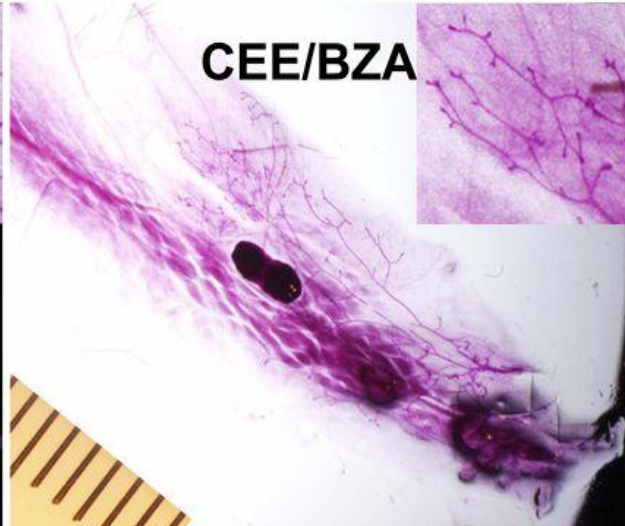
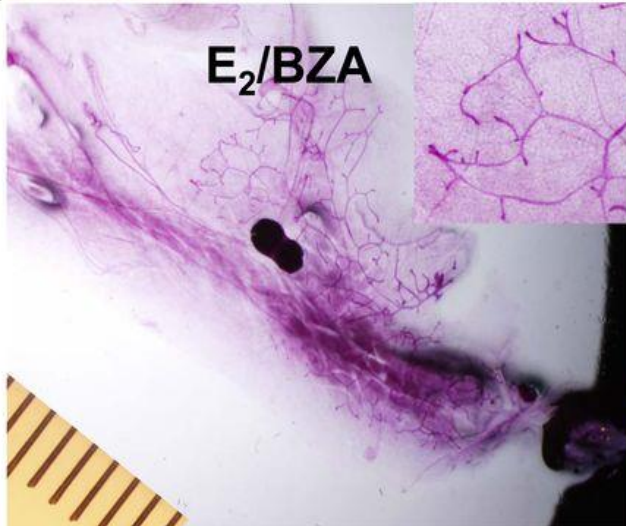
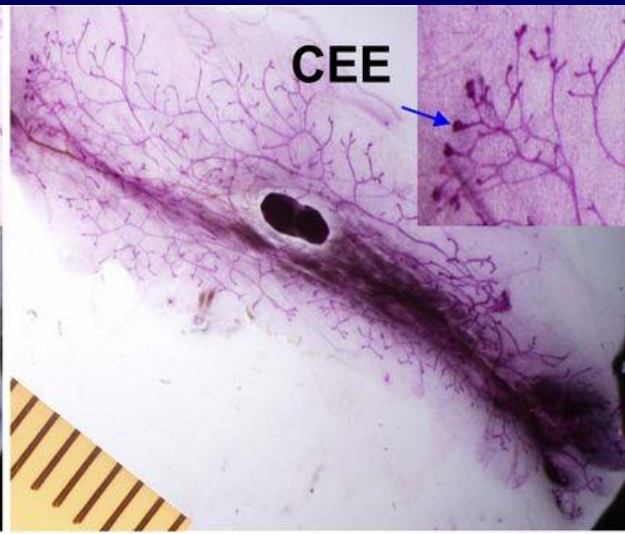
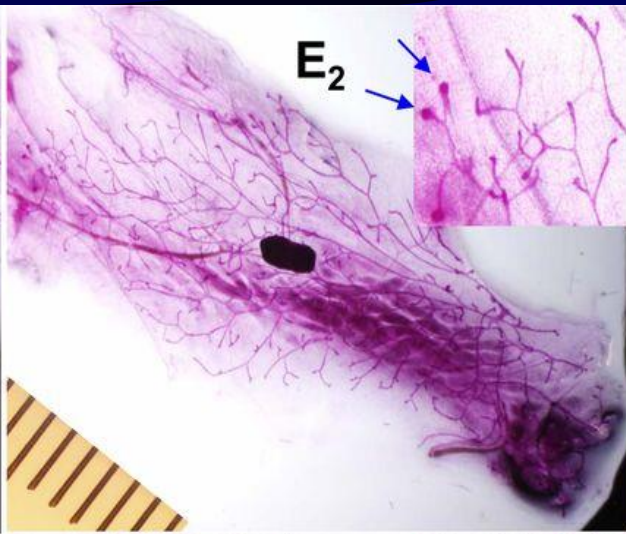
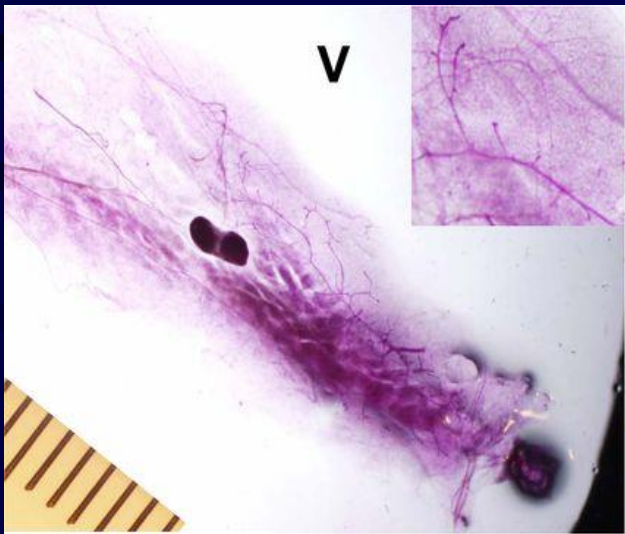
	Hormone Therapy	Placebo	HR (95% CI)	P value
All-cause mortality				
Pooled trials	70 (0.23)	98 (0.34)	0.69 (0.51-0.94)	.01
CEE alone vs placebo	35 (0.28)	50 (0.39)	0.71 (0.46-1.09)	.04
CEE plus MPA vs placebo	35 (0.20)	48 (0.30)	0.67 (0.43-1.04)	.20
CVD mortality				
Pooled trials	18 (0.060)	22 (0.076)	0.79 (0.42-1.47)	.85
CEE alone vs placebo	8 (0.063)	10 (0.077)	0.81 (0.32-2.04)	.34
CEE plus MPA vs placebo	10 (0.058)	12 (0.075)	0.77 (0.33-1.79)	.47
Cancer mortality				
Pooled trials	37 (0.12)	48 (0.17)	0.74 (0.48-1.14)	.05
CEE alone vs placebo	20 (0.16)	26 (0.20)	0.78 (0.43-1.40)	.06
CEE plus MPA vs placebo	17 (0.099)	22 (0.14)	0.71 (0.38-1.33)	.37

