ORMONI SESSUALI E REGOLAZIONE DEL BILANCIO REDOX NELL'ANZIANO

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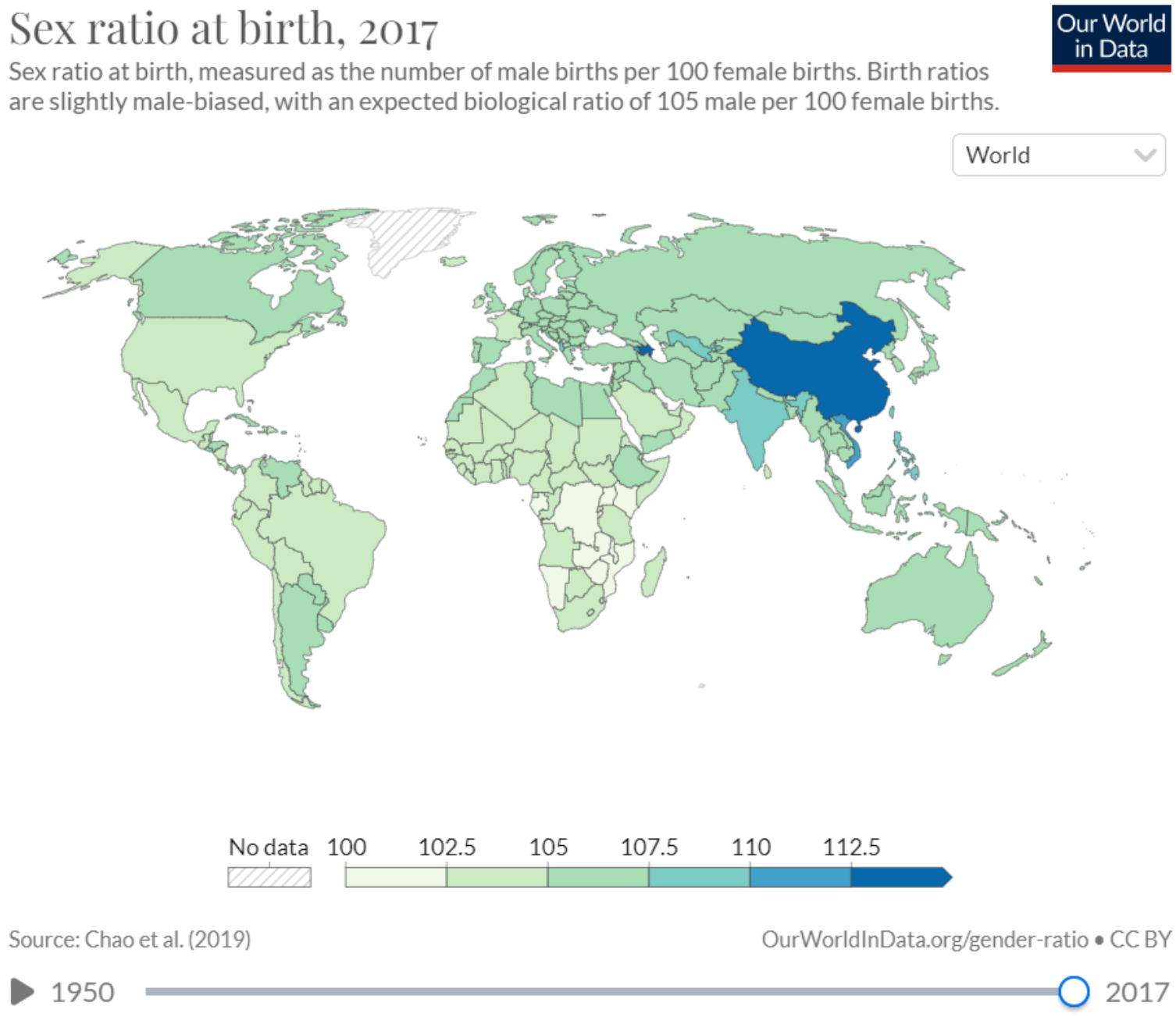
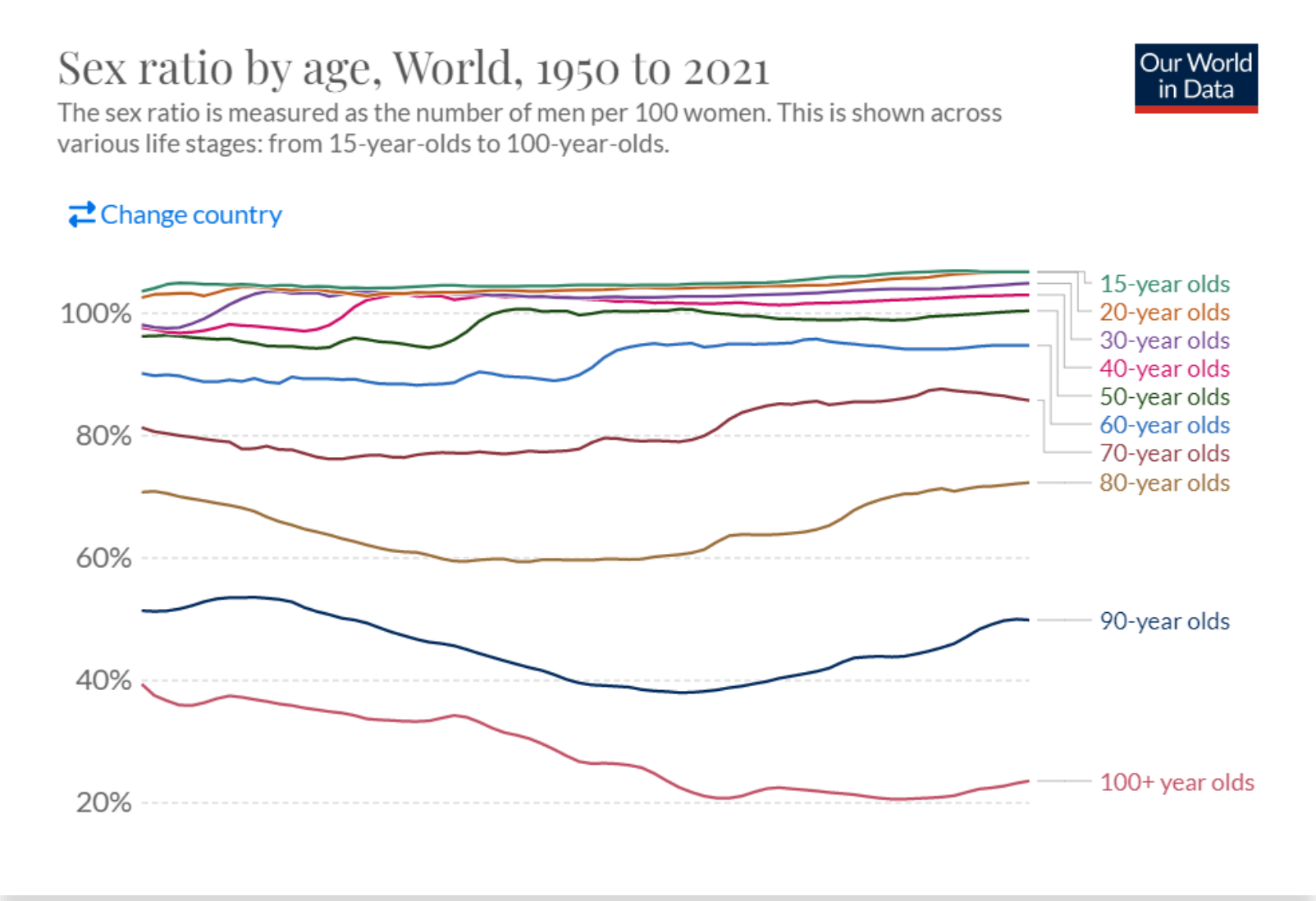
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

AGENDA

1. Maschi contro Femmine: chi vive di più, e perché?
2. Longevità e disparità sessuale: una questione di ormoni?
3. Invecchiamento, ormoni sessuali e bilancio redox
4. Ripristinare l’equilibrio redox nell’anziano: antiossidanti o terapia ormonale sostitutiva?

More men than women are born every year in the World…





…but women get a survival benefit!

