Wellaging and Hormonal Replacement Therapy in Women

H·E·A·T

H.E.A.T. International Congress on Anti-Aging Medicine
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Dr Serge Ginter
Luxembourg

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

FIRST TO KNOW®

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This special issue of *First to Know* evolved from the lively discussion following NAMS coverage of Dr. Philip Sarrel et al's article "The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years" from the *American Journal of Public Health* in our July issue. Included in this special issue are commentaries from current and past NAMS Board Members, well-known experts in the field of menopause. The original summary of the article and the original commentary are included.

Margery L.S. Gass, MD, NCMP—*Executive Director*

Is ET avoidance associated with early death in women with hysterectomy?

Study covers decline in estrogen use, 2002-2011

Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of est
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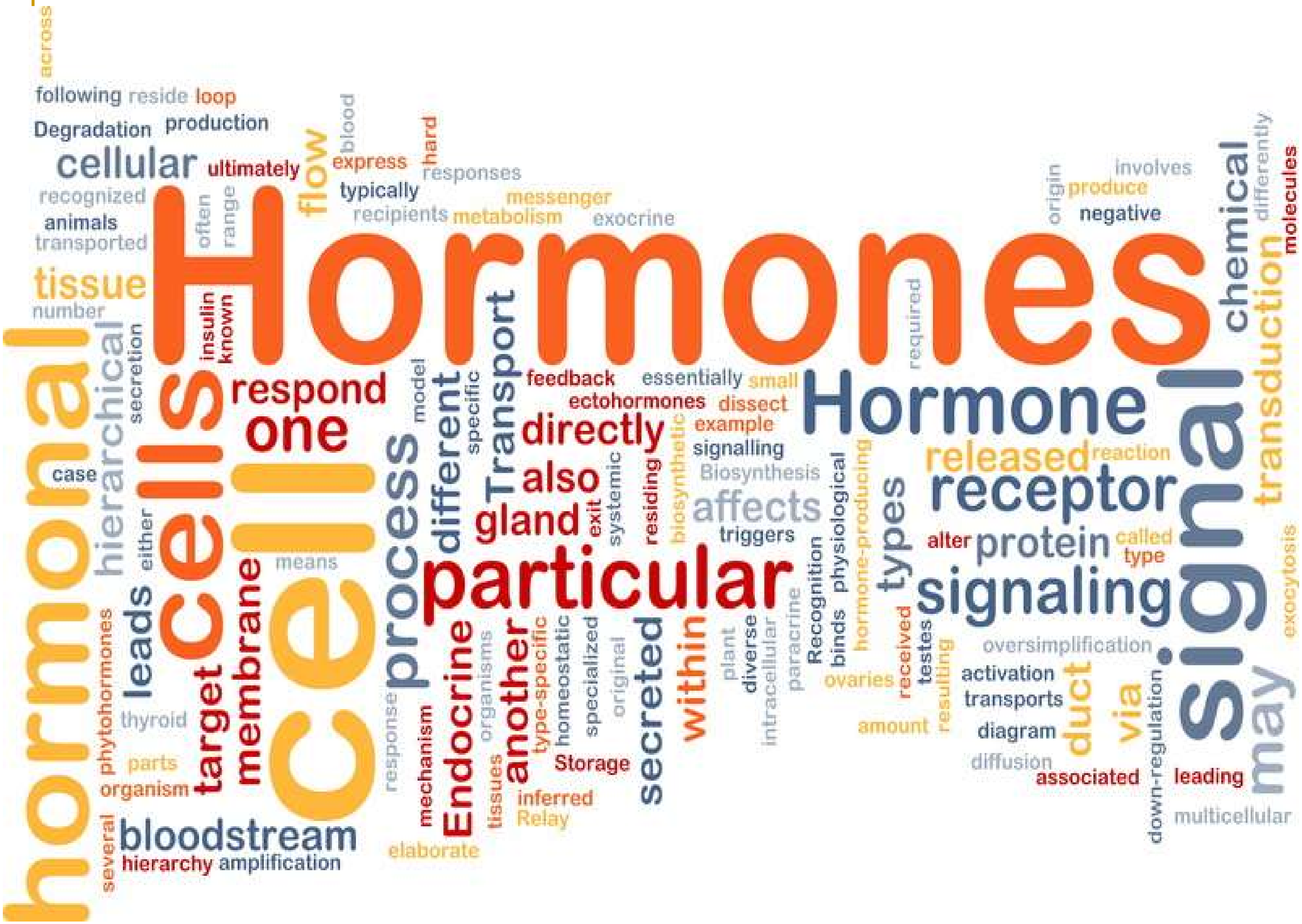
> Based on these estimates and estimates of the number of US women undergoing surgical menopause, Sarrel et al examined excess mortality that might be attributed to declining rates of estrogen therapy in the wake of early WHI publications. Their calculations—based on reasonable but inherently messy assumptions—suggested about 1,900 to 9,200 "excess deaths" annually within the 50- to 59-year-old age group.

provider about ET effects is of vital importance.

Comment #1. In 2011, LaCroix et al[1] analyzed by age at randomization, were based on therapy during the trial (~6 y) and follow-up after the trial (~5 additional y). All-cause mortality was reduced among women aged 50 to 59 years assigned to CEE (hazard ration [HR], 0.73; 95% confidence interval [CI], 0.53-1.00) and was relatively unchanged among CEE users aged 60

Although subgroup analyses must always be interpreted cautiously, findings from WHI indicate that age modifies the risks and benefits


Hormones
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bloodstream
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cellular
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protein
types
via
duct
another
following
reside
loop
Degradation
production
ultimately
flow
express
blood
hard
responses
typically
messenger
recipients
metabolism
exocrine
recognized
animals
transported
often
range
insulin
known
number
secretion
case
either
means
model
specific
feedback
essentially
small
ectohormones
dissect
example
signalling
Biosynthesis
biosynthetic
residing
systemic
exit
triggers
alter
called
type
reaction
required
origin
produce
involves
negative
differently
molecules
exocytosis
oversimplification
activation
transports
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multicellular
down-regulation
amount
resulting
testes
received
ovaries
hormone-producing
physiological
binds
Recognition
paracrine
intracellular
diverse
plant
original
specialized
homeostatic
type-specific
organisms
tissues
inferred
Relay
Storage
mechanism
response
elaborate
phytohormones
thyroid
parts
organism
several
hierarchy
amplification
across


Hormones
HGH
Estrogen
DHEA
Progesterone
Thyroid
Melatonin
Testosterone

Bioidentical Hormone Therapy

The term "bioidentical hormone therapy" began as a marketing term for custom-compounded hormones. The term now usually refers to compounds that have the same chemical and molecular structure as hormones that are produced in the body, the definition that NAMS uses.

Bioidentical hormones do not have to be custom-compounded (meaning custom mixed). There are many well-tested, FDA-approved hormone therapy products that meet this definition and are commercially available from retail pharmacies.