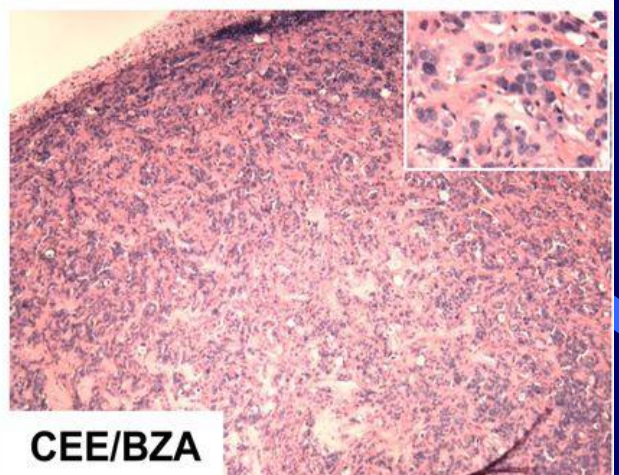
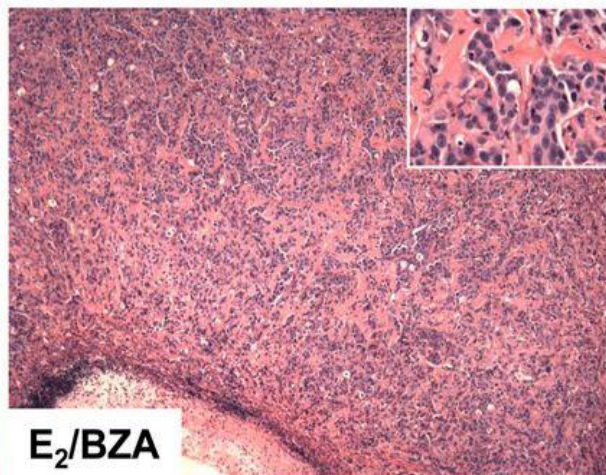
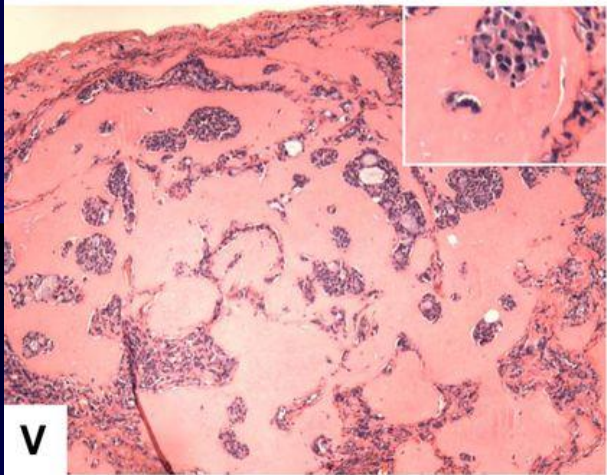
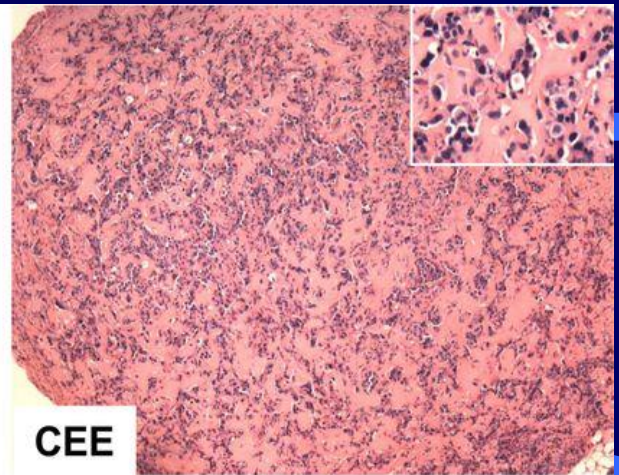
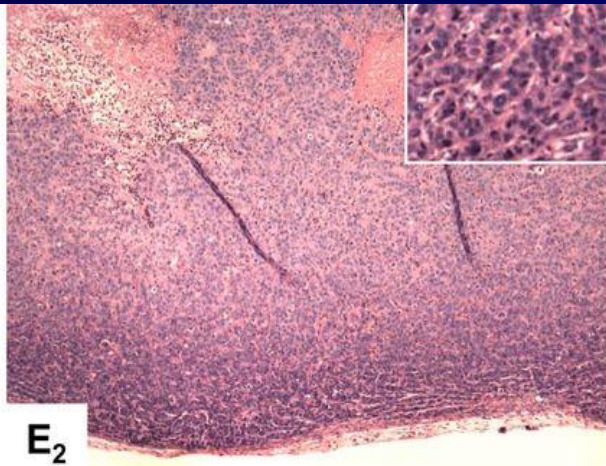
Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials
 JoAnn E. Manson, MD, DrPH; Aaron K. Aragaki, MS; Jacques E. Rossouw, MD; Garnet L. Anderson, PhD; Ross L. Prentice, PhD; Andrea Z. LaCroix, PhD;
 Rowan T. Chlebowski, MD, PhD; Barbara V. Howard, PhD; Cynthia A. Thomson, PhD; Karen L. Margolis, MD, MPH; Cora E. Lewis, MD, MSPH; JAMA 2017