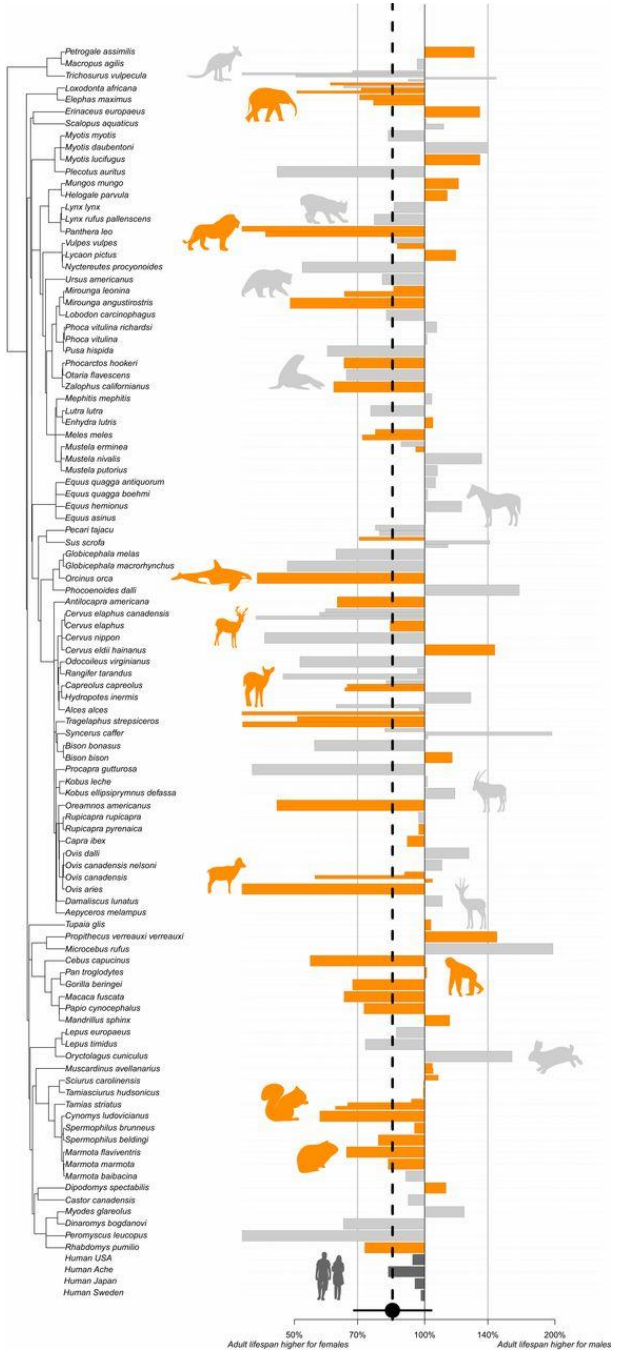
ASPETTATIVA DI VITA

85,2 anni

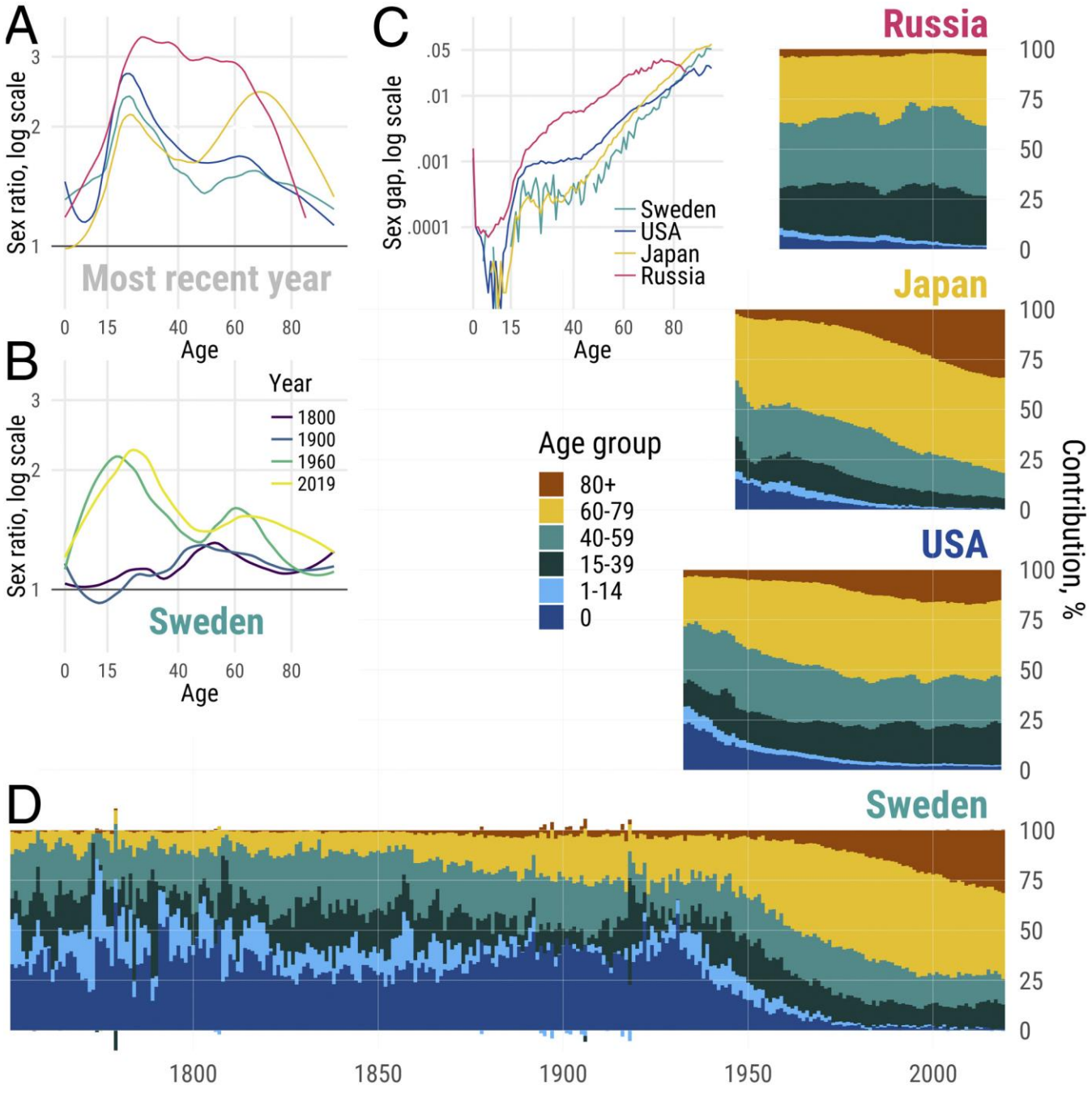
80,8 anni

Fonte ISTAT 2019

Adult lifespan is higher for females

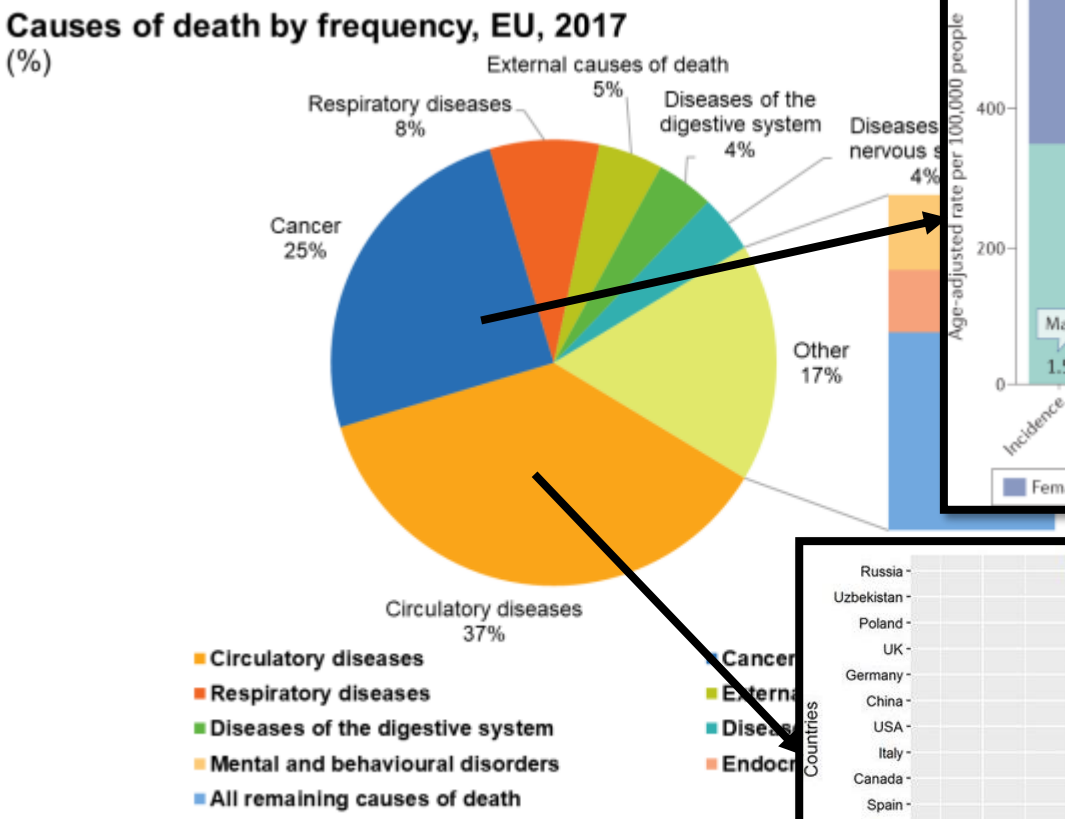


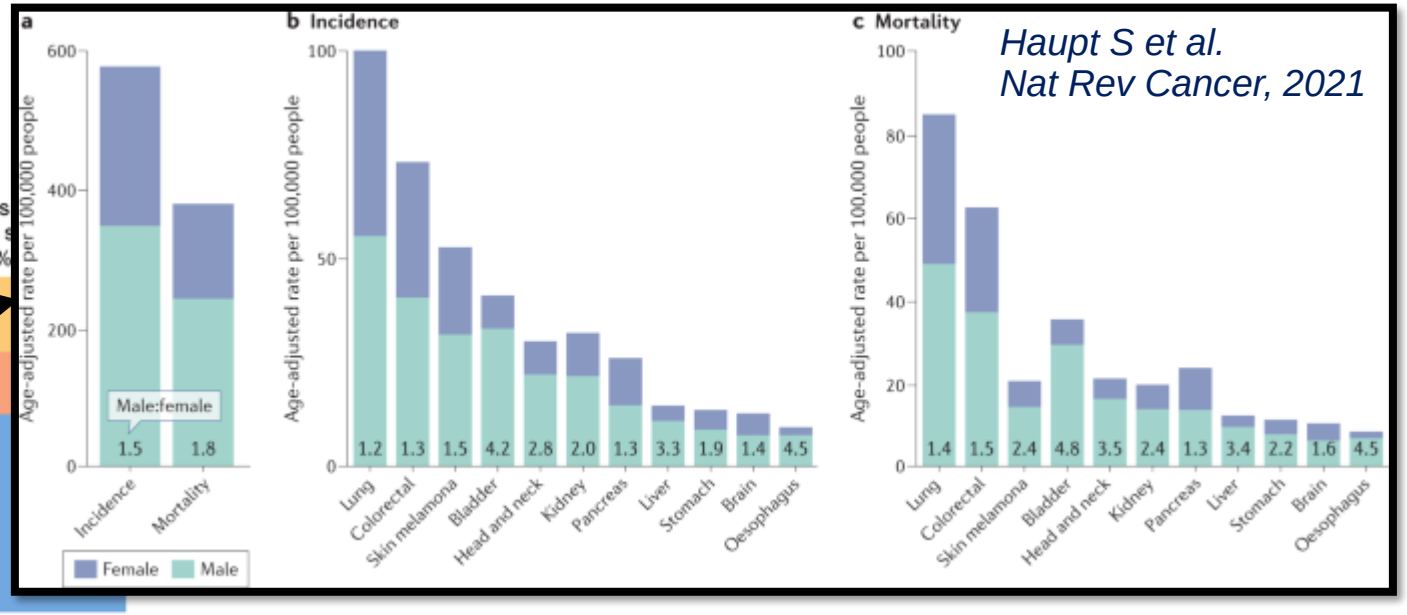
Lemaitre JF et al., PNAS, 2020



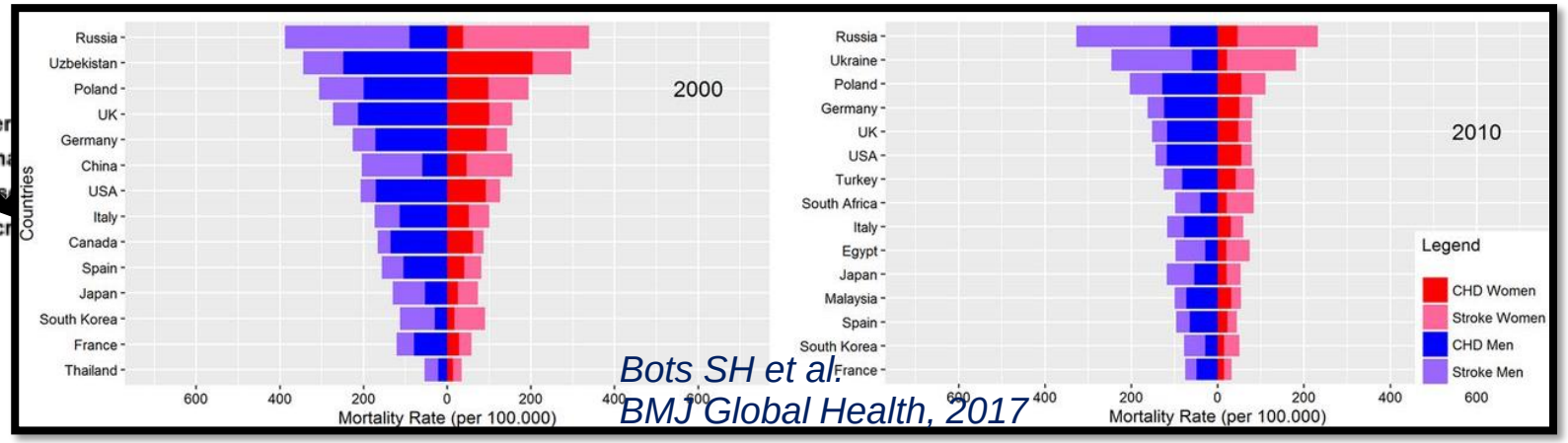
After the early decades of the XX century, the life expectancy gap resulted from higher mortality among men > 60y old

Zarulli V et al., PNAS, 2020



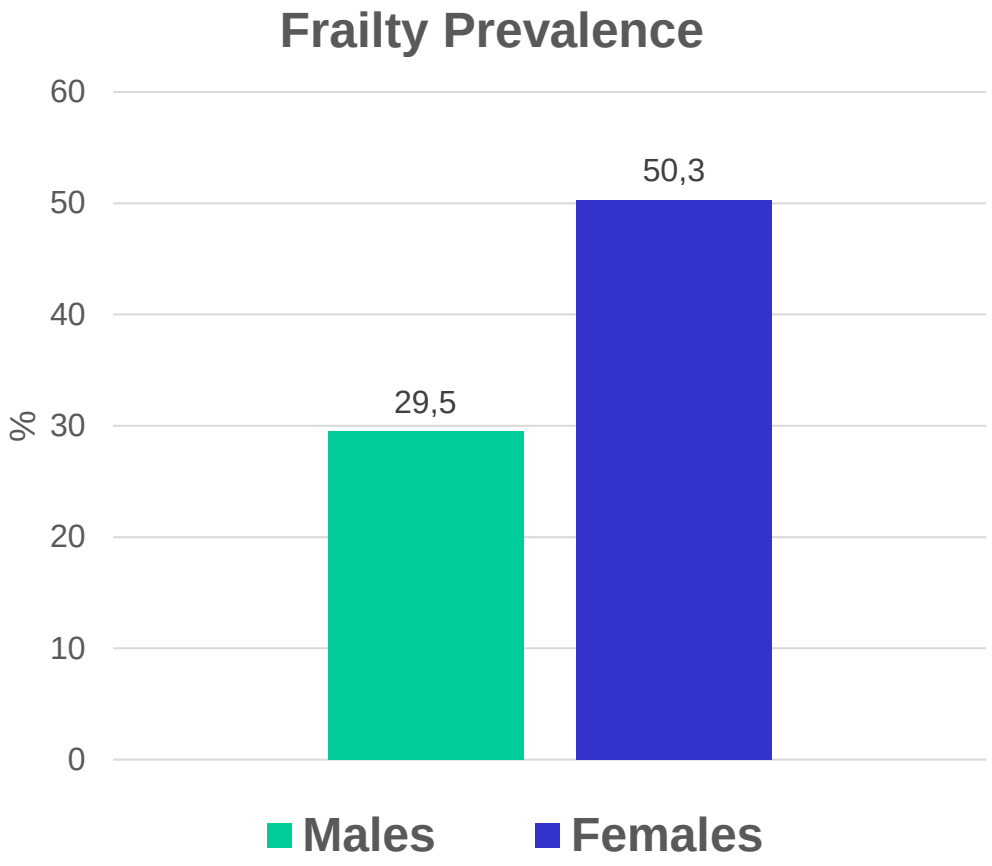


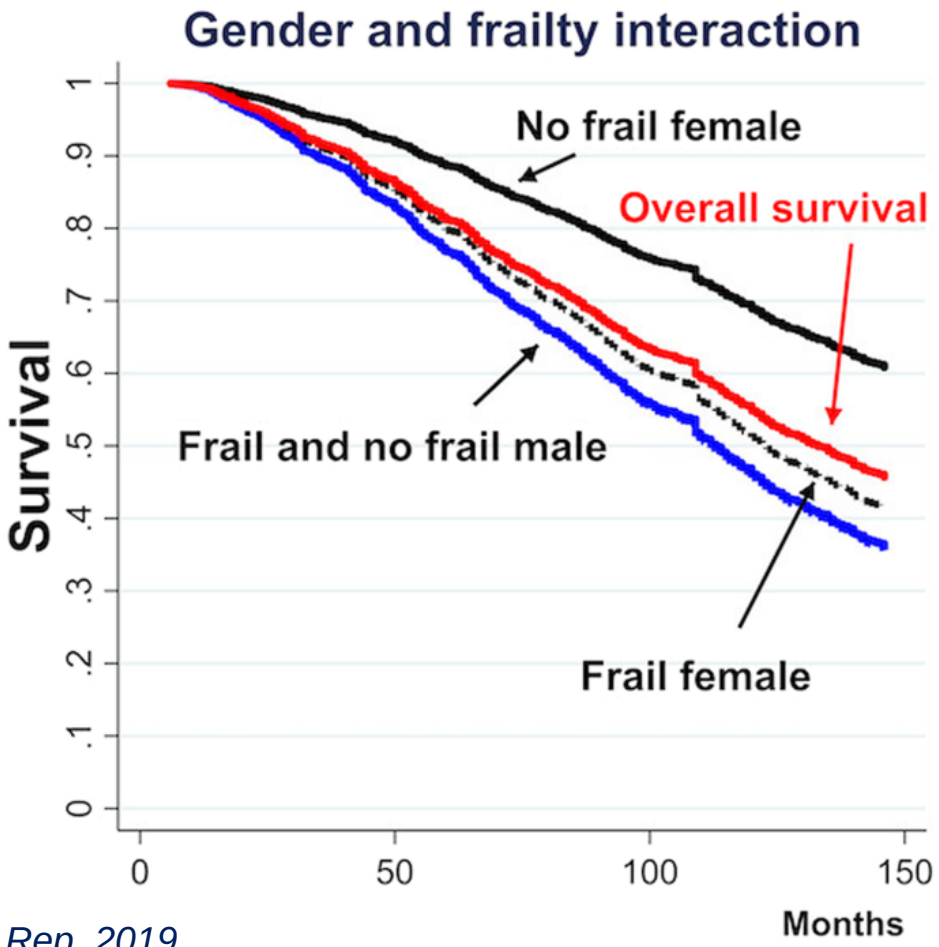
Haupt S et al.
Nat Rev Cancer, 2021



Bots SH et al.
BMJ Global Health, 2017

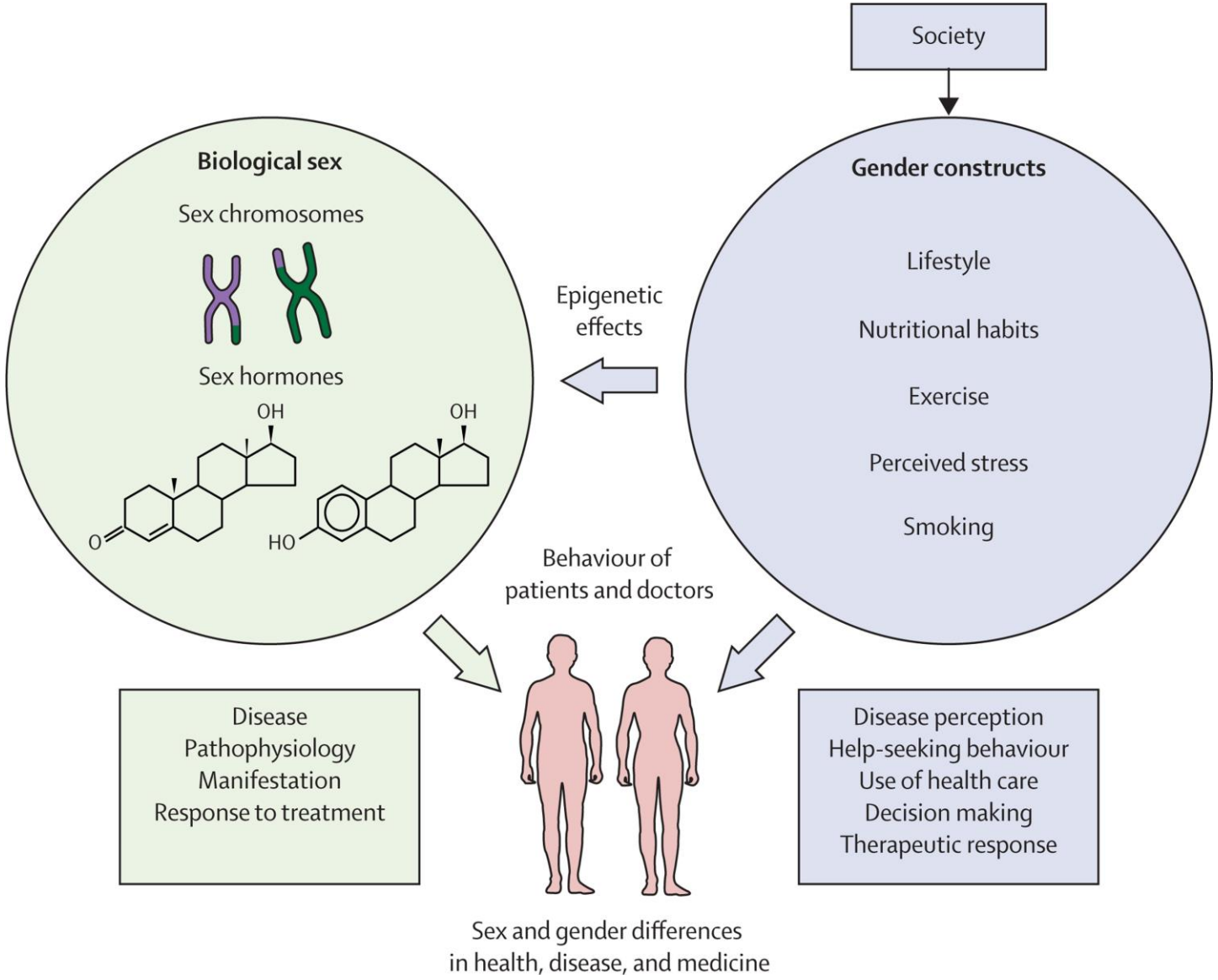
The “frailty paradox”





Corbi G et al., Sci Rep, 2019

The chromosomal theory does not fully explain the biological differences between males and females in survival and aging