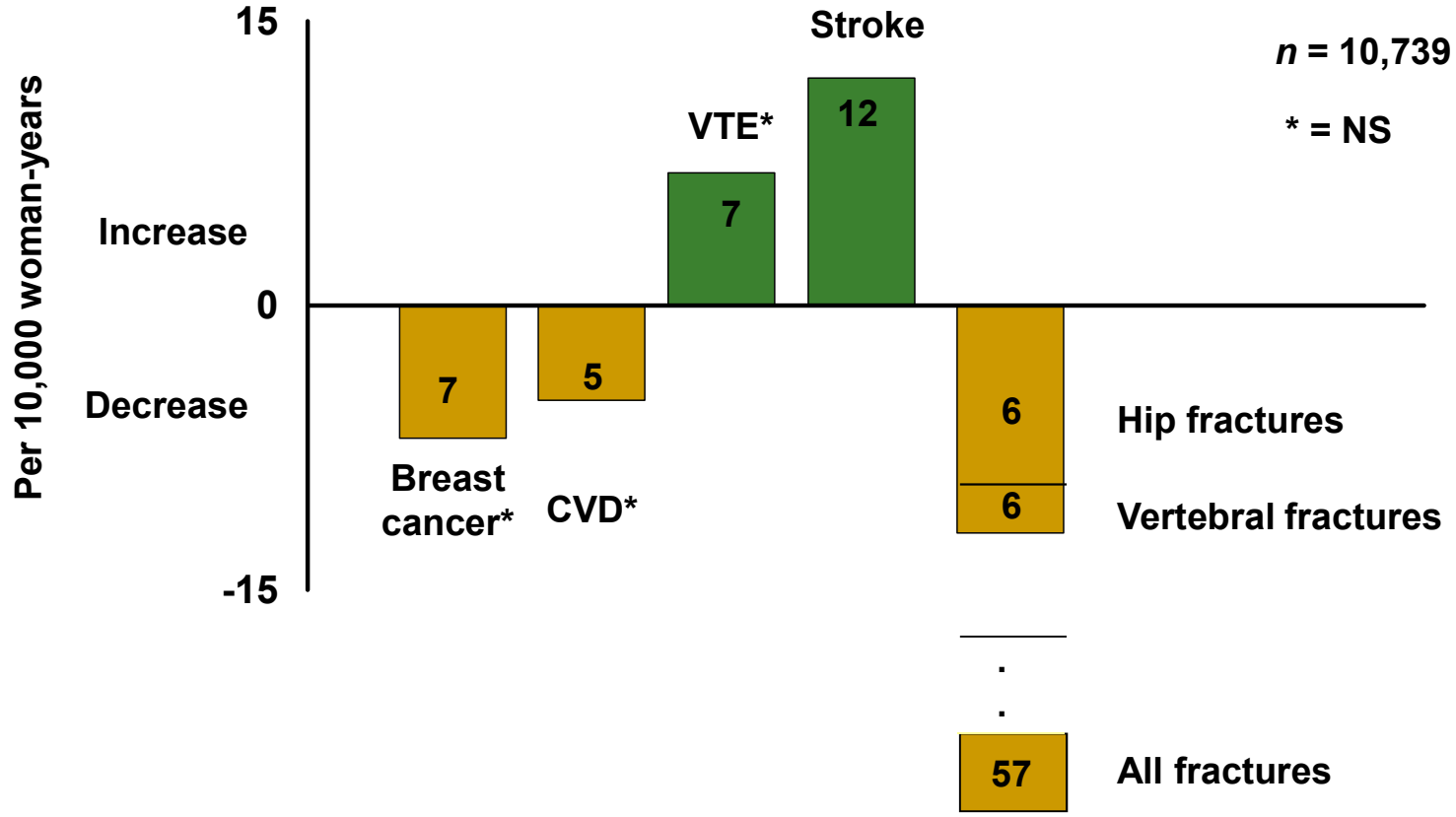
- Should we use HRT in Primary Prevention ?

Primary Prevention ?

- **Preventive healthcare** consists of measures taken for disease prevention, as opposed to disease treatment

- Disease prevention relies on anticipatory actions that can be categorized as primary, secondary, and tertiary prevention (Wikipedia)

Annual risks and benefits after 7 years of estrogen-only HT



Adapted from *JAMA* 2004;291:1701–12
MacLennan A, Sturdee D. *Climacteric* 2004

WHI population characteristics

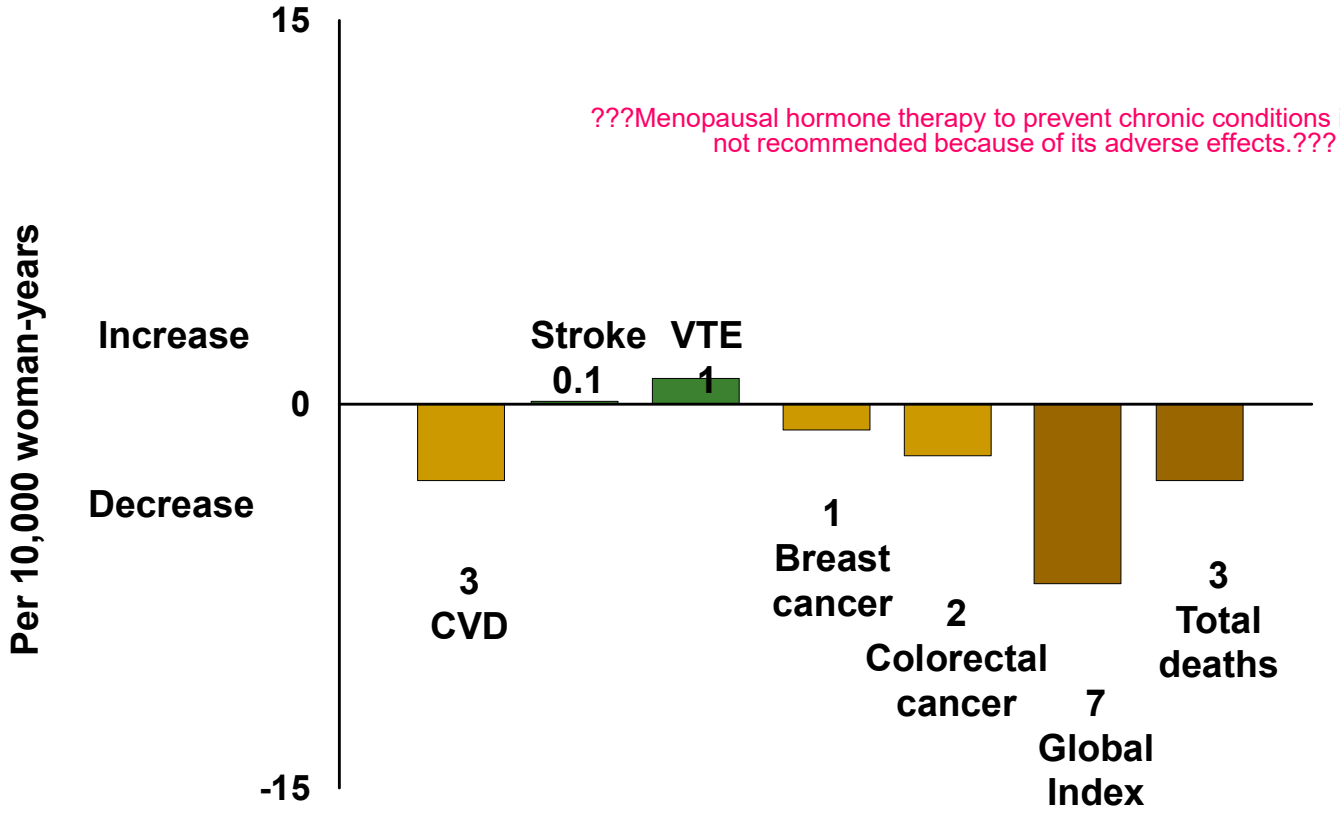
	WHI EP arm		WHI E arm	
	Mean	%	Mean	%
Age (years)	63		63.6	
< 60		33.4		30.8
60–69		45.3		45.0
70–79		21.3		24.2
Body mass index	28.5		30.1	
< 25		30.4		21
25–29		35.3		34
> 30		34.2		45
Hypertensive		35.7		48