But we aim to do better and decrease breast cancer
SERM- TSEC

More en core studie









Prof J Russo



Prof J Janssens

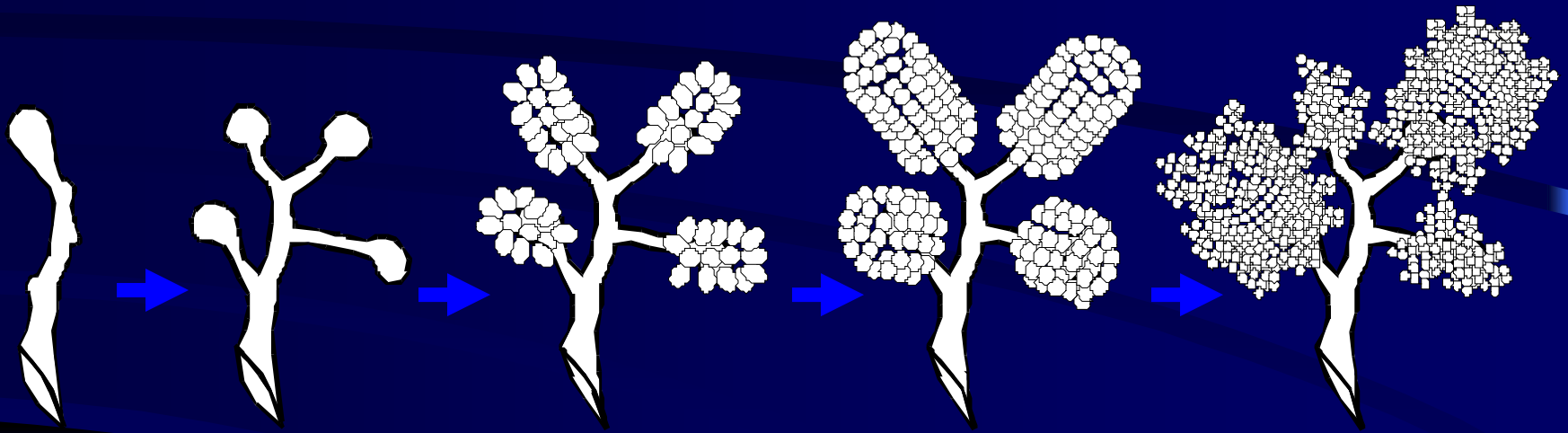


Puberty

*Development
of breast*

pregnancy

Lactation



*but
formation*

*Lobule