Mauvais-Jarvis F et al., Lancet, 2020

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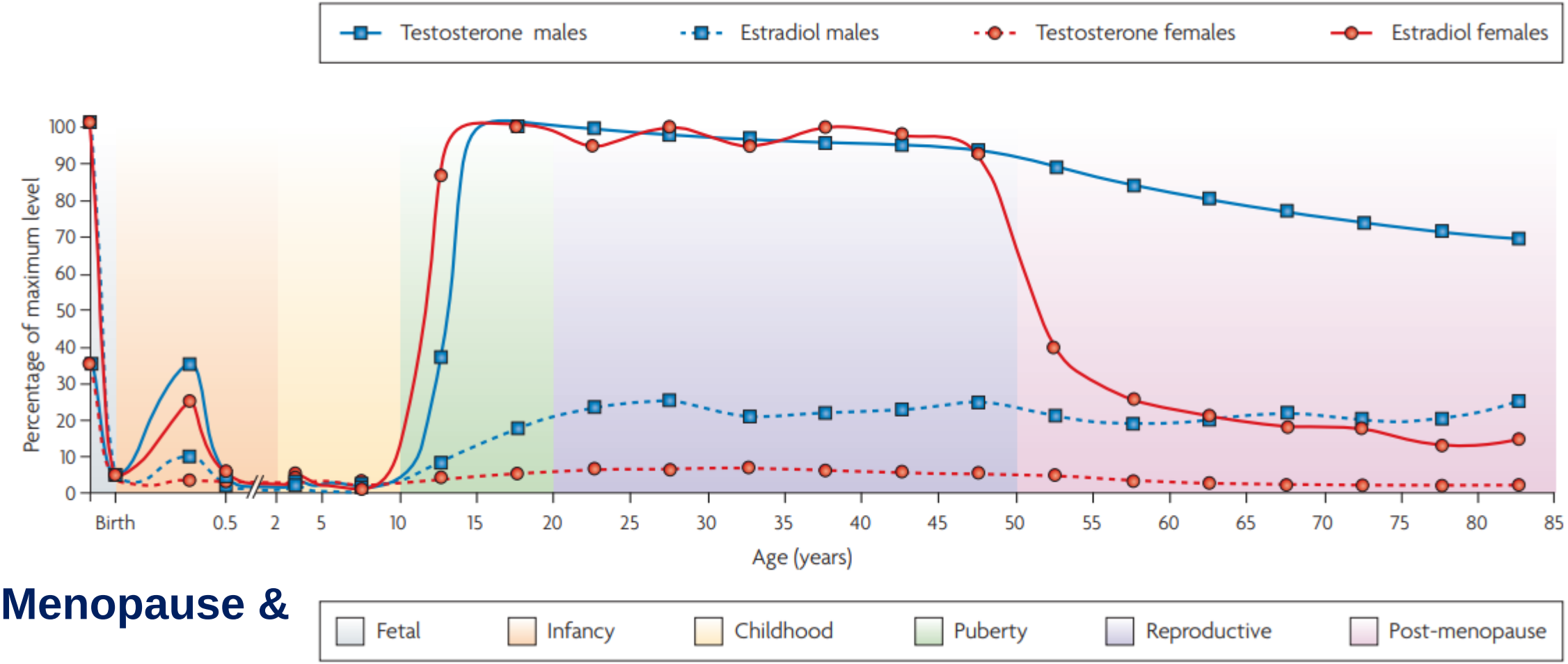
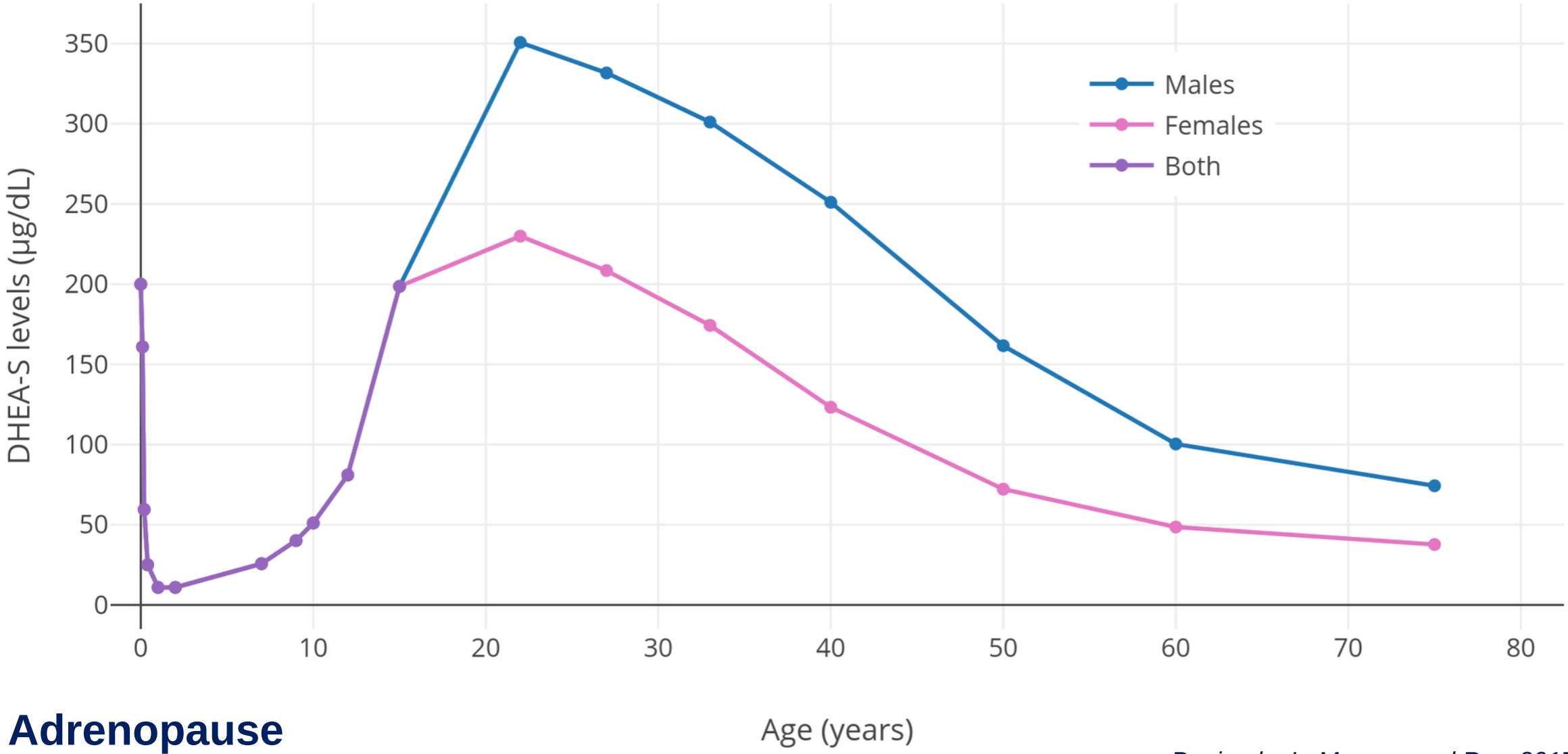


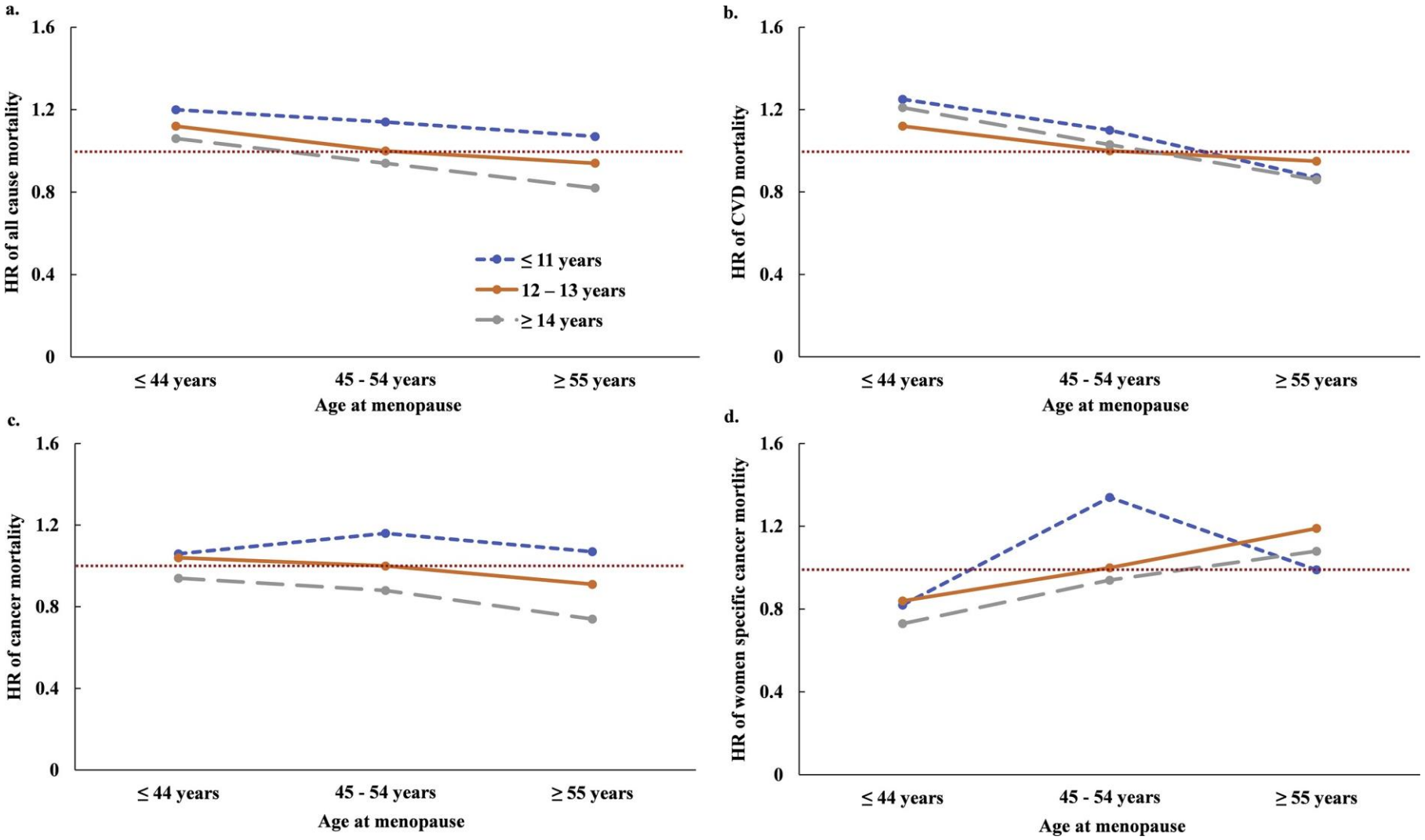
Menopause & Andropause

Ober C et al., Nat Gen, 2008



Adrenopause

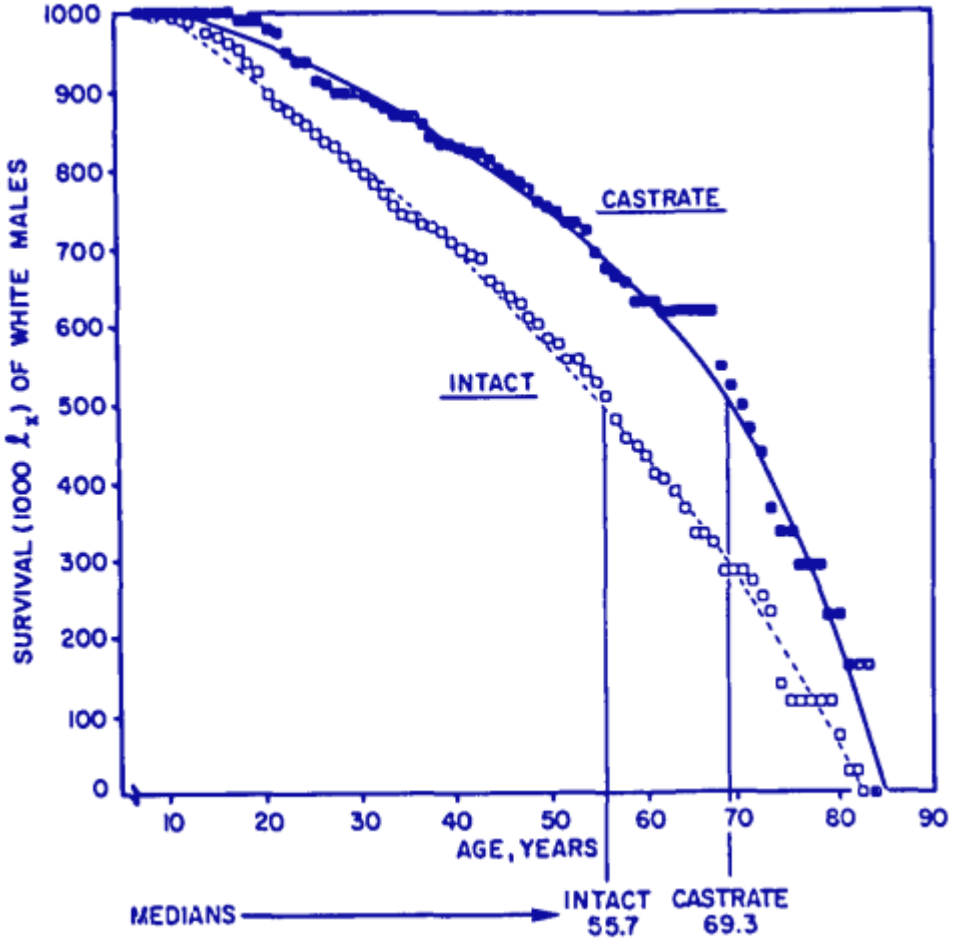
Papierska L, Menupausal Rev, 2017

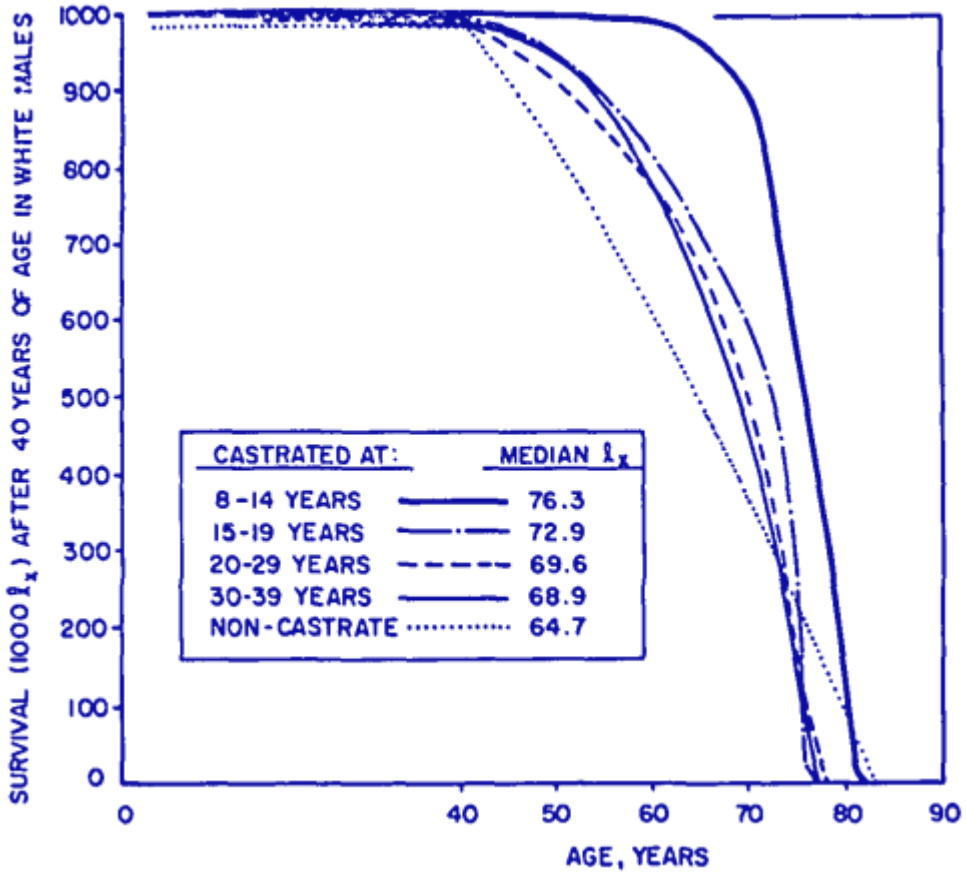


Early menarche and early menopause exert an additive effect on all-cause mortality