Rossouw JE, *et al*. *J Am Med Assoc* 2002;288:321–33

The Women's Health Initiative Steering Committee. *J Am Med Assoc* 2004;291:1701–12

WHI E-only clinical outcomes when initiated age 50–59

Annual change in risk.



Adapted from *JAMA* 2004;291:1701–12
MacLennan A, Sturdee D. *Climacteric* 2004

Primary Prevention of CHD with HRT in Clinical Perspective*

Outcome	Hormone Therapy[1,2*]	Lipid Lowering[3]	Aspirin[4]
CHD	0.68 (0.48-0.96)	0.89 (0.69-1.09)	0.91 (0.80-1.03)
Total Mortality	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.
[1]Salpeter S, et al. *J Gen Intern Med* 2004;19:791-804.
[2]Salpeter S, et al. *J Gen Intern Med* 2006;21:363-366.
[3]Walsh JME, et al. *JAMA* 2004;21:363-366.
[4]Ridker PM, et al. *N Engl J Med* 2005;352:1293-1304.

International IMS Menopause Society
Promoting education and research on midlife women's health

2016 IMS Recommendations on women's midlife health and menopause hormone therapy

The IMS Writing Group

THE UNIVERSITY OF SYDNEY

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

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IMS governing principles on MHT

- Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women
- MHT must be individualized and tailored according to symptoms, the need for prevention, personal and family history, results of investigations and each woman's preferences and expectations
- The risks and benefits of MHT differ with age and years since the last menstrual period

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

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IMS governing principles on MHT

- Women experiencing a spontaneous or iatrogenic menopause before age 45 and particularly before age 40 are at higher risk of cardiovascular disease and osteoporosis. In these women, in the absence of contraindications, MHT is advised at least until the average age of menopause

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

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Cardiovascular disease

Key points

- In women under age 60 and recently postmenopausal with no evidence of cardiovascular disease, the initiation of estrogen-alone therapy reduces coronary heart disease (CHD) and all-cause mortality [A]
- Recent meta-analyses and WHI 13-year follow-up data all show a consistent reduction in all-cause mortality for MHT users [A]
- It is not recommended to initiate MHT beyond age 60 years solely for primary prevention of CHD [A]

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

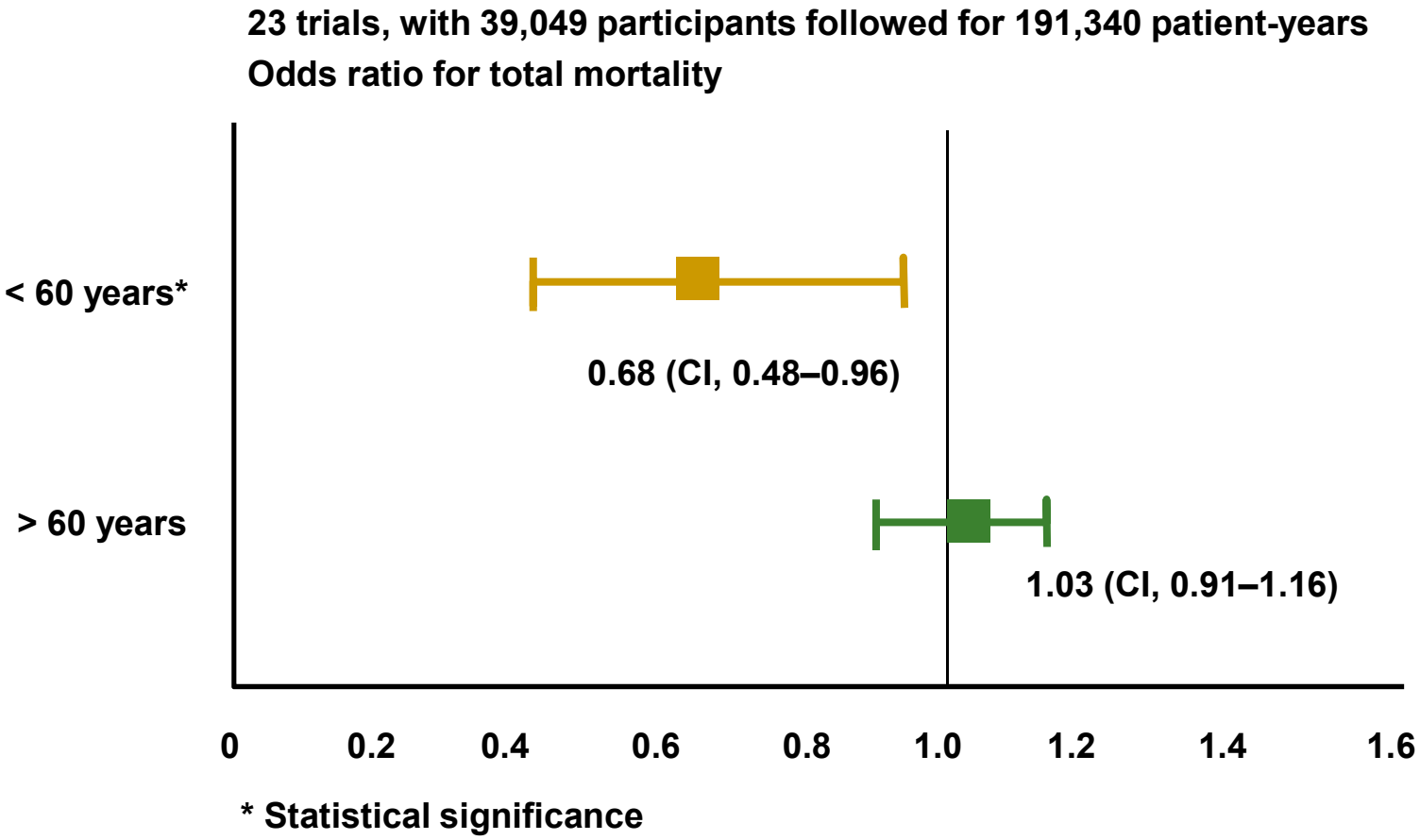
HT and risk of cardiovascular disease by years since menopause