Type 1*

*Lobule
Type 2*

*Lobule
Type 3*

*Lobule
Type 4*

Proliferation

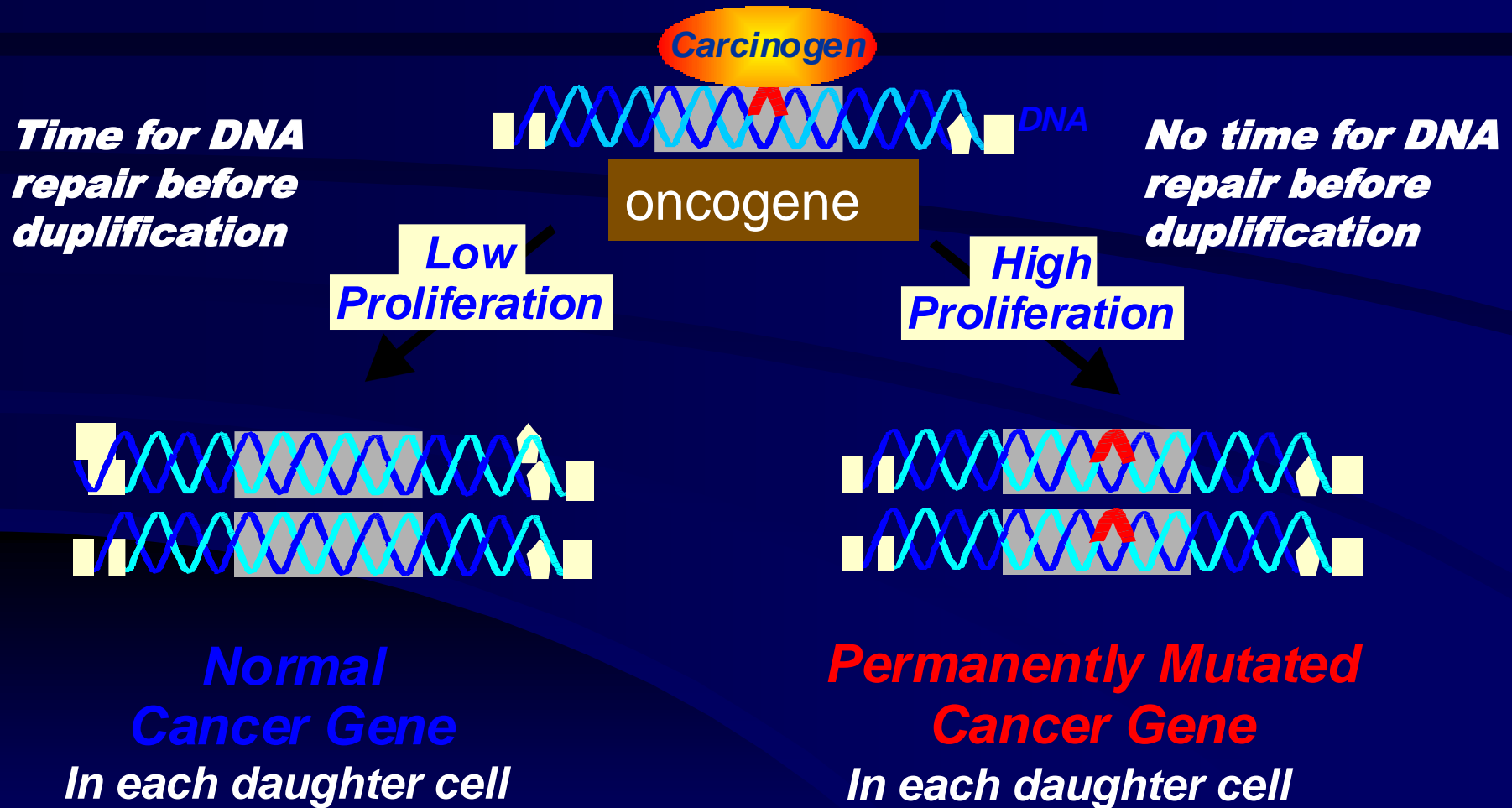
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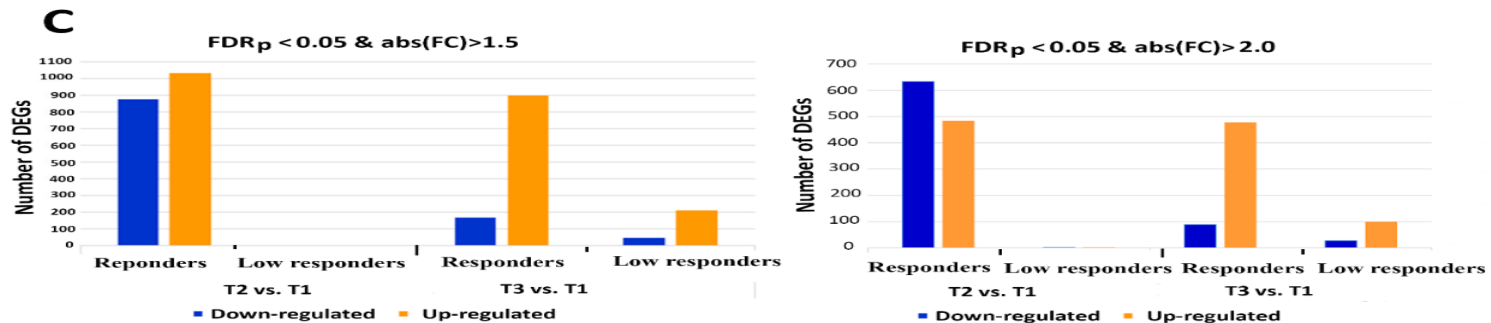
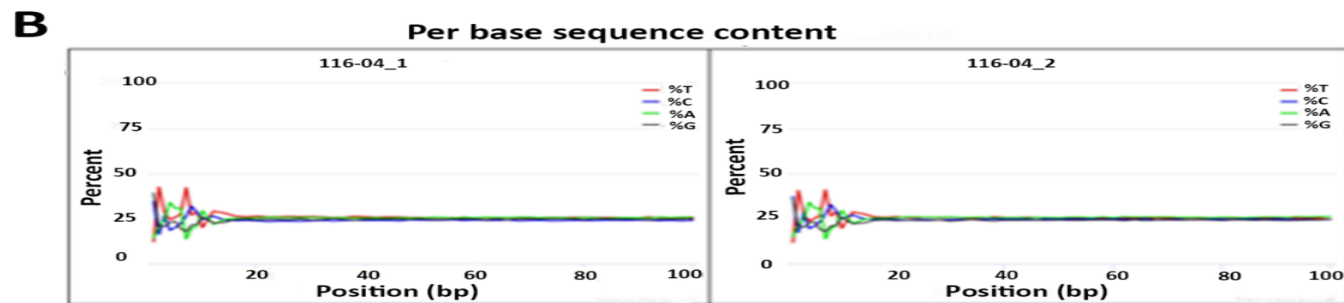
22