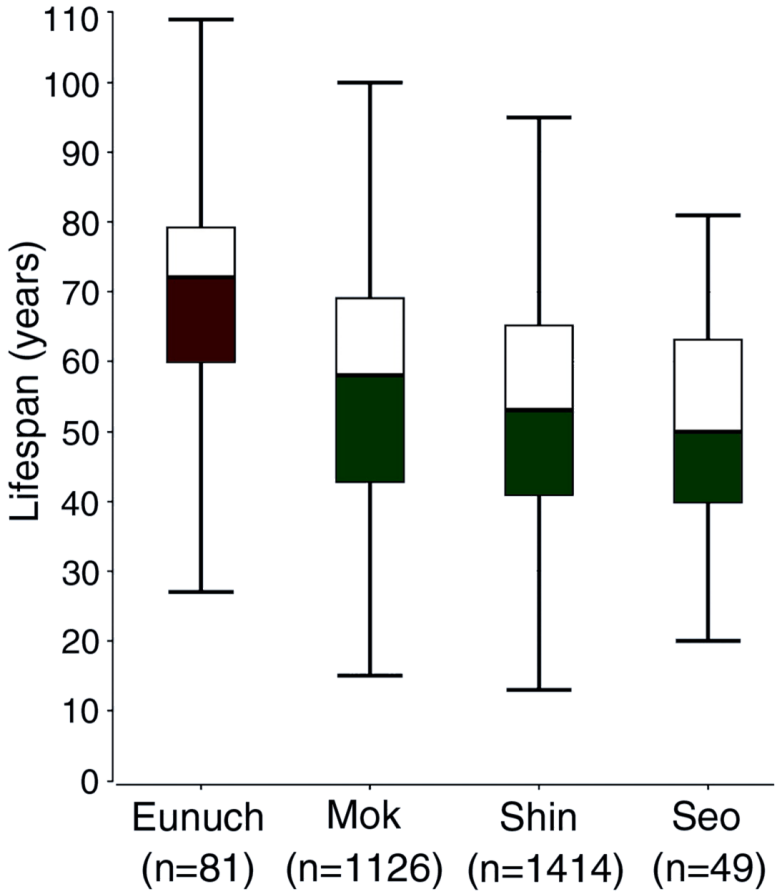
Zhang X et al., Maturitas, 2019

Orchiectomy increases life expectancy





Hamilton JB et al., J Gerontol, 1969



Min KJ et al., Curr Biol, 2012

Table 1
Prospective population-based cohort studies on DHEA/-S and all-cause mortality.

Reference	Cohort age at baseline	Follow-up time[a]	Association with mortality	Comments
Barrett-Connor et al. [5]	Rancho-Bernardo 50–79 yrs *n* = 242 ♂	12 yrs	↑ all-cause and CV mortality with lower DHEA-S (♂)	• No similar association in an extended cohort with 19-yr follow-up [58]
Barrett-Connor et al. [6]	Rancho-Bernardo 60–79 yrs *n* = 289 ♀	12 yrs	↔ (DHEA-S vs all-cause and CV mortality; ♀)	• No association in an extended cohort with 19-yr follow-up [59]
Berr et al. [7]	PAQUID >65 yrs *n* = 266 ♂, 356 ♀	2–4 yrs	↑ all-cause mortality with lower DHEA-S in ♂ ↔ in ♀	• Similar results in 8-yr follow-up [19]
Tilvis et al. [8]	Helsinki Aging Study 75–85 yrs *n* = 150 ♂, 421 ♀	5 yrs	↔ (DHEA-S vs all-cause and CV mortality)	
Trivedi et al. [9]	Cambridge General Practice Study 65–76 yrs *n* = 963 ♂, 1171 ♀	7.4 yrs	↑ all-cause and CV mortality with lower DHEA-S in ♂ ↔ in ♀	• U-shaped trend in ♀
Glei et al. [10]	Taiwanese cohort 54–91 yrs *n* = 963 ♂ + ♀	3 yrs	(↑) all-cause mortality with lower DHEA-S, ♂ + ♀ pooled	• No sex-specific analysis
Maggio et al. [11]	InCHIANTI 65–92 yrs *n* = 410 ♂	6 yrs	↑ all-cause mortality with lower DHEA-S (♂)	
Cappola et al. [12]	Cardiovascular Health Study >65 yrs *n* = 466 ♂, 484 ♀	Up to 17 yrs	↔ (DHEA-S vs all-cause mortality, ♂ and ♂ + ♀ pooled)	• Trajectories, but not baseline levels, of DHEA-S predicted all-cause mortality • U-shaped trend with baseline levels in ♀
Ohlsson et al. [13]	MrOS Study in Sweden 69–81 yrs *n* = 2644 ♂	4.5 yrs	↑ all-cause and CV mortality with lower DHEA and DHEA-S (♂)	• Association with CV, but not cancer mortality • Mass spectrometry-based assays • Similar results with DHEA and DHEA-S
Forti et al. [14]	Conselice Study of Brain Aging >65 yrs *n* = 416 ♂, 504 ♀	8 yrs	↔ (DHEA-S vs all-cause mortality; ♂ = ♀)	
Haring et al. [15]	Framingham 69–81 yrs *n* = 254 ♂	5 and 10 yrs	↔ (DHEA-S vs all-cause and CV mortality; ♂)	• Neither trajectories nor baseline levels of DHEA-S predicted mortality

CV, cardiovascular.
[a] As defined by the authors.

Ohlsson C et al., J Steroid Biochem Mol Biol, 2015

There is an association between low DHEA/-S and risk of death, at least in elderly men

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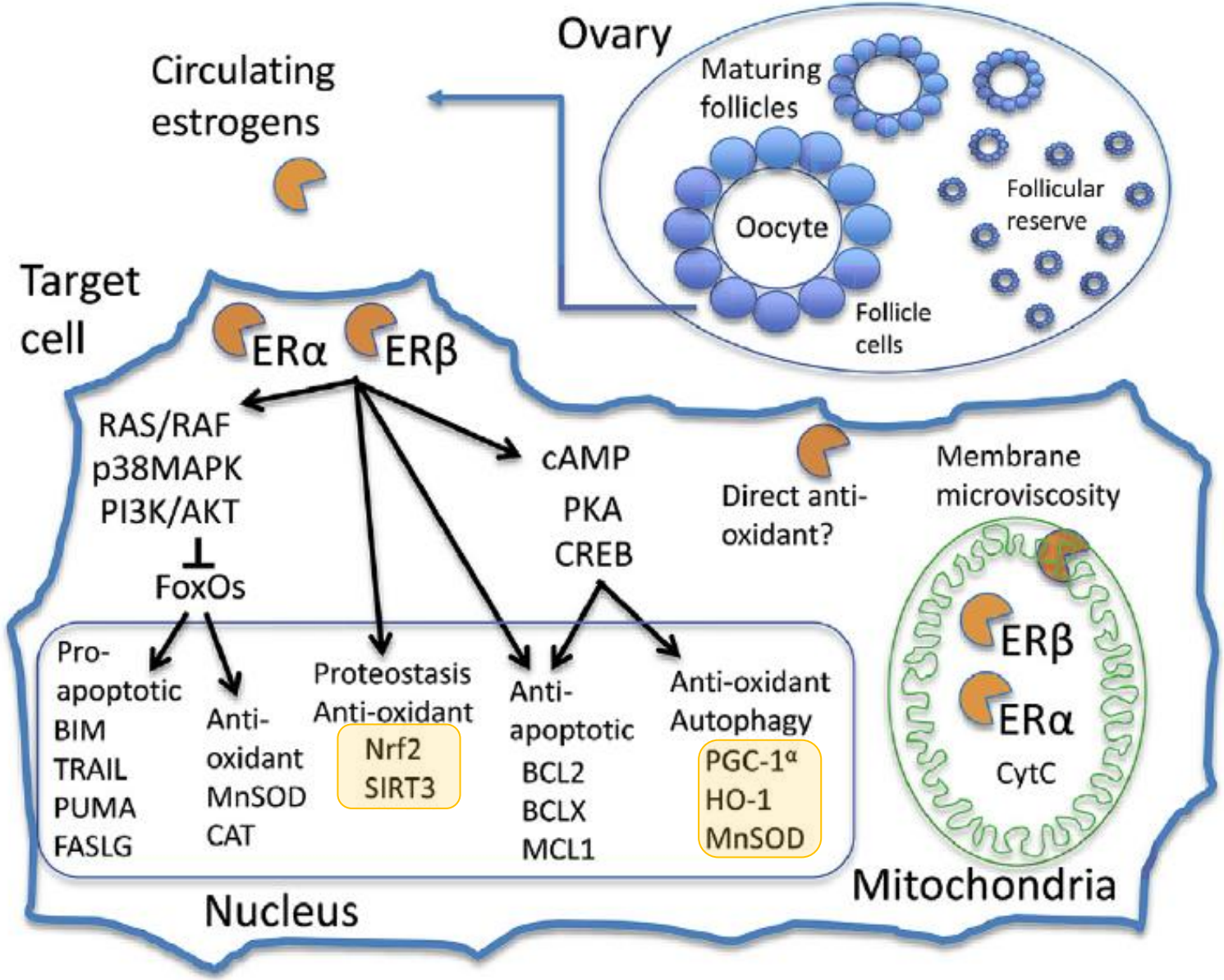
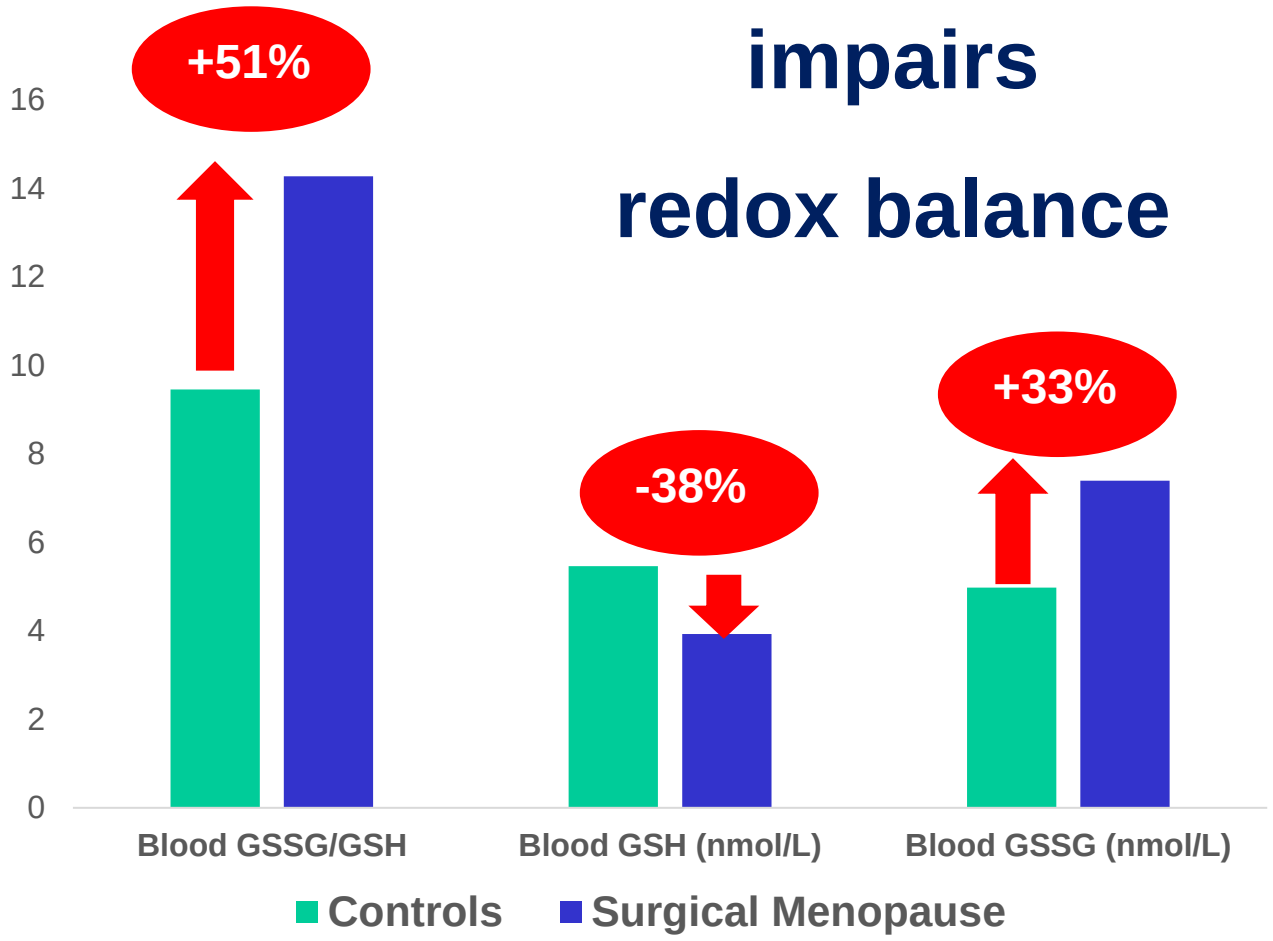
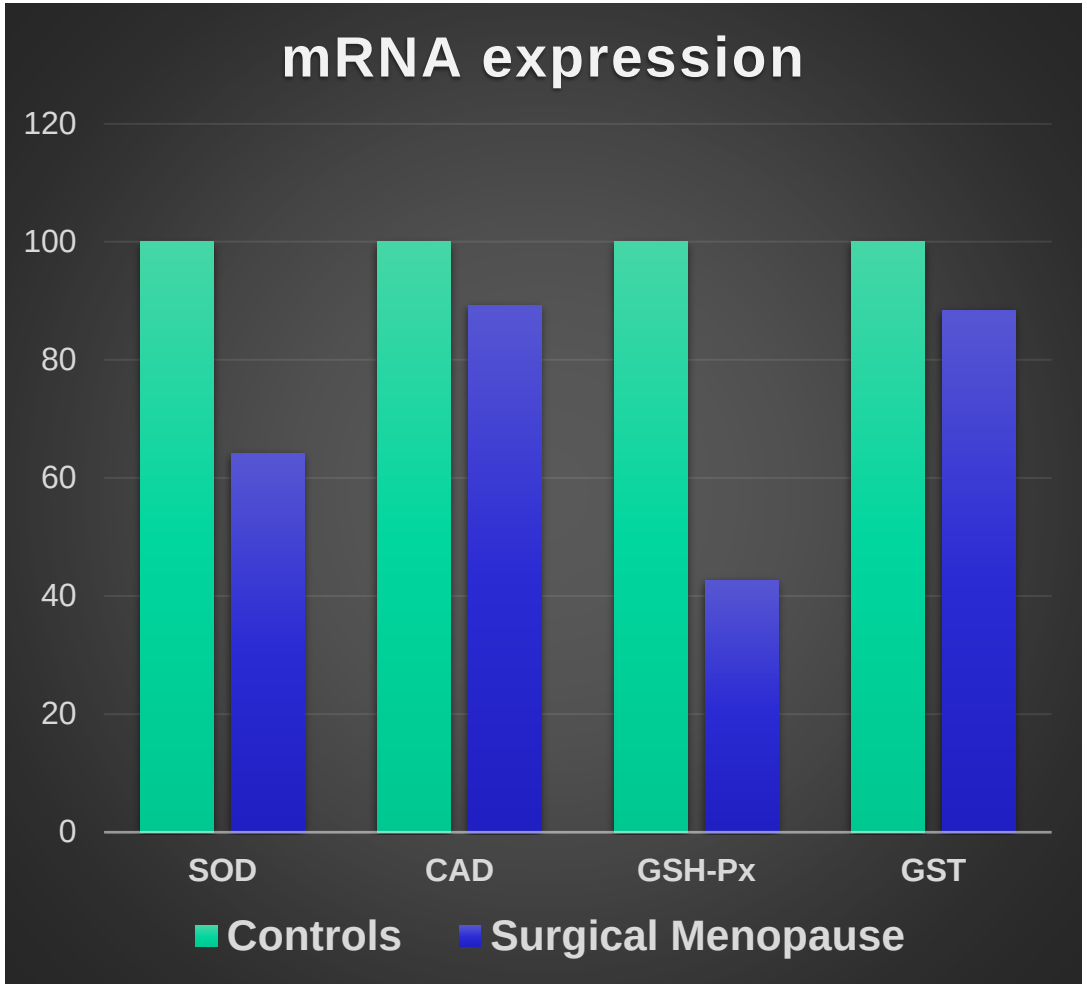
Estrogens exert cytoprotective and antioxidant effects