Years since menopause	Hazard ratio	CI	Absolute excess risk (per 10,000 person-years)
< 10	0.76	0.50–1.16	-6
10–19	1.10	0.84–1.45	4
> 20	1.28	1.03–1.58	17

p for trend = 0.02

Adapted from Rossouw JE, *et al*. *JAMA* 2007;297:1465–77

Coronary heart disease events associated with hormone therapy in younger and older women: a meta-analysis



Adapted from Salpeter SR, *et al*. *J Gen Intern Med* 2006;21:363–6

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Postmenopausal osteoporosis
The underestimated aging risk

HRT is the most appropriate therapy for fracture prevention in early menopause

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

Fracture risk in the WHI study

	Hazard ratio (95% CI)	
	Estrogen + progestin hormone therapy	Estrogen hormone therapy
Hip	0.67 (0.47–0.96)*	0.61 (0.41–0.91)*
Vertebral	0.65 (0.46–0.92)*	0.62 (0.42–0.93)*
Total	0.76 (0.69–0.83)*	0.70 (0.63–0.79)*

* significant

Adapted from *JAMA* 2003;290:1729 and *JAMA* 2004;291:1701

Potential serious adverse effects of HT

Breast cancer

endometrial cancer,

venous thromboembolism (pulmonary embolism or deep vein thrombosis),

Stroke

coronary events

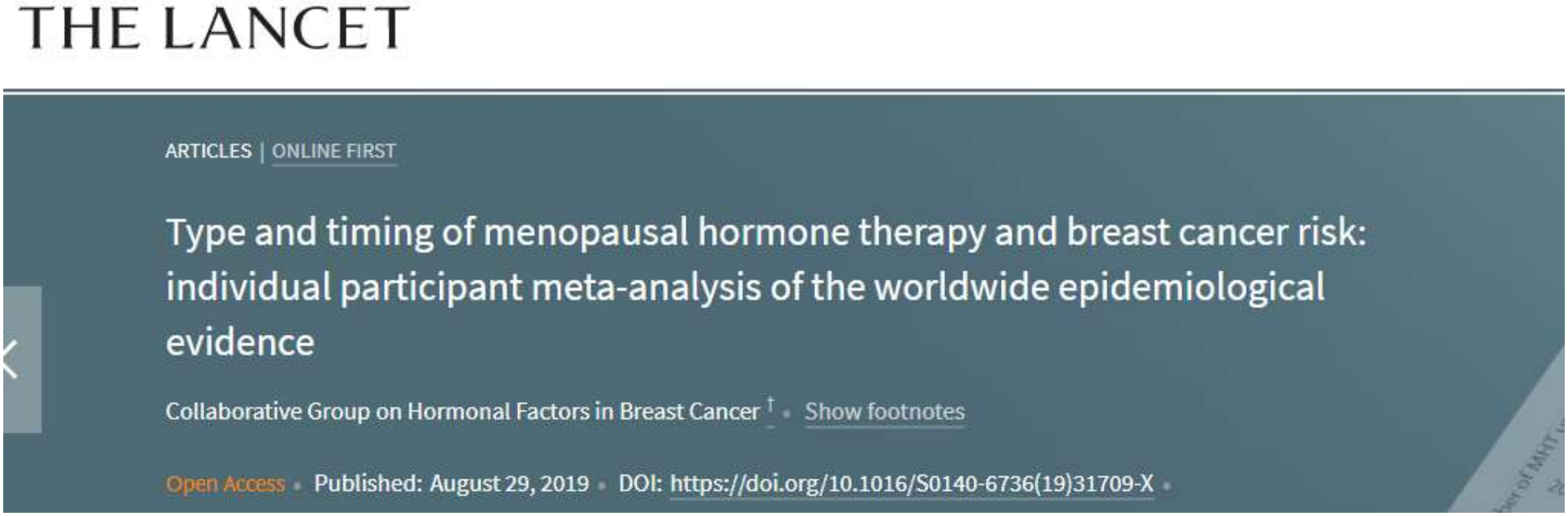
Climacteric 2007;10:181–94

Breast cancer

- The incidence of breast cancer varies in different countries. Therefore, currently available data cannot necessarily be generalized

Breast cancer

- The degree of association between breast cancer and postmenopausal HT remains controversial. Women should be reassured that the possible risk of breast cancer associated with HT is small (less than 0.1% per annum)


THE LANCET
ARTICLES | ONLINE FIRST
Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence
Collaborative Group on Hormonal Factors in Breast Cancer †
Show footnotes
Open Access
Published: August 29, 2019
DOI: https://doi.org/10.1016/S0140-6736(19)31709-X

Breast cancer risk with HRT may persist for years

Endocrinologie Gynécologie Oncologie

NEW YORK (Reuters Health) 05/09 - All types of menopausal hormone therapy (MHT), except vaginal estrogens, are associated with increased risk of breast cancer and the risk may persist for 10 years after stopping MHT, a large new meta-analysis shows.

Liens / Fichiers

- Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

In a phone interview with Reuters Health, study co-author Dr. Richard Peto from the Nuffield Department of Population Health, University of Oxford, UK, said, "The study confirms that there is some increase in risk of breast cancer with menopausal hormone therapy. That's been known for some time. But earlier studies suggested that the risk was there only while you were on it, but not in the years after, and that just really isn't true. What we have shown is that after you stop it, some excess risk still remains. That's what's new here."

The study, by the Collaborative Group on Hormonal Factors in Breast Cancer, was published in The Lancet, online August 29.

The researchers combined data from 58 relevant studies from 1992 to 2018 and used a nested case-control design to examine breast-cancer risk and account for factors such as age at first use, duration of use, and time since last use.

The analysis included more than 108,000 incident cases of invasive breast cancer (diagnosed at age 65 on average) matched to up to four controls. About half of women who developed breast cancer had used MHT, starting at age 50 on average. Average MHT duration was 10 years in current users and seven years in past users.

The data show that compared with never users, women who initiated MHT shortly after menopause had a significantly increased risk of invasive breast - and the longer women used MHT, the greater the risk.