4

1

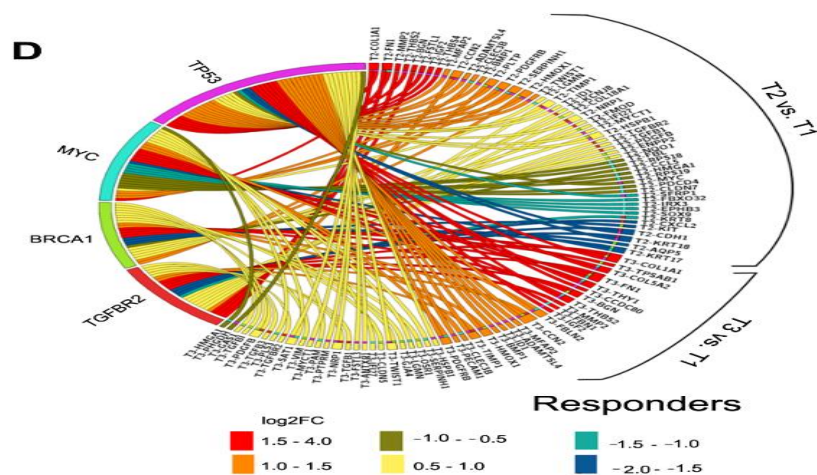
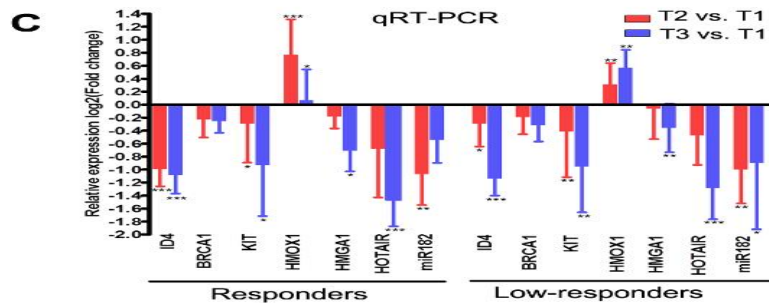
Proliferation rate reduces mutation recovery



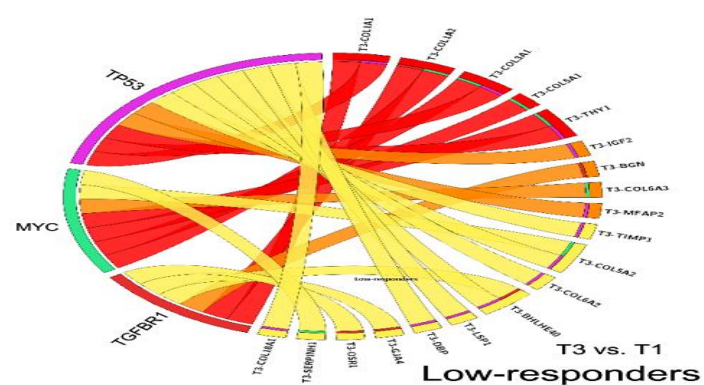
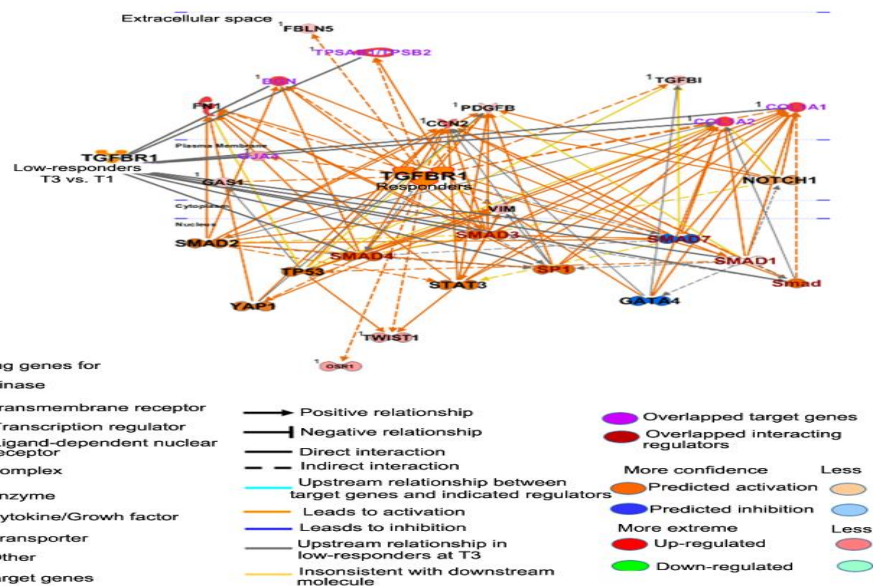