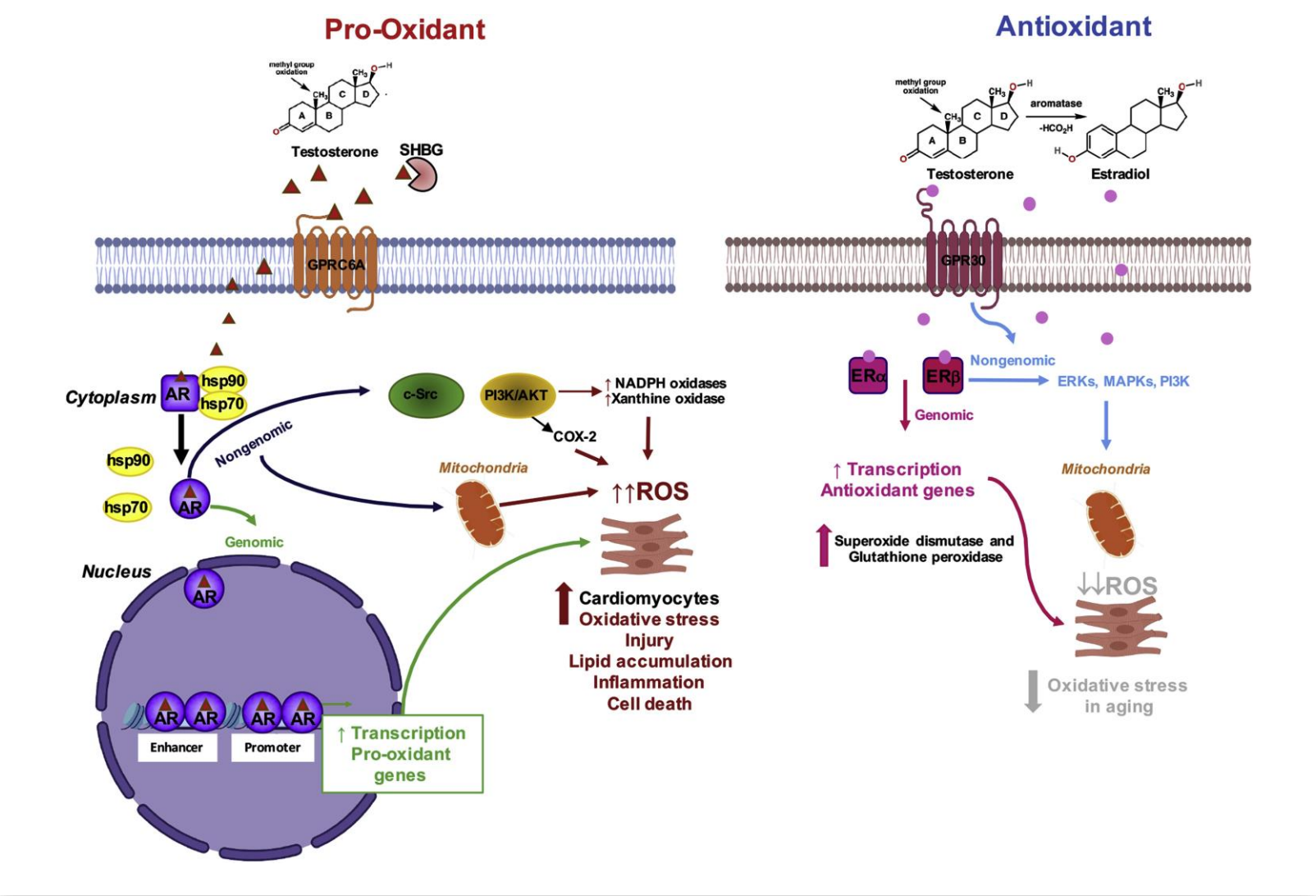
Tower J et al., Redox Biol, 2020

Oophorectomy impairs redox balance





Bellanti F et al., Redox Biol, 2013



The pro-oxidant effect of testosterone

Cruz-Topete D et al., Redox Biol, 2020

DHEA

ANTI AGING
ANTIOXIDANT

200 Count
300MG

GOOD MANUFACTURING PRACTICES GMP

SATISFACTION GUARANTEED 100% SATISFACTION GUARENTEED

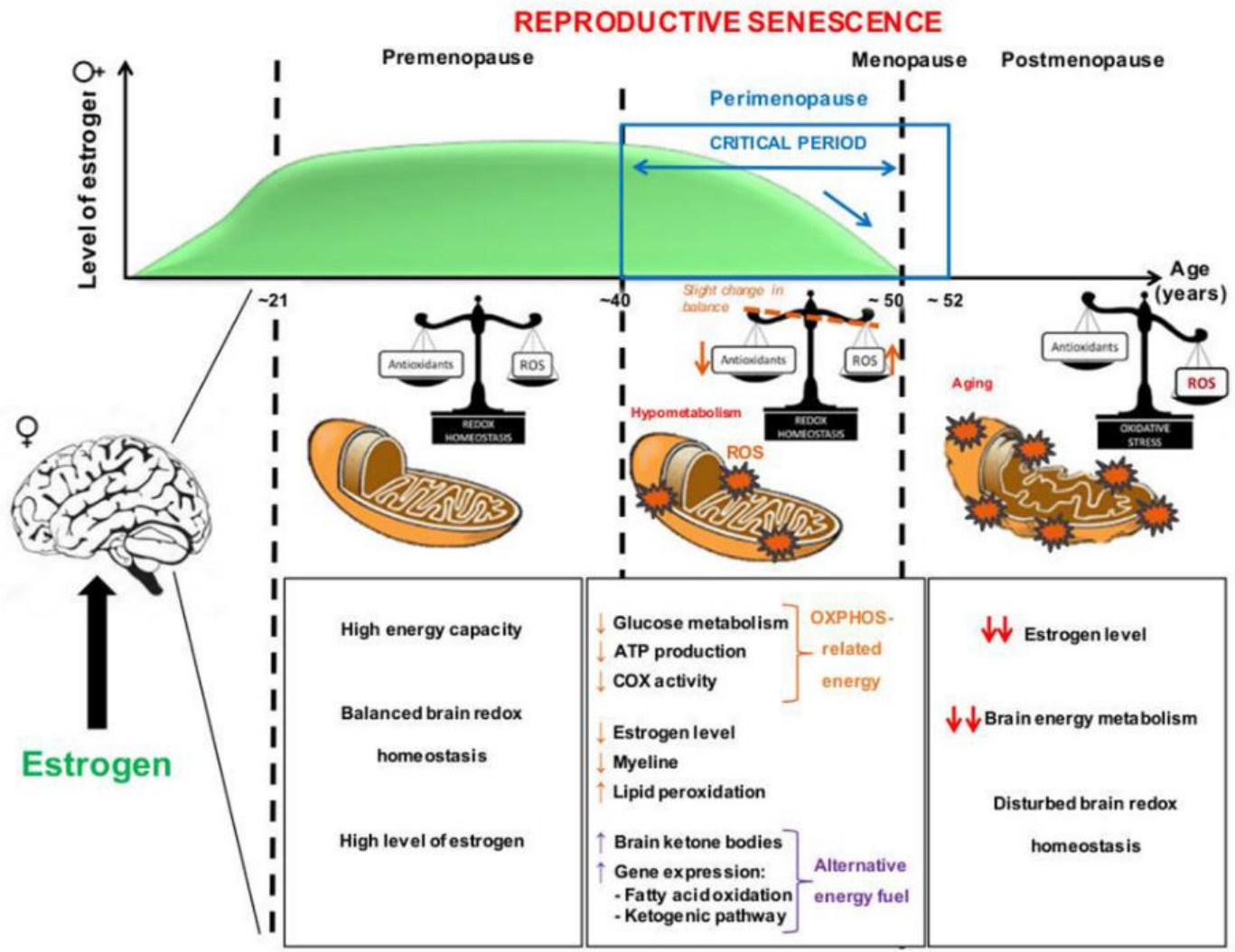
MADE IN U.S.A

TOP 5 BENEFITS OF NATURE'S LAB™ DHEA

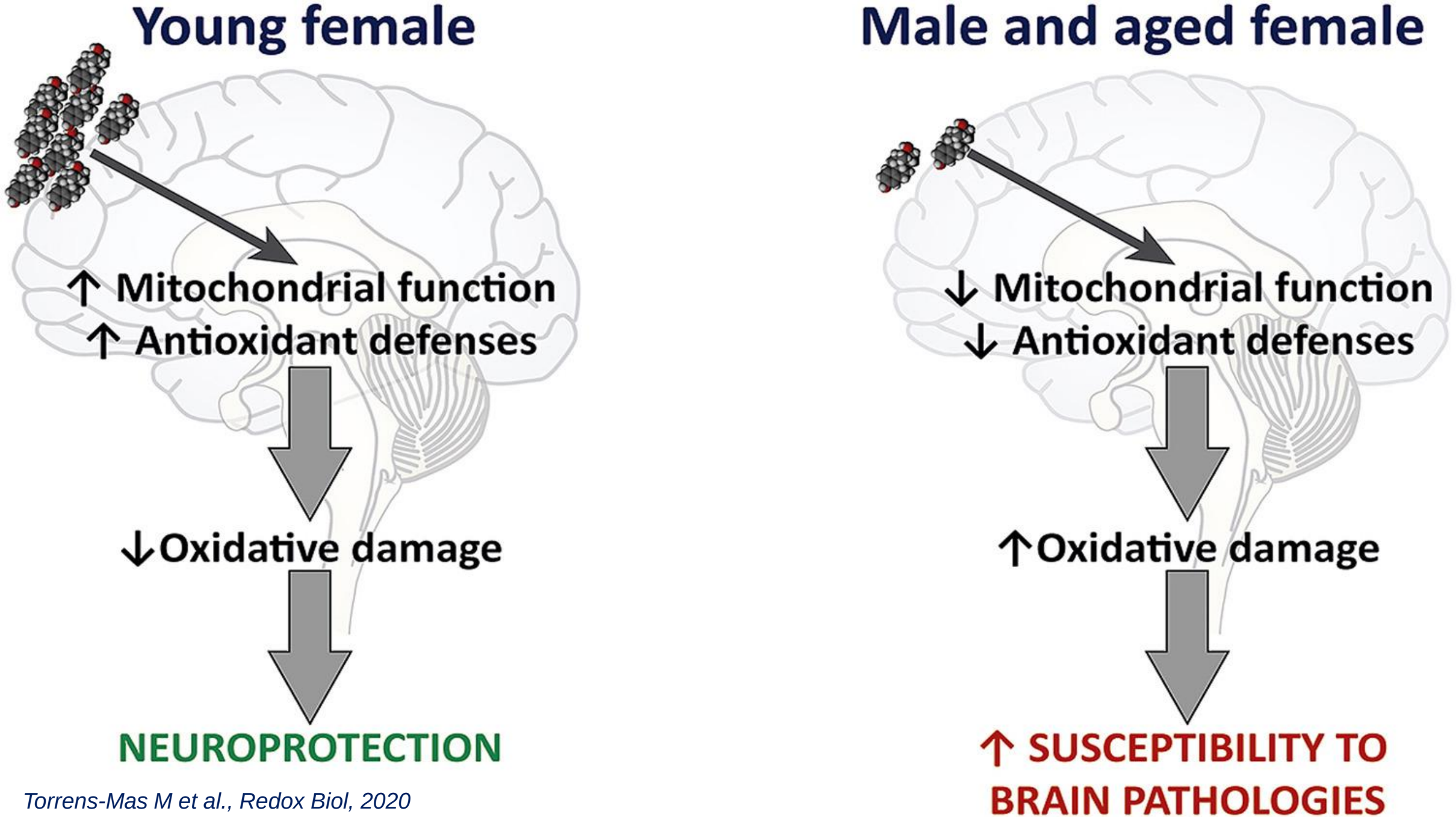
- ✓ Powerful antioxidant†
- ✓ Hormone regulator †
- ✓ Supports cholesterol health†
- ✓ Supports immune system†
- ✓ Increases the sensitivity of cells to insulin†

† These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Estrogen-dependent downregulation of antioxidant enzymes and mitochondria may contribute to neurodegeneration in aged women