For example, among current users, the risk ratio associated with one to four years of use was 1.17 for estrogen-only and 1.60 for estrogen-progestagen, and increased during years five to 14 of use to 1.33 for estrogen-only and 2.08 for estrogen-progestagen. The estrogen-progestagen risks during years five to 14 were greater with daily use than with less-frequent use (RR, 2.30 vs. 1.93).

These risk increases were all statistically significant.

In past MHT users, the relative risks were lower than in current users, but risks remained elevated more than 10 years after stopping, with the risk being greater the longer the duration of previous MHT use.

"Use of menopausal hormone therapy for 10 years results in about twice the excess breast cancer risk associated with 5 years of use," co-author Dr. Gillian Reeves from the University of Oxford, UK, said in a statement. "But, there appears to be little risk from use of menopausal hormone therapy for less than one year, or from topical use of vaginal estrogens that are applied locally as creams or pessaries and are not intended to

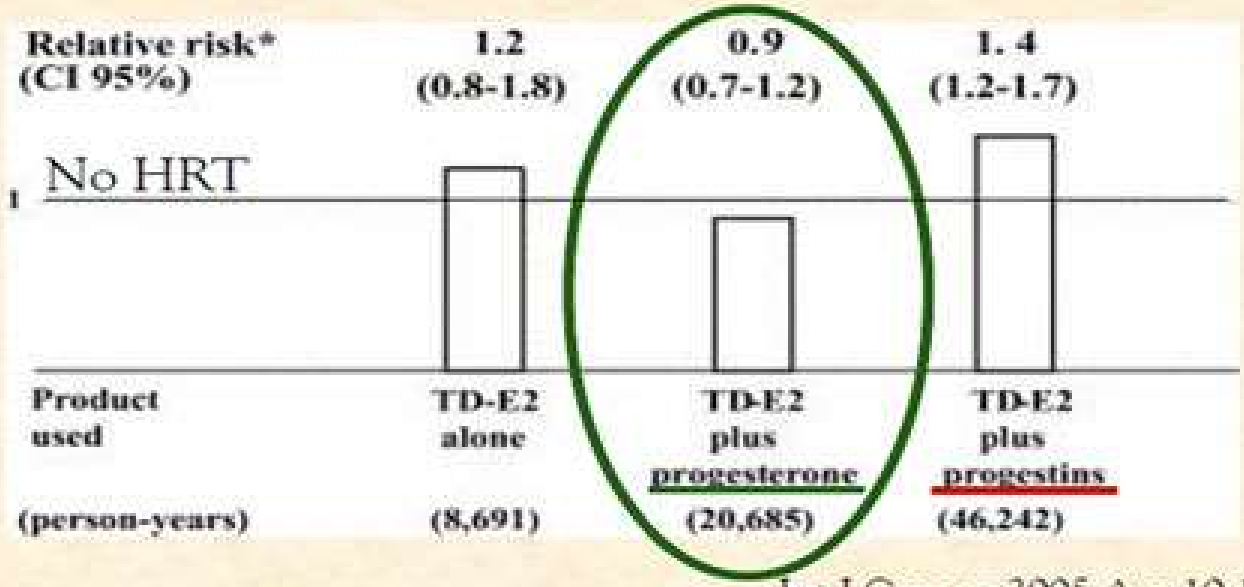
Body mass index: the risk with hormone therapy is (more) apparent in lean women

- BMI > 24.4 kg/m^2 – no additional risk
  Schairer C, *et al*. *JAMA* 2000;283:485–91
- BMI > 26 kg/m^2 – no additional risk
  Rosenberg L, *et al*. *Arch Intern Med* 2006;166:760–5
- Inverse relationship between the risk and BMI with estrogen or combined hormone therapy
  Million Women Study. Reeves GK, *et al*. *Lancet Oncol* 2006;7:910–18
- 80% of users have a BMI < 25
  E3N-EPIC. Fournier A, *et al*. *Int J Cancer* 2005;114:448–54

E3N-EPIC Study

Cohort study
55,000 women
8 years f/u
c/w WHI--
16,000, 6 yr. f/u

TD-E2 = transdermal estradiol



Int J Cancer. 2005 Apr 10;114(3):448-54

E2 plus progesterone: no increased risk of breast cancer!

Similar study: estradiol + progesterone 0.4; estradiol + synthetic progestin 0.94
Espié, Gynecol Endocrinol. 2007 Jul;23(7):391-7.

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Alzheimer's disease and dementia

Key points

- For women with Alzheimer's disease, MHT initiated after the onset of dementia symptoms does not benefit cognitive function or slow disease progression [A]
- MHT initiated within 10 years of a woman's last menstrual period is associated with reduced risk of Alzheimer's disease and dementia [B]
- MHT using estrogen plus progestin initiated at age 65+ increases risk of dementia [A]

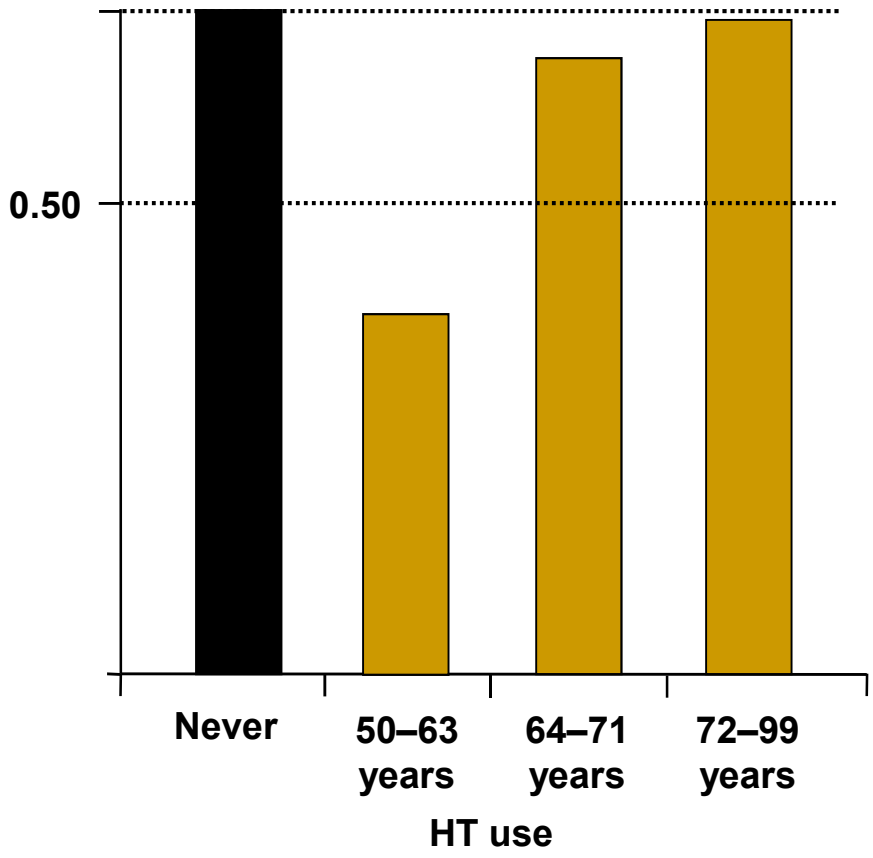
2016 IMS Recommendations. *Climacteric* 2016;19:109–50

Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age

MIRAGE study:
426 cases, 545 family controls

Significant interaction between age and HT use on AD risk (p = 0.03).
Protective association was seen only in the youngest age tertile (50–63 years; odds ratio = 0.35, 95% CI= 0.19–0.66)

HT may protect younger women from AD or reduce the risk of early-onset forms of AD, or HT used during the early postmenopause may reduce AD risk

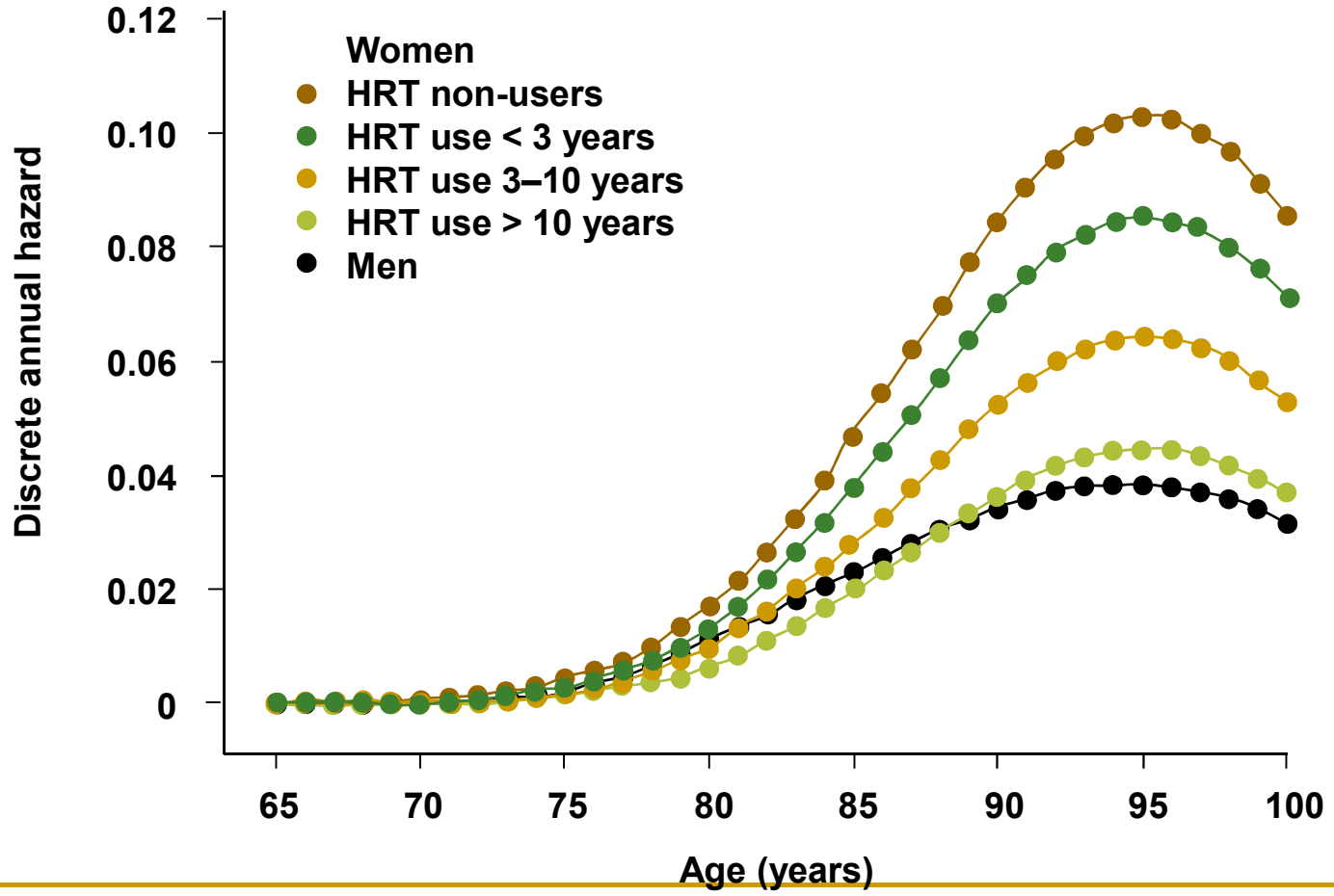


Adapted from Henderson VW, *et al.*; MIRAGE Study Group. *J Neurol Neurosurg Psychiatry* 2005;76:103–5

Effect of hormone therapy

Incidence of Alzheimer's disease

The Cache County Memory Study



Adapted from Zandi PP, *et al*. *JAMA* 2002;288:2123–9

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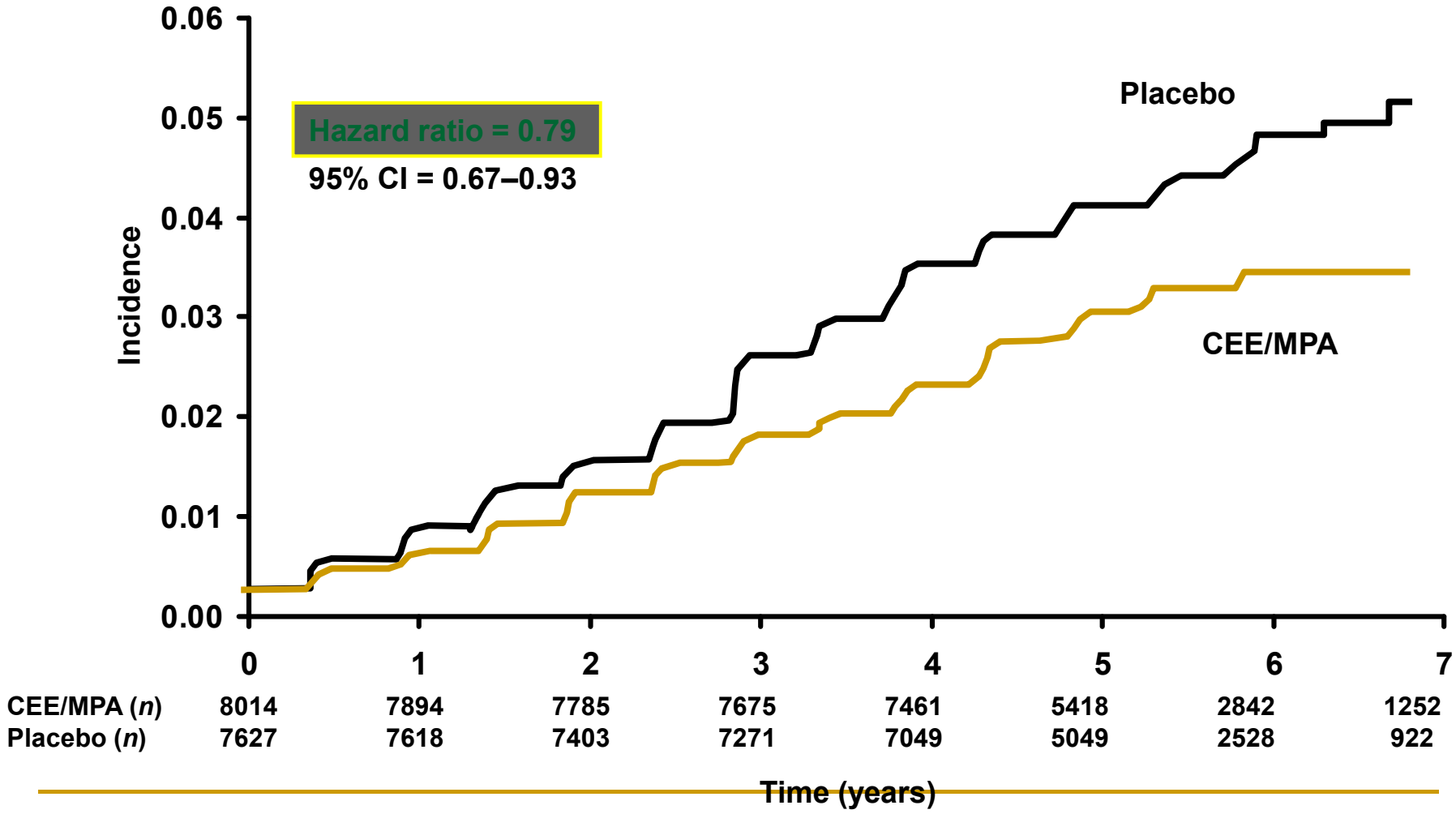
Weight gain