Depypere, Herman^a; Su, Yanrong^b; Dang, Nhib^b; Poppe, Bruce^c; Stanczyk, Frank^d; Janssens, Jaak^e; Russo, Jose^b
 Prolonged recombinant pregnancy hormone use in BRCA1 and BRCA2 mutation carriers. European Journal of
 Cancer Prevention: [March 12, 2021 - Volume Publish Ahead of Print - Issue](#) - doi: 10.1097/CEJ.0000000000000664

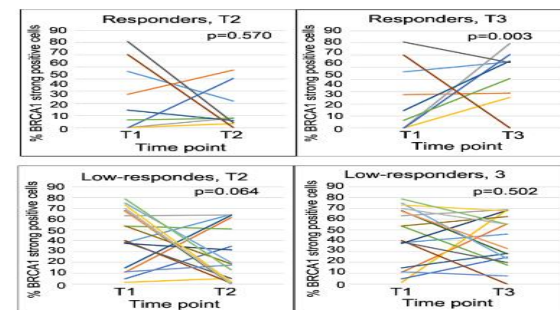
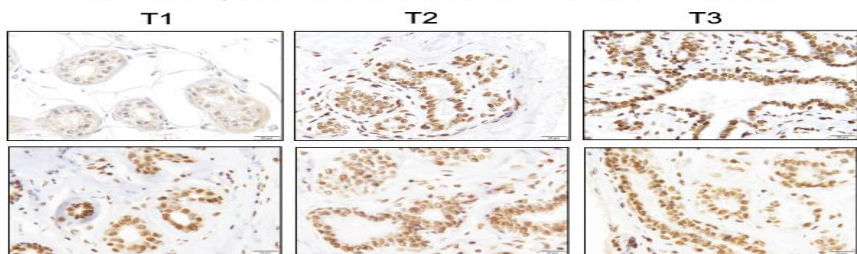
Responders (T2 vs. T1)			Responders (T3 vs. T1)			Low-responders (T3 vs. T1)		
Upstream regulators	Z-score	Prediction score	Upstream regulators	Z-score	Prediction score	Upstream regulators	Z-score	Prediction score
TGFB2	Activated	2.4	TGFB2	Increased activity	1.9	TGFB2	Increased activity	1.7
TGFB1	Activated	5.6	TGFB1	Activated	6.31	TGFB1	Activated	4.2
TGFB1	Activated	3.1	TGFB1	Activated	3.1	TGFB1	Activated	2.2
TGFB2	Activated	2.3	TGFB2	Increased activity	1.9	TGFB2	Activated	2.7
BRCA1	Increased activity	1.0	BRCA1	Activated	2.1	TGFB3	Activated	2.9
TP53	Activated	2.0	TP53	Activated	2.7	TP53	Increased activity	1.8
MYC	Inhibited	-3.0	MYC	Inhibited	-2.6	MYC	Decreased activity	-0.8



B TGFB1 is predicted activated at T2 and T3 in the responders, and at T3 in the low-responders



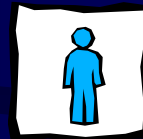
E BRCA1 expression in the breast of BRCA1/2 carriers



Incidentie van osteoporose > 50 jaar :



1/3



1/8

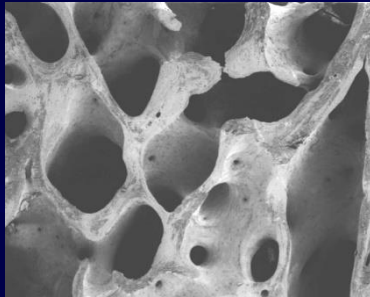
De incidentie zal de komende 50 jaar verdubbelen

2^{de} grootste gezondheidsprobleem na
cardiovasculaire ziekte



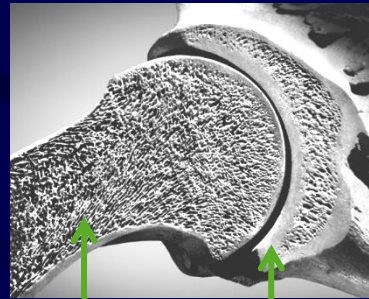
Osteoporose

Trabecular bone

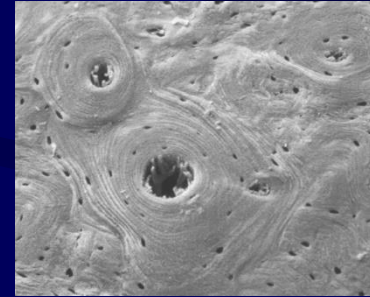


© David W. Dempster, PhD, 2000.