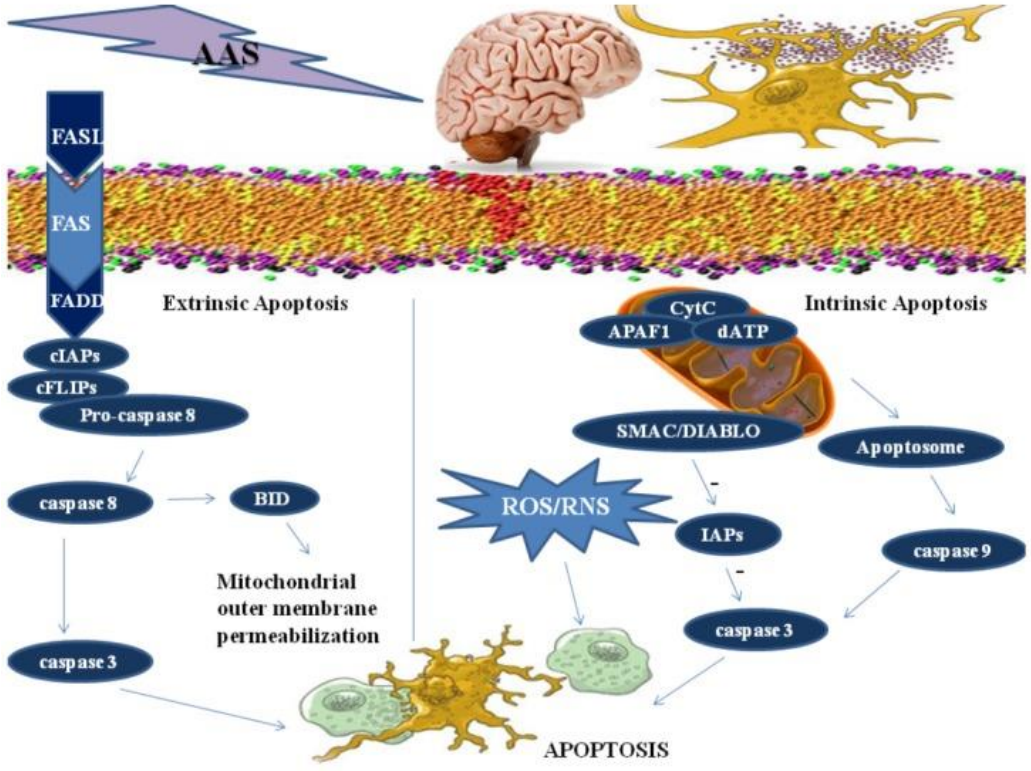


Lejri I et al., Front Aging Neurosci, 2018

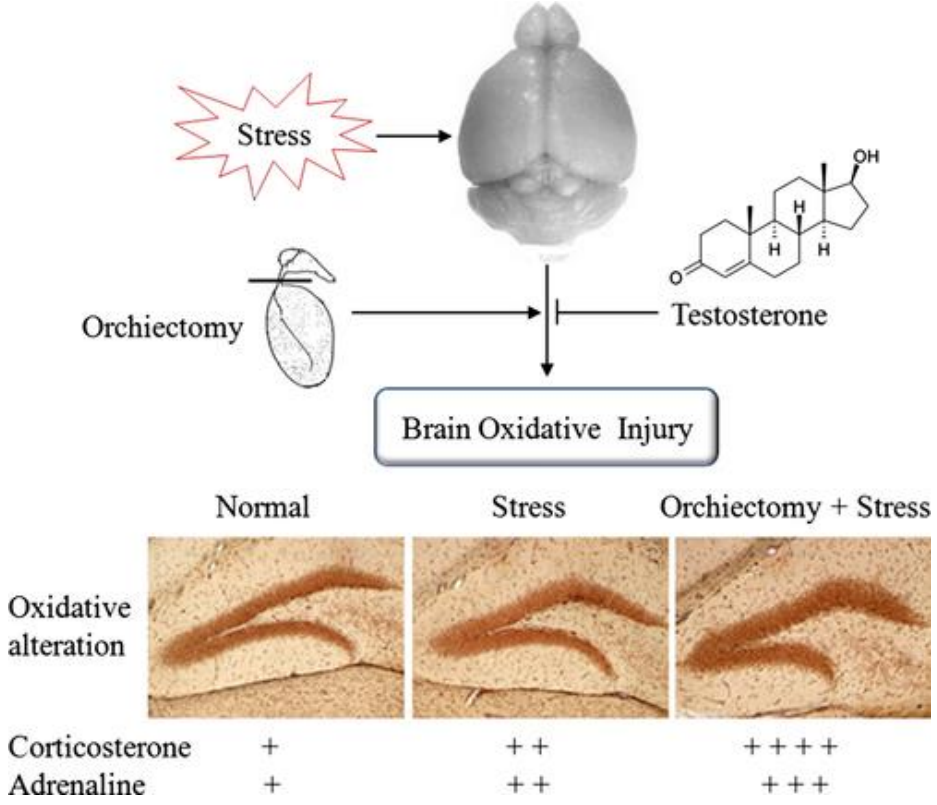


Torrens-Mas M et al., Redox Biol, 2020

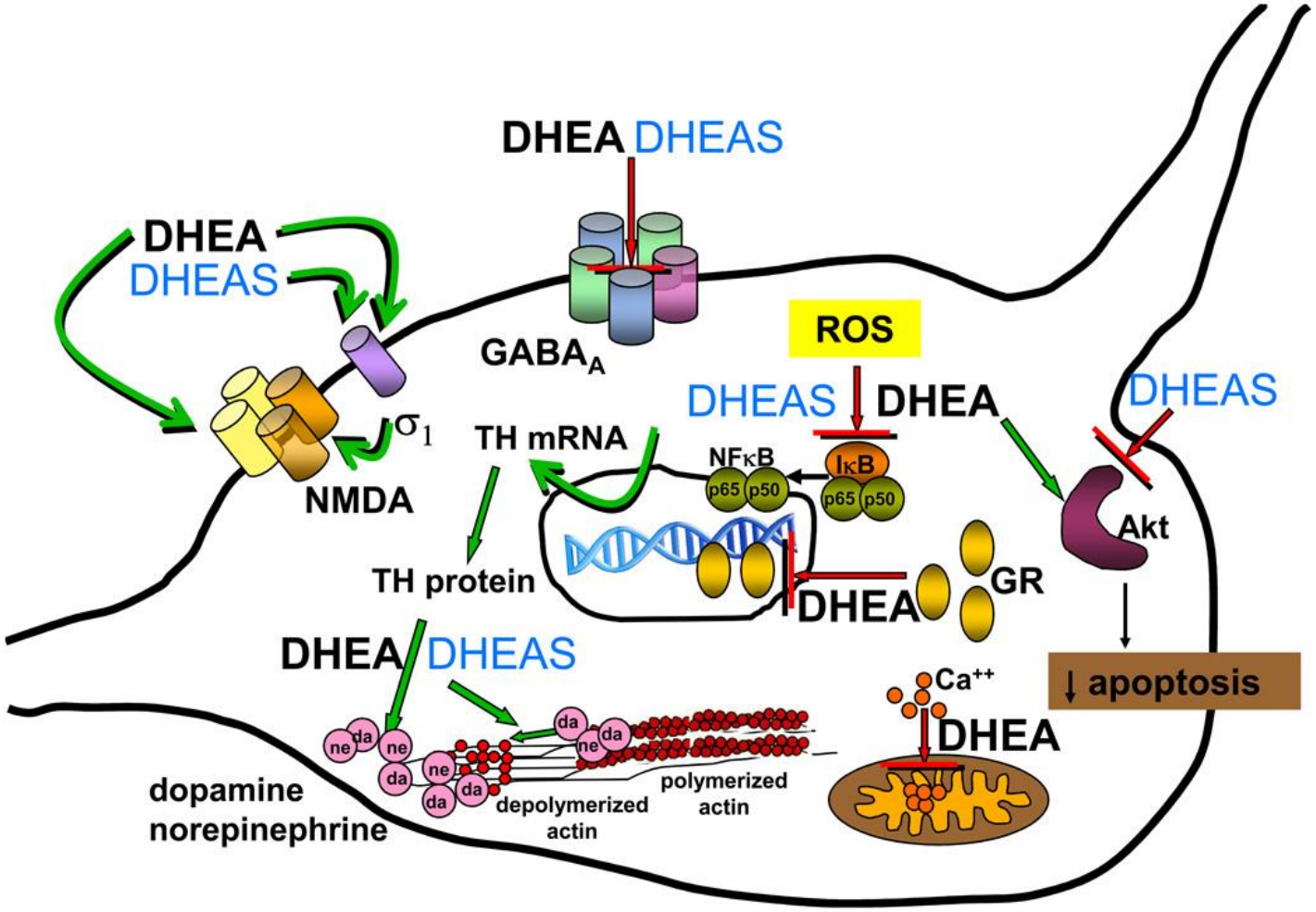
What is the contribution of testosterone in neurodegeneration?



Pomara C et al., Curr Neuropharmacol, 2015



Son SW et al., J Neurochem, 2015



DHEA and DEAHS exert neuroprotective and antioxidant effects in the brain

Maninger N et al., Front Neuroendocrinol, 2008

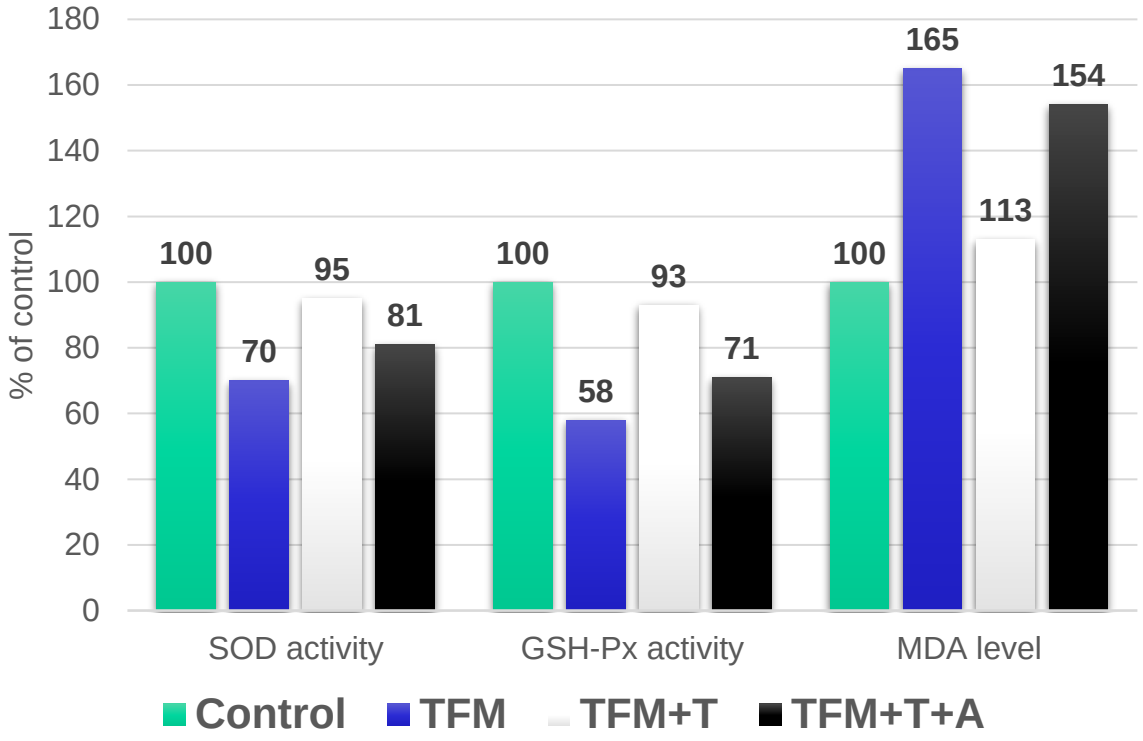
Expression of antioxidant enzymes (SOD, CAT, GR, GPx, GST)

	Males	Females
Myocardium	↓	↑
Endothelial cells	↓	↑
Smooth muscle cells	↓	↑

Estrogen could explain the lower levels of cardiac oxidative stress observed in females

Cruz-Topete D et al., Redox Biol, 2020

Testosterone retards cardiomyocyte aging via AR-independent pathway



Zhang L et al., Chin Med Sci J, 2013

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Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention

Systematic Review and Meta-analysis

Data Extraction We included 68 randomized trials with 232 606 participants (385 publications).

Conclusions Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.

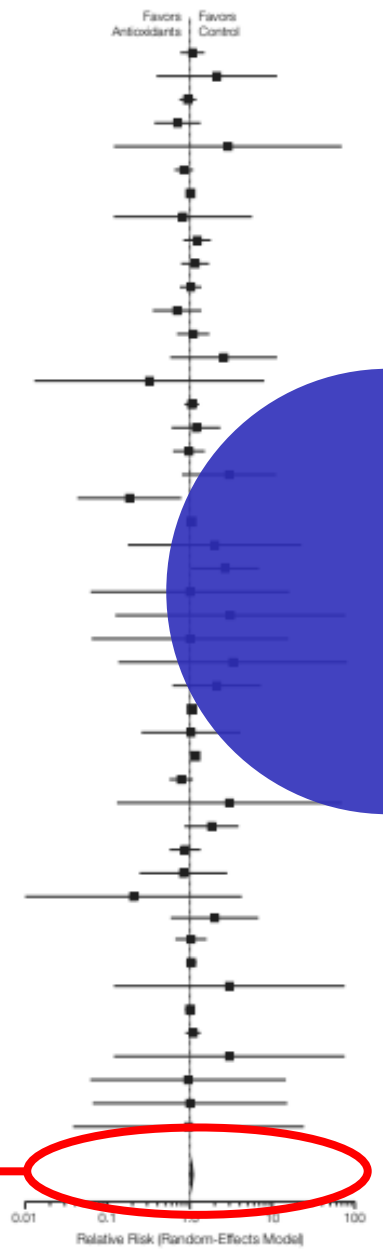
JAMA. 2007;297:842-857 www.jama.com

Figure 2. Intervention Effect of Antioxidant Supplements vs Placebo on Mortality in Trials With Low Risk of Bias

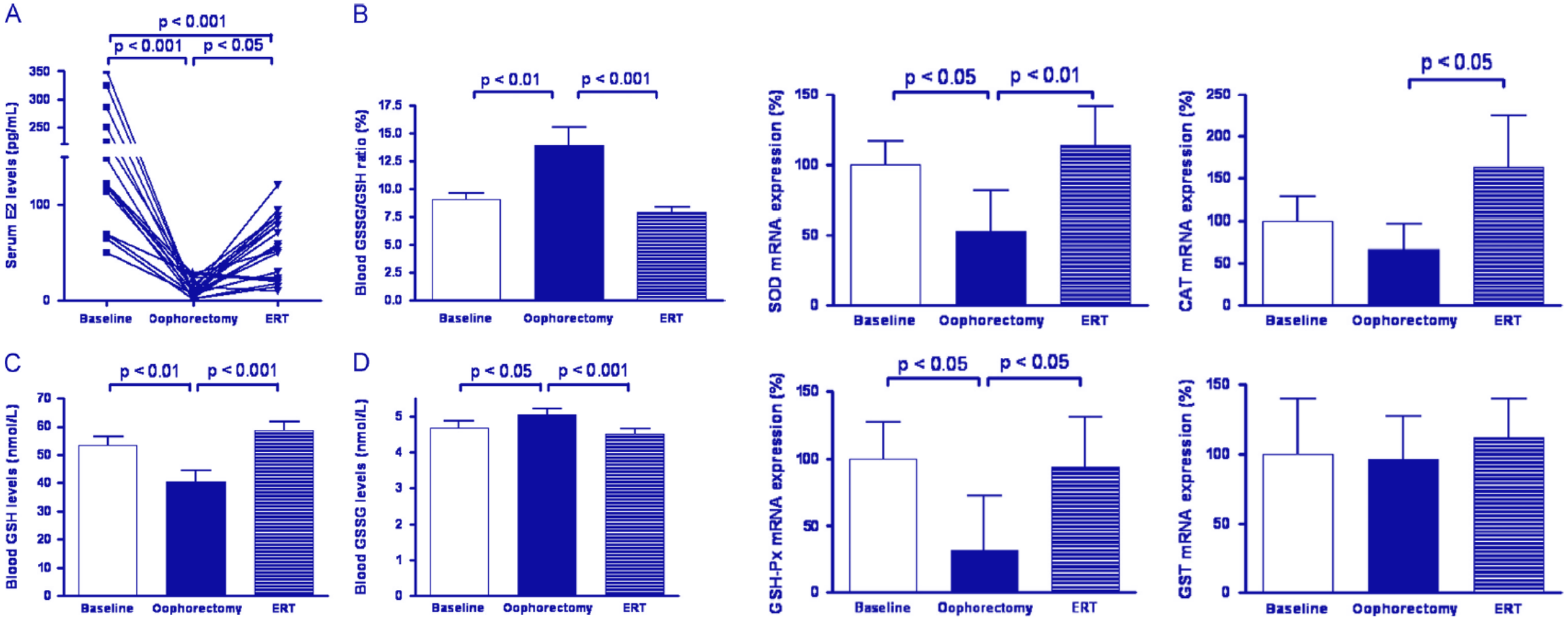
Source	Mortality: Antioxidants, No./Total	Mortality: Control, No./Total	Relative Risk (Random-Effects Model) (95% CI)
Greenberg et al,[37] 1990	79/913	72/892	1.07 (0.79-1.46)
Murphy et al,[40] 1992	4/53	2/56	2.11 (0.40-11.06)
Li et al,[42] 1993	157/1657	167/1661	0.94 (0.77-1.16)
Greenberg et al,[44] 1994	30/850	14/214	0.71 (0.38-1.31)
Pike et al,[45] 1995	1/24	0/23	2.88 (0.12-67.29)
Clark et al,[48] 1996	108/653	129/659	0.84 (0.67-1.07)
Hennekens et al,[50] 1996	979/11036	968/11035	1.01 (0.93-1.10)
Richer,[52] 1996	2/39	2/32	0.82 (0.12-5.50)
Stephens et al,[53] 1996	68/1035	52/967	1.22 (0.86-1.73)
Moon et al,[55] 1997	62/1157	53/1140	1.15 (0.81-1.65)
Girodon et al,[58] 1999	155/543	51/182	1.02 (0.78-1.33)
Green et al,[60] 1999	15/801	22/820	0.70 (0.36-1.34)
Boaz et al,[61] 2000	31/97	29/99	1.09 (0.72-1.66)
Correa et al,[62] 2000	16/739	2/237	2.57 (0.59-11.08)
Jacobson et al,[63] 2000	0/57	1/55	0.32 (0.01-7.74)
AREDS,[64] 2001	251/2370	240/2387	1.05 (0.89-1.25)
Brown et al,[65] 2001	17/84	13/76	1.18 (0.62-2.27)
Desmuelle et al,[66] 2001	34/144	35/144	0.97 (0.64-1.47)
Chylack et al,[71] 2002	9/149	3/148	2.98 (0.82-10.79)
Graat et al,[72] 2002	3/499	5/153	0.18 (0.04-0.76)
Heart Protection Study,[73] 2002	1446/10269	1389/10267	1.04 (0.97-1.11)
Hodis et al,[74] 2002	2/177	1/176	1.99 (0.18-21.73)
Waters et al,[75] 2002	16/212	6/211	2.65 (1.06-6.65)
White et al,[76] 2002	1/50	1/50	1.00 (0.06-15.55)
Wluka et al,[77] 2002	1/67	0/69	3.09 (0.13-74.50)
Collins et al,[78] 2003	1/26	1/26	1.00 (0.07-15.15)
Prince et al,[79] 2003	1/29	0/32	3.30 (0.14-77.95)
Salonen et al,[80] 2003	19/390	3/130	2.11 (0.63-7.02)
Virtamo et al,[83] 2003	8226/21846	2605/7287	1.05 (1.02-1.09)
Allsup et al,[84] 2004	4/81	4/83	1.02 (0.27-3.96)
Goodman et al,[85] 2004	1855/9420	1509/8894	1.16 (1.09-1.23)
Hercberg et al,[86] 2004	76/6481	98/6536	0.78 (0.58-1.05)
Manuel-y-Keenoy et al,[87] 2004	1/12	0/12	3.00 (0.13-67.06)
McNeil et al,[88] 2004	20/595	11/598	1.83 (0.88-3.78)
Meydani et al,[89] 2004	39/311	44/306	0.87 (0.58-1.30)
Mosey et al,[90] 2004	4/25	5/26	0.83 (0.25-2.75)
Richer et al,[91] 2004	0/30	2/31	0.21 (0.01-4.13)
Avenell et al,[92] 2005	8/456	4/454	1.99 (0.60-6.57)
Graf et al,[93] 2005	31/83	28/77	1.03 (0.68-1.54)
Lee et al,[94] 2005	636/19937	615/19939	1.03 (0.93-1.15)
Limburg et al,[95] 2005	1/180	0/180	3.00 (0.12-73.16)
Lonn et al,[96] 2005	799/4761	801/4780	1.00 (0.92-1.10)
Marras et al,[97] 2005	154/399	142/401	1.09 (0.91-1.31)
Mooney et al,[98] 2005	1/142	0/142	3.00 (0.12-73.03)
Tam et al,[100] 2005	1/20	1/19	0.95 (0.06-14.13)
Witte et al,[101] 2005	1/16	1/16	1.00 (0.07-14.64)
Rayman et al,[102] 2006	1/380	0/121	0.96 (0.04-23.43)
Overall	[illegible]	[illegible]	[illegible]