Key points

- An absolute increase in weight at midlife is not attributable to the menopause [B]
- The hormonal changes that accompany menopause are associated with increases in total body fat and abdominal fat, even in lean women [B]
- Maintenance of a healthy diet, avoidance of caloric excess and physical activity are important components of weight management [A]
- Menopausal abdominal fat accumulation is ameliorated by estrogen therapy, with a reduction in overall fat mass, improved insulin sensitivity and a lower rate of development of type 2 diabetes [A]

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

WHI CEE/MPA study: incidence of diabetes



Adapted from Margolis KL, *et al*. *Diabetologia* 2004;47:1175–87

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Skin, cartilage and connective tissues

Key points

- Estrogen has an effect on connective tissue throughout the body [A]
- The marked increase in osteoarthritis in women after the menopause suggests that female sex steroids are important for cartilage homeostasis [B]
- Cartilage degradation and the need for joint replacement surgery are reduced among users of MHT [A]
- Menopause is associated with a number of changes in skin health that may be reduced with the use of MHT or topical estrogen therapy [A]

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

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Colorectal cancer

Key points

- Observational studies show a reduced risk of colorectal cancer (CRC) amongst users of oral MHT [B]
- Three meta-analyses have reported a reduced risk of CRC with MHT use [A]
- Results from WHI showed no effect for estrogen-only therapy on CRC risk [A]
- Results from WHI showed reduced risk of CRC with estrogen + progestin therapy [A]
- There are limited data on the effect of non-oral MHT on CRC risk
- One randomized, controlled trial in older osteoporotic women using tibolone reported a reduced risk of colorectal cancer [A]
- MHT should not be used solely for the prevention of CRC [D]

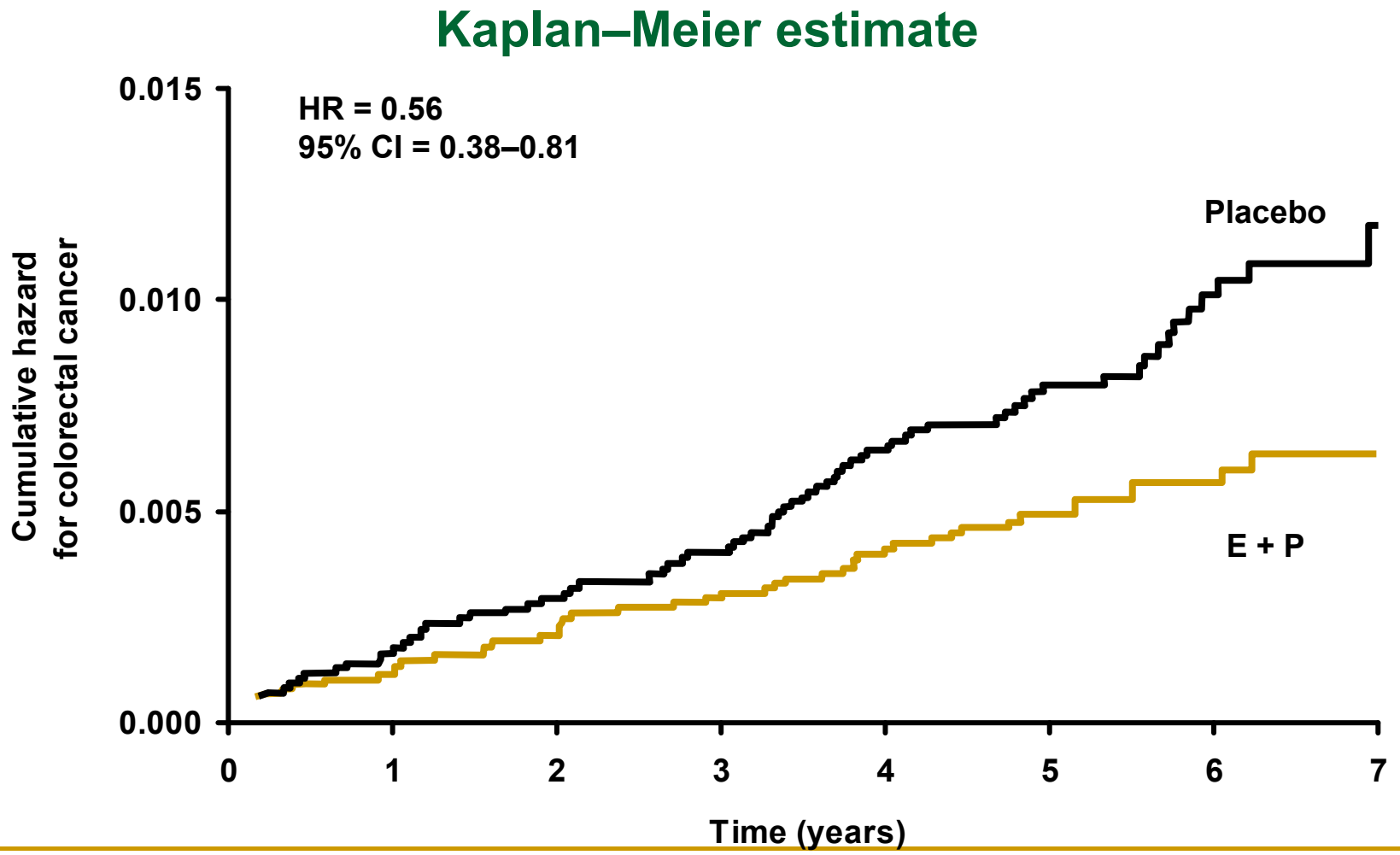
2016 IMS Recommendations. *Climacteric* 2016;19:109–50