- Spongy¹
- Favours flexibility
- 20% of bone mass



Cortical bone

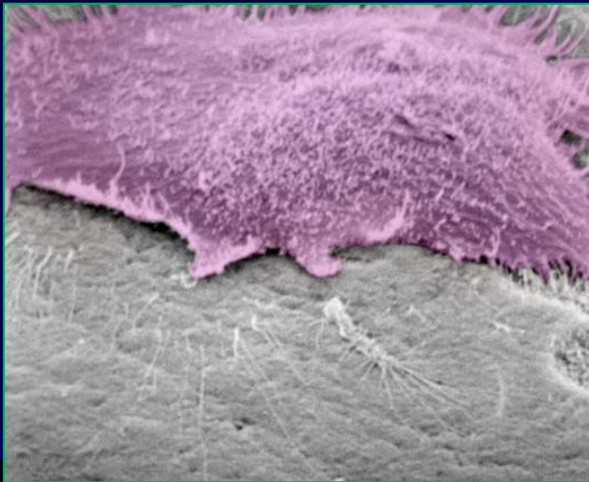


- Compact¹
- Offers stiffness en biomechanical strength
- 80% of bone mass

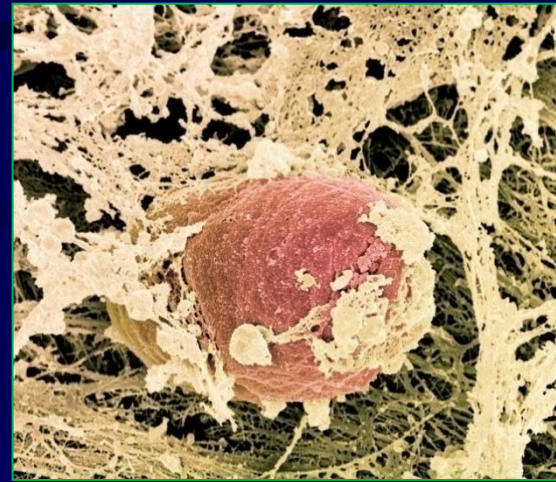
1. Dempster DW. Chapter 2. Anatomy and Functions of the Adult Skeleton. In: Favus M, editor. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 6th ed. 2006:7–11. 2. Seeman E et al. *New Engl J Med* 2006;354:2250–2261.

Osteoclasts and osteoblasts are essential to maintain bone quality and bone mass

Osteoclast



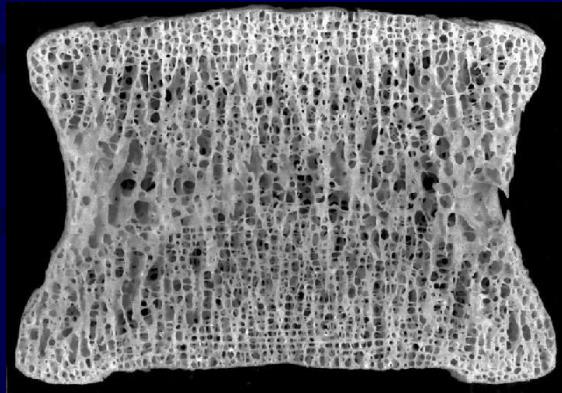
- Osteoclasten resorb old or damaged bone