Test for Heterogeneity: $\chi^2_{44} = 49.47$; $P = .34$; $I^2 = 7.0\%$

Test for Overall Effect: $Z = 3.06$; $P = .002$



Estrogen Replacement Therapy restores redox balance



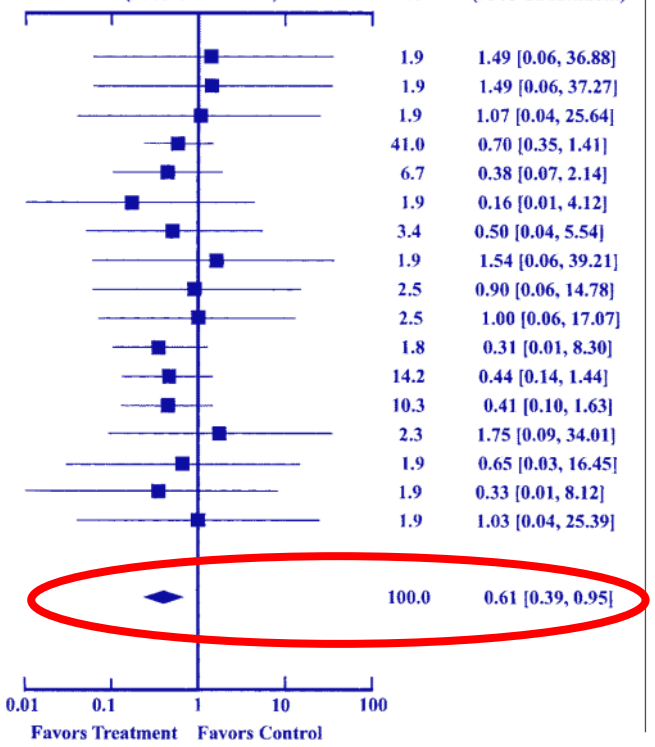
Bellanti F et al., Redox Biol, 2013

Estrogen Replacement Therapy reduces mortality in younger women

Mean age < 60 years
Hormone replacement and total mortality

Study	Treatment n/N	Control n/N	Weight %	Odds Ratio (95% CI Random)
Angerer 2000	1 / 215	0 / 106	1.9	1.49 [0.06, 36.88]
Arrenbrecht 2002	1 / 108	0 / 53	1.9	1.49 [0.06, 37.27]
Giske 2002	1 / 123	0 / 43	1.9	1.07 [0.04, 25.64]
Guidozzi 1999	32 / 62	41 / 68	41.0	0.70 [0.35, 1.41]
Hall 1994	3 / 37	3 / 16	6.7	0.38 [0.07, 2.14]
Hall 1998	0 / 40	1 / 20	1.9	0.16 [0.01, 4.12]
Komulainen 1999	1 / 115	2 / 115	3.4	0.50 [0.04, 5.54]
Kyllonen 1998	1 / 52	0 / 26	1.9	1.54 [0.06, 39.21]
Lindsay 1976	1 / 63	1 / 57	2.5	0.90 [0.06, 14.78]
MacDonald 1994	1 / 22	1 / 22	2.5	1.00 [0.06, 17.07]
Mijatovic 1998	0 / 13	1 / 13	1.8	0.31 [0.01, 8.30]
Mosekilde 2000	4 / 502	9 / 504	14.2	0.44 [0.14, 1.44]
Nachtigall 1979	3 / 84	7 / 84	10.3	0.41 [0.10, 1.63]
PEPI 1995	3 / 701	0 / 174	2.3	1.75 [0.09, 34.01]
Perez-Jaraiz 1996	0 / 26	1 / 52	1.9	0.65 [0.03, 16.45]
Ravn 1999	0 / 110	1 / 109	1.9	0.33 [0.01, 8.12]
Watts 2000	1 / 303	0 / 103	1.9	1.03 [0.04, 25.39]
Total (95% CI)	53 / 2576	68 / 1565	100.0	0.61 [0.39, 0.95]

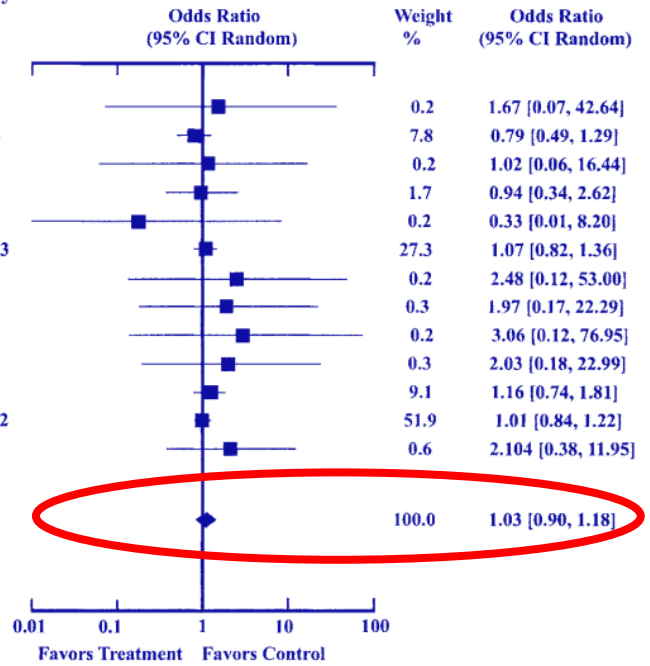
Test for heterogeneity p = 0.99
Test for overall effect p = 0.03



Mean age > 60 years
Hormone replacement and total mortality

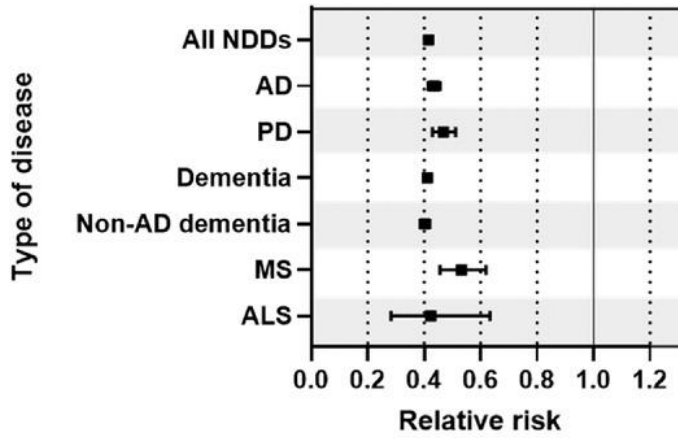
Study	Treatment n/N	Control n/N	Weight %	Odds Ratio (95% CI Random)
Binder 2001	1 / 41	0 / 22	0.2	1.67 [0.07, 42.64]
Cherry 2002	32 / 513	39 / 504	7.8	0.79 [0.49, 1.29]
Gallagher 2001	1 / 121	1 / 123	0.2	1.02 [0.06, 16.44]
Herrington 2000	11 / 204	6 / 105	1.7	0.94 [0.34, 2.62]
Hodis 2001	0 / 111	1 / 111	0.2	0.33 [0.01, 8.20]
Hulley 1998	130 / 1380	123 / 1383	27.3	1.07 [0.82, 1.36]
Mulnard 2000	2 / 81	0 / 39	0.2	2.48 [0.12, 53.00]
Os 2000	2 / 60	1 / 58	0.3	1.97 [0.17, 22.29]
Raz 1993	1 / 50	0 / 50	0.2	3.06 [0.12, 76.95]
Recker 1999	2 / 64	1 / 64	0.3	2.03 [0.18, 22.99]
Viscoli 2001	48 / 337	41 / 327	9.1	1.16 [0.74, 1.81]
WHI 2002	231 / 8506	218 / 8102	51.9	1.01 [0.84, 1.22]
Waters 2002	4 / 103	2 / 108	0.6	2.104 [0.38, 11.95]
Total (95% CI)	465 / 11571	433 / 10996	100.0	1.03 [0.90, 1.18]

Test for heterogeneity p = 0.98
Test for overall effect p = 0.7



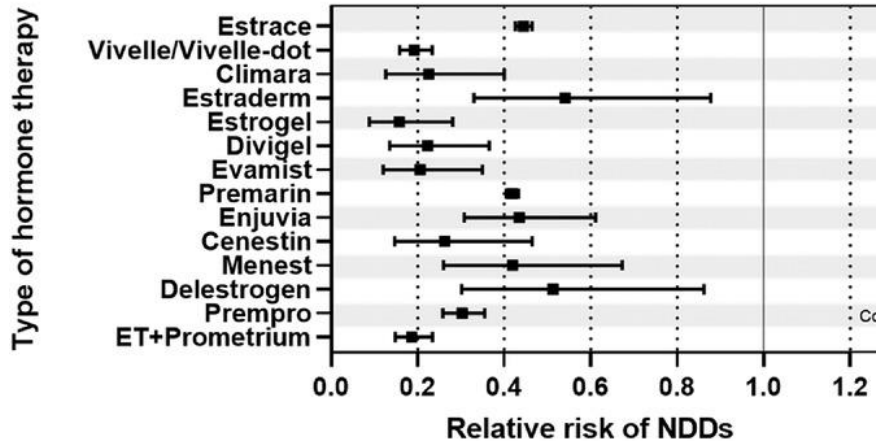
Salpeter SR et al., J Gen Int Med, 2004

A



	Control, No. (%) (N=189,676)	Treatment, No. (%) (N=189,676)	RR (95% CI)	NNT	P-value
All NDDs	14,920 (7.87)	6,260 (3.30)	0.42 (0.40 to 0.43)	21.56	<0.001
AD	5,414 (2.85)	2,361 (1.24)	0.43 (0.41 to 0.46)	61.81	<0.001
PD	1,574 (0.83)	739 (0.39)	0.47 (0.43 to 0.51)	226.3	<0.001
Dementia	12,711 (6.70)	5,263 (2.77)	0.41 (0.40 to 0.43)	25.22	<0.001
Non-AD dementia	7,896 (4.16)	3,192 (1.68)	0.40 (0.39 to 0.42)	40.01	<0.001
MS	473 (0.25)	252 (0.13)	0.53 (0.46 to 0.62)	855.9	<0.001
ALS	78 (0.04)	33 (0.02)	0.42 (0.28 to 0.63)	4,215	<0.001

B

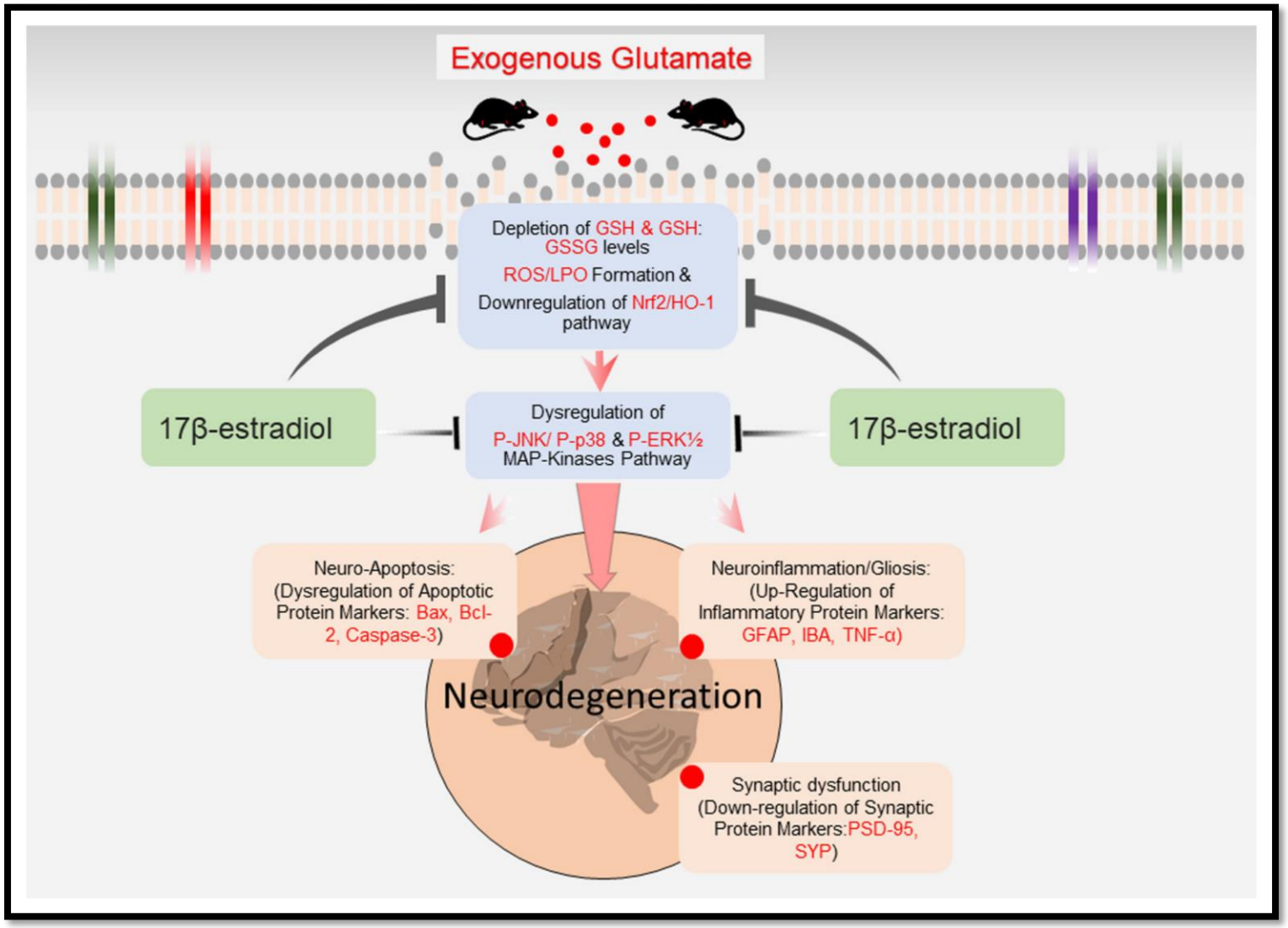


	Active ingredient	Mode of administration/type of dosage form	Number of HT users	RR (95% CI)	P-value
Estrace	Estradiol	PO tablet	63,164	0.45 (0.43 to 0.46)	<0.001
Vivelle/Vivelle-dot	Estradiol	TD patch	6,553	0.19 (0.16 to 0.23)	<0.001
Climara	Estradiol	TD patch	613	0.23 (0.13 to 0.40)	<0.001
Estraderm	Estradiol	TD patch	349	0.54 (0.33 to 0.88)	0.010
Estrogel	Estradiol	TD gel	877	0.16 (0.09 to 0.28)	<0.001
Divigel	Estradiol	TD gel	847	0.22 (0.14 to 0.37)	<0.001
Evamist	Estradiol	TD spray	796	0.21 (0.12 to 0.35)	<0.001
Premarin	Conjugated estrogen	PO tablet or IM injection	123,982	0.42 (0.40 to 0.43)	<0.001
Enjuvia	Synthetic conjugated estrogens	PO tablet	898	0.43 (0.31 to 0.61)	<0.001
Cenestin	Synthetic conjugated estrogen	PO tablet	524	0.26 (0.15 to 0.46)	<0.001
Menest	Esterified estrogen	PO tablet	480	0.42 (0.26 to 0.67)	<0.001
Delestrogen	Estradiol valerate	IM injection	319	0.51 (0.30 to 0.86)	0.009
Prempro	Conjugated estrogen/medroxyprogesterone acetate	PO tablet	6,197	0.30 (0.26 to 0.36)	<0.001
ET+Prometrium	Progesterone	PO capsule	4,865	0.19 (0.15 to 0.23)	<0.001

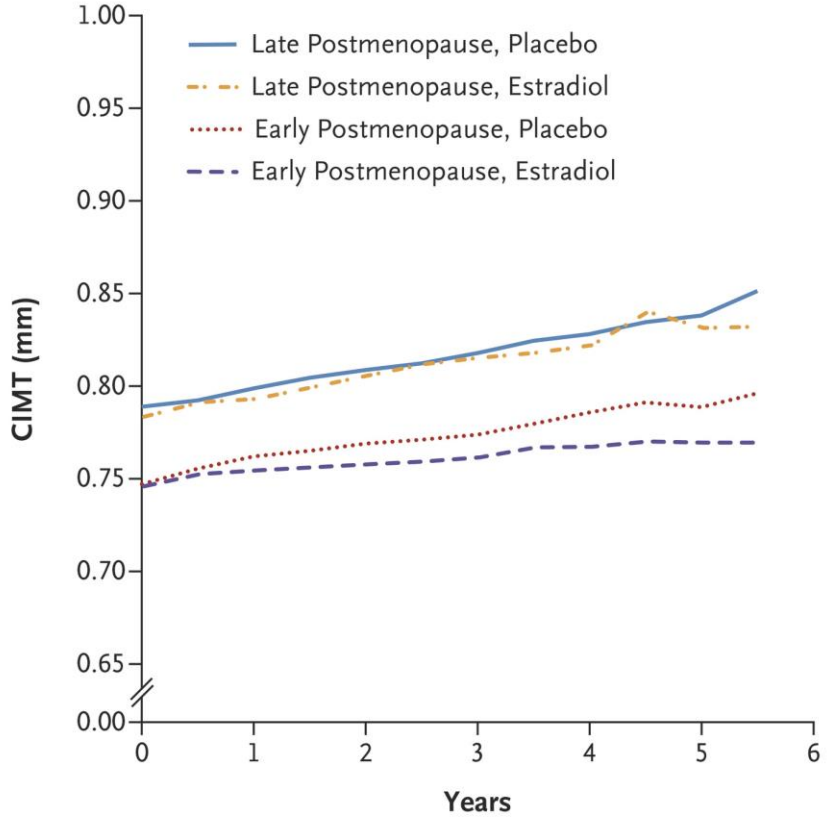
Estrogen Replacement Therapy reduces risk of NDDs

Kim YJ et al., Alzheimer's Dement, 2021

17β-estradiol protects from glutamate-induced neurotoxicity by upregulating the Nrf2/HO-1 antioxidant pathway



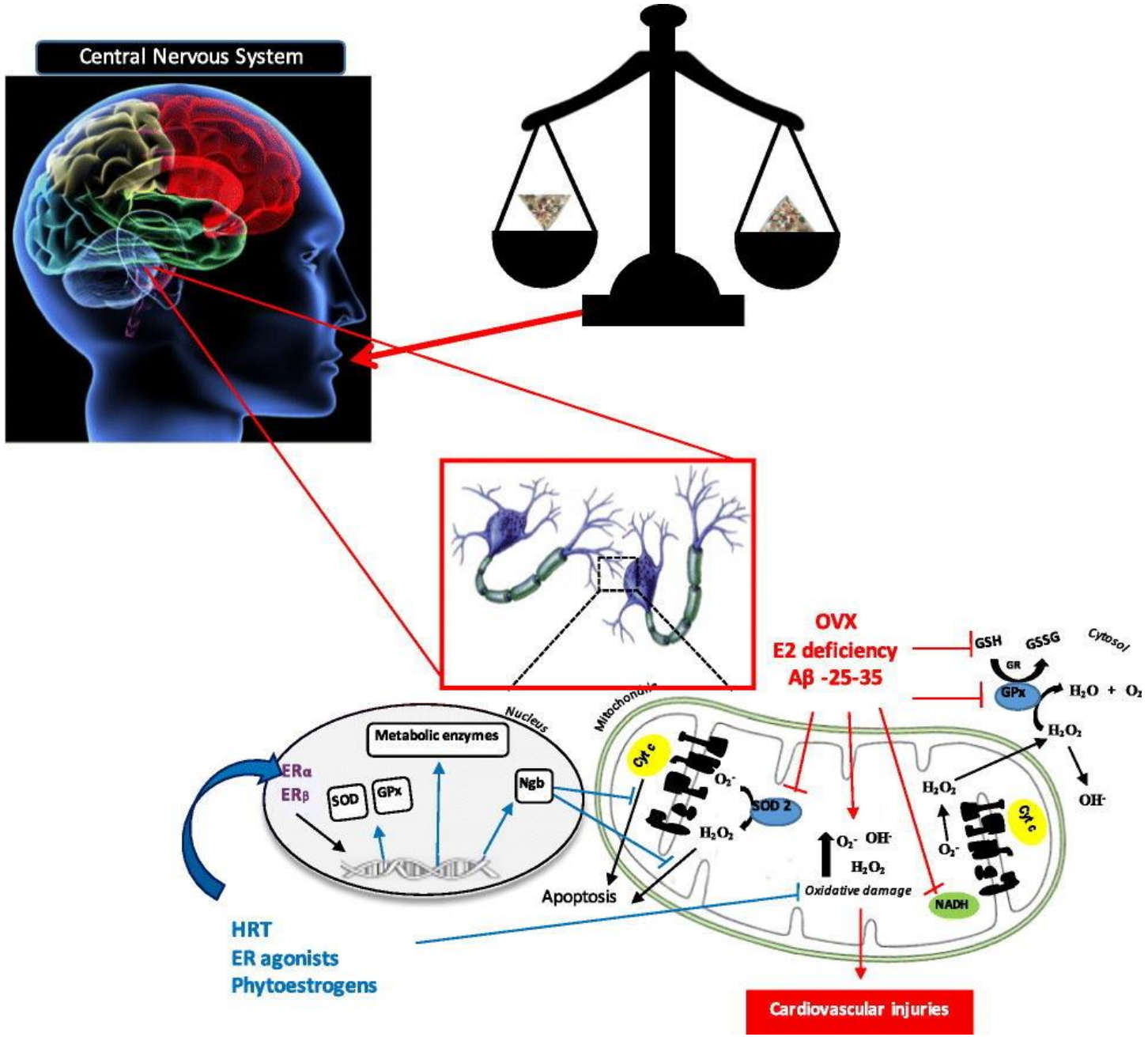
Khan I et al., Antioxidants, 2021



No. of Participants							
With CIMT data	643	533	522	515	424	295	56
Who completed or discontinued study	0	106	119	128	215	345	582
Without CIMT data	0	4	2	0	4	3	5

Hormone-timing hypothesis: progression of subclinical atherosclerosis was limited by estradiol initiated early (within 6 y after menopause)

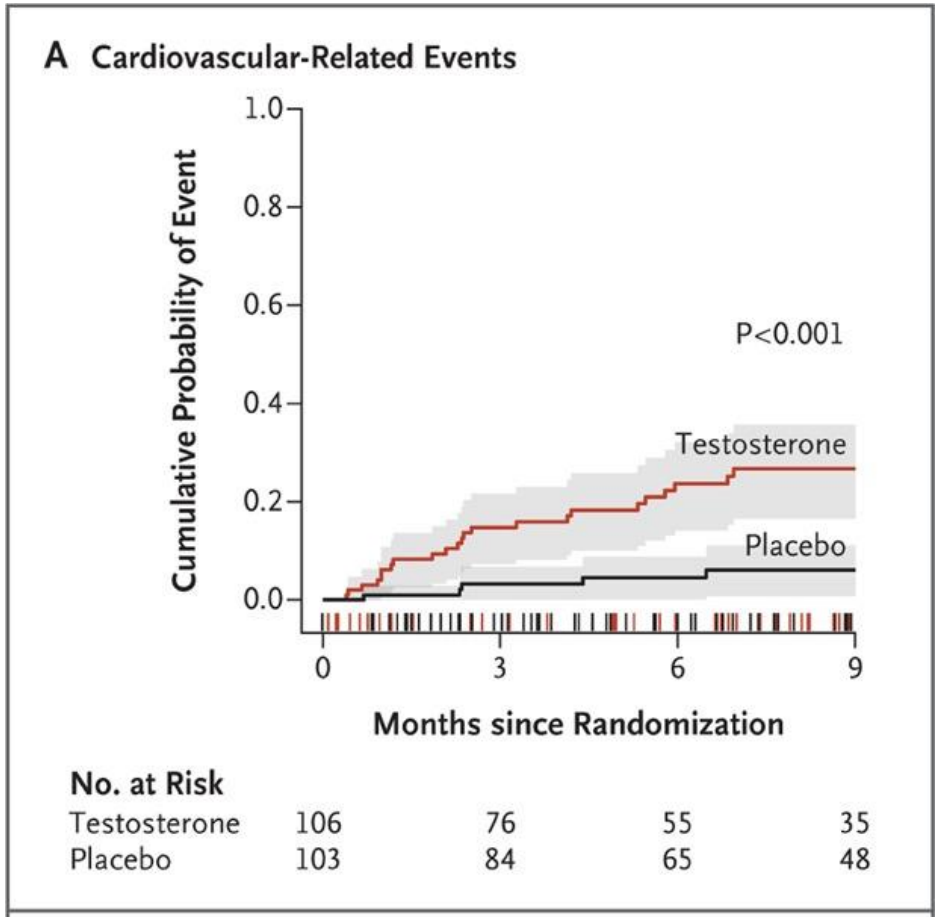
Hodis HN et al., N Engl J Med, 2016



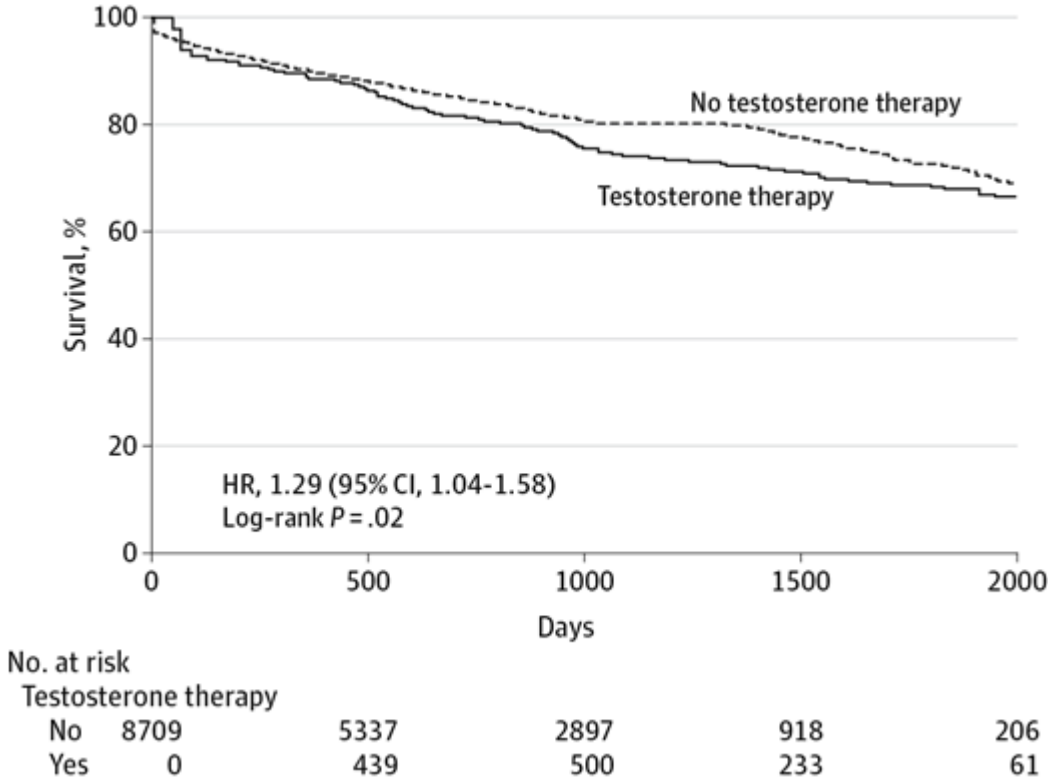
Estrogen-dependent integration of Antioxidant Signaling: protective effects against CVD mediated by reducing oxidative stress in the brain

Lagranha CJ et al., Life Sci, 2018

Testosterone Therapy increases CV mortality and events in men



Basaria S et al., N Engl J Med, 2010



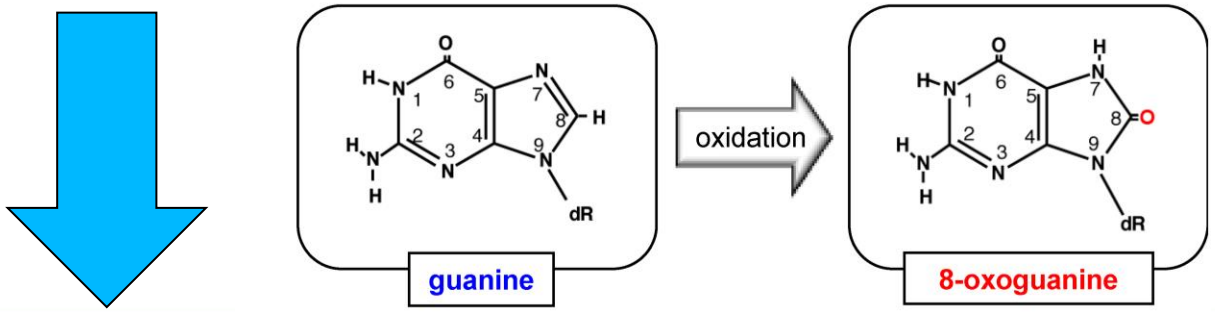
Vigen R et al., JAMA, 2013

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
67° CONGRESSO NAZIONALE SIGG
LA LONGEVITÀ DECLINATA AL FEMMINILE

Endocrine Abstracts (2022) **81** P311 | DOI: 10.1530/endoabs.81.P311

Oxidative stress decreased after six months testosterone treatment compared to placebo in ageing men – a randomized, double-blind trial

Louise Lehmann Christensen [1], Marianne Andersen [1], Henrik Enghusen Poulsen [2] & Dorte Glintborg [1]



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ESTABLISHED IN 1812 OCTOBER 19, 2006 VOL. 355 NO. 16

DHEA in Elderly Women and DHEA or Testosterone in Elderly Men

CONCLUSIONS

Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life. (ClinicalTrials.gov number, NCT00254371.)

Per concludere:

I cambiamenti senili negli ormoni sessuali circolanti si associano alla maggiore vita media (ma anche ad aumento della fragilità) femminile

Le alterazioni età-correlate dei livelli circolanti di ormoni sessuali sono integrate con la «free radical theory of aging»

Gli effetti antiossidanti di un trattamento ormonale sostitutivo al momento sono evidenti solo per gli estrogeni