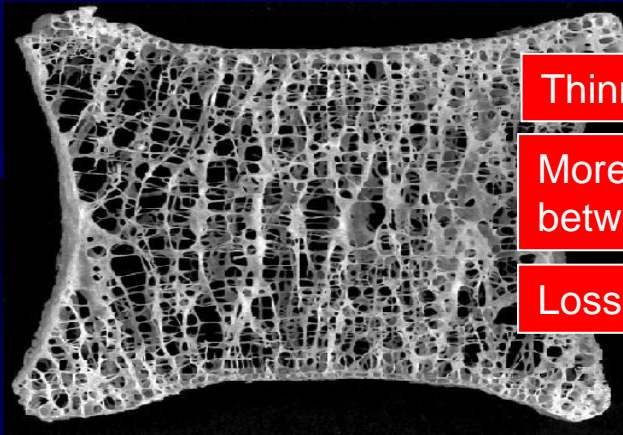
- De osteoblasts form new bone¹

1. Seeman E et al. *New Engl J Med* 2006;354:2250-2261.

Normal bone



Osteoporosis

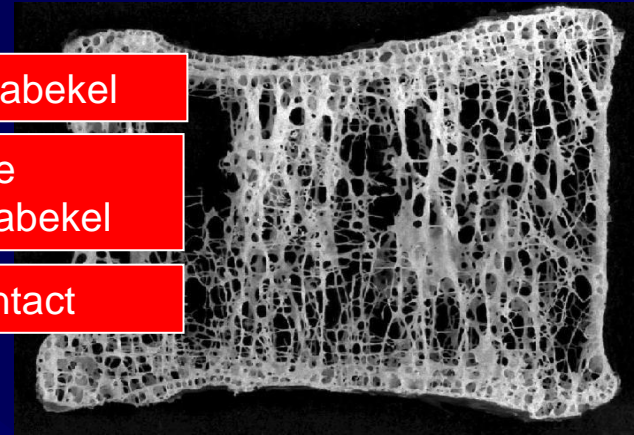


Thinning trabekel

More space
between trabekel

Loss of contact

Severe Osteoporosis

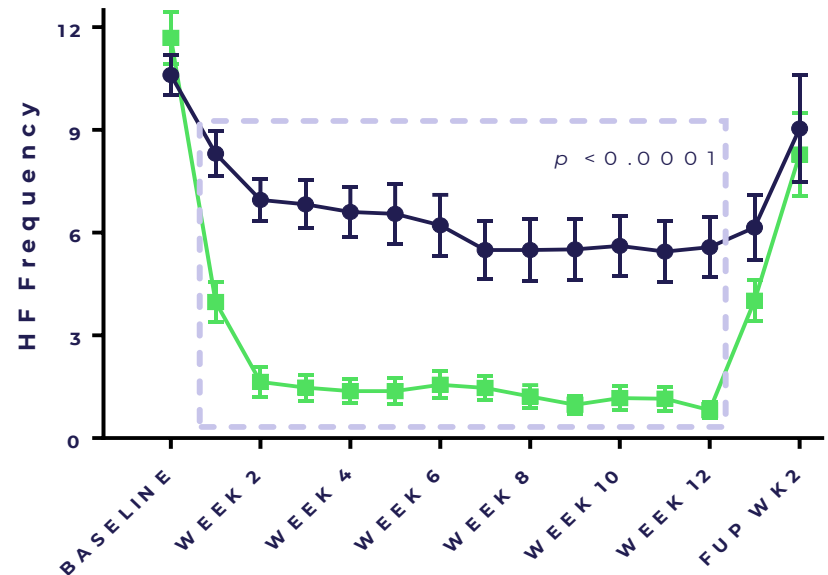
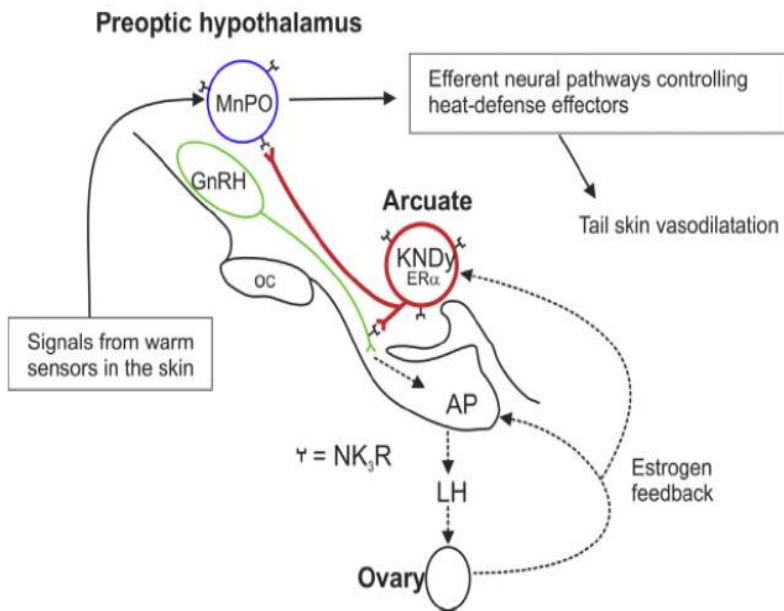


Heupfracturen hebben de hoogste klinische, sociale en economische impact van alle types osteoporotische fracturen^{1,2}

- **Bijna 20% van de patiënten overlijdt binnen het eerste jaar na een heupfractuur¹**
- **> 50% van de voordien mobiele patiënten die een heupfractuur hebben gehad, zal niet in staat zijn om zonder hulp te stappen na 1 jaar³**
- **Alhoewel heupfracturen slechts 14% van alle fracturen uitmaken zijn ze toch verantwoordelijk voor 72% van de kosten als gevolg van fracturen²**



Neurokinine 3 receptor antagonisten: een nieuwe behandeling voor menopauzale warmteopwellingen



Depypere H, Timmerman D, Donders G, et al. Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: A phase 2a trial. *J Clin Endocrinol Metab* 2019;104:5893-5905.

*warmteopwellingen,
slaap- en geheugenstoornissen,
vermoeidheid, concentratiemoeilijkheden, hoofdpijn,
angst, prikkelbaarheid en stemmingswisselingen,
depressieve neiging,
uitdrogingsgevoel van de vagina, opwindingsstoornissen,
pijn bij betrekkingen,
stramheid van de spieren,...*

*Oestrogel/lenzetto met progebel cc of mirena
Progynova 1mg met progebel cc of mirena
Femoston conti/femoston low
Angeliq
activelle*

Een volledige generatie vrouwen heeft door de slechte of foute communicatie over hormoongebruik geen effectieve (hormonale) behandeling gehad voor menopauzale klachten' (JoAnn Pinkerton (executive director of the North American Menopause Society))

'Veel jonge artsen zijn na de publicatie van de WHI-studie in 2002 gestopt met het zich bijscholen over hormonengebruik tijdens de menopauze.'
(Cynthia Stuenkel, interniste en endocrinologe van de Universiteit van Californië).

'Meer dan 50 miljoen Amerikaanse vrouwen zullen ouder zijn dat 51 jaar in 2020'. Desalniettemin is het voor veel vrouwen moeilijk om vandaag een dokter te vinden die voldoende ervaring heeft om hormonen voor te schrijven, laat staan om adequaat menopauzesymptomen te behandelen'
(JoAnn Manson, professor aan Harvard University, VS).

Snel na de menopauze starten

Precutaan of lage dosis oraal

**Titreeren op de kliniek na controle afspraak kort na
initiatie van hormonen**