Benefits of HRT

Colorectal cancer

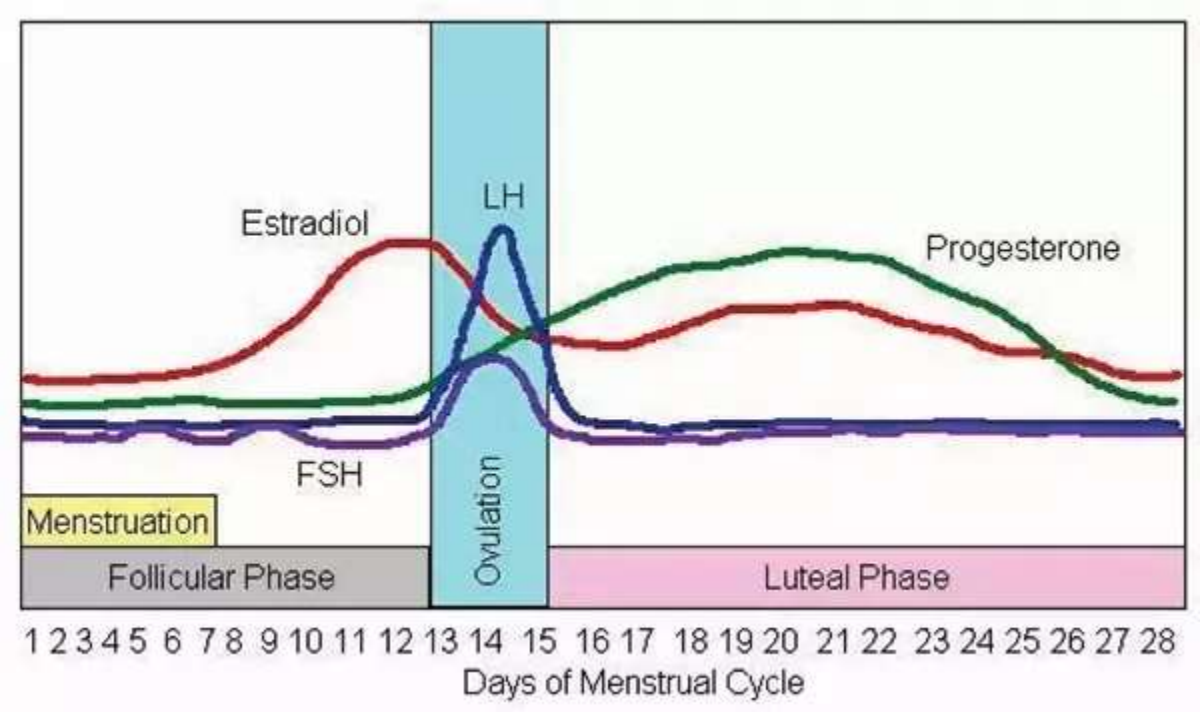
- The majority of observational studies show a reduced risk of colorectal cancer amongst users of oral HRT.
- Three meta-analyses have reported a reduced risk of colorectal cancer with HRT use with benefit persisting for 4 years after cessation of therapy.
- There are no data for an effect of non-oral HRT on risk of colorectal cancer.

WHI results: effect of HT on risk of colorectal cancer

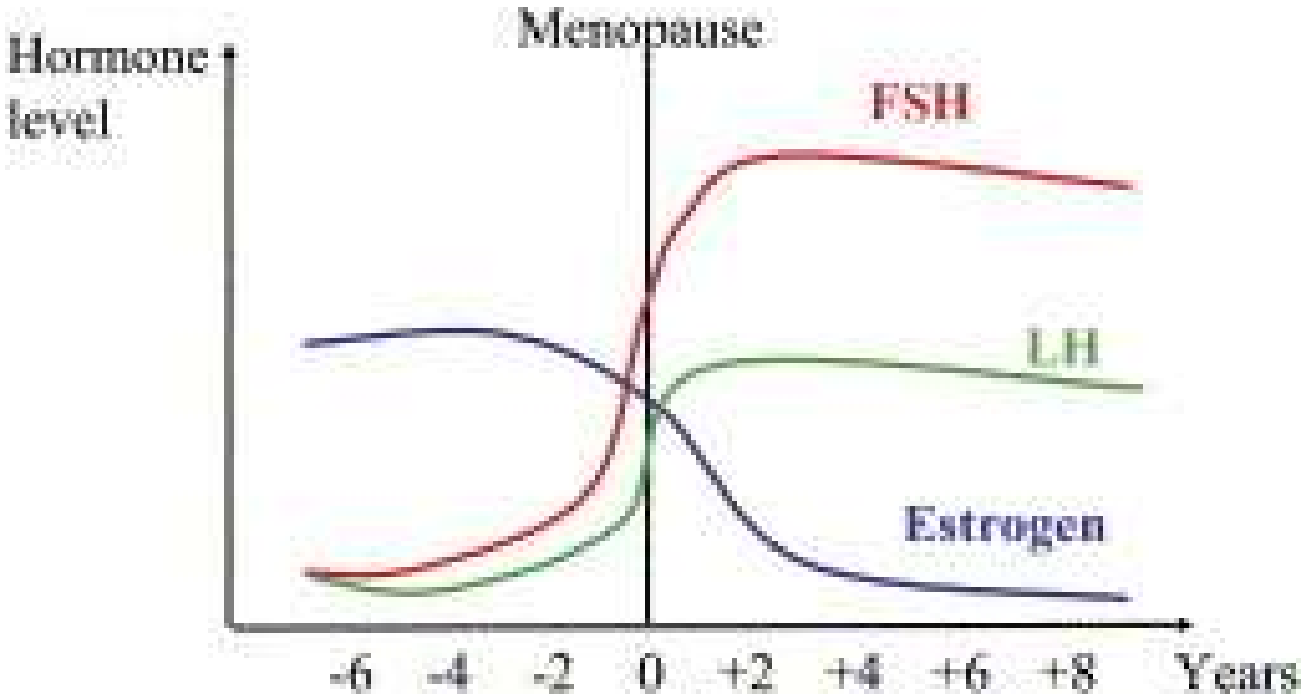


Adapted from Chlebowski RT, *et al. N Engl J Med* 2004;350:991–1004

Follicle Stimulating Hormone (FSH)



Follicle Stimulating Hormone (FSH)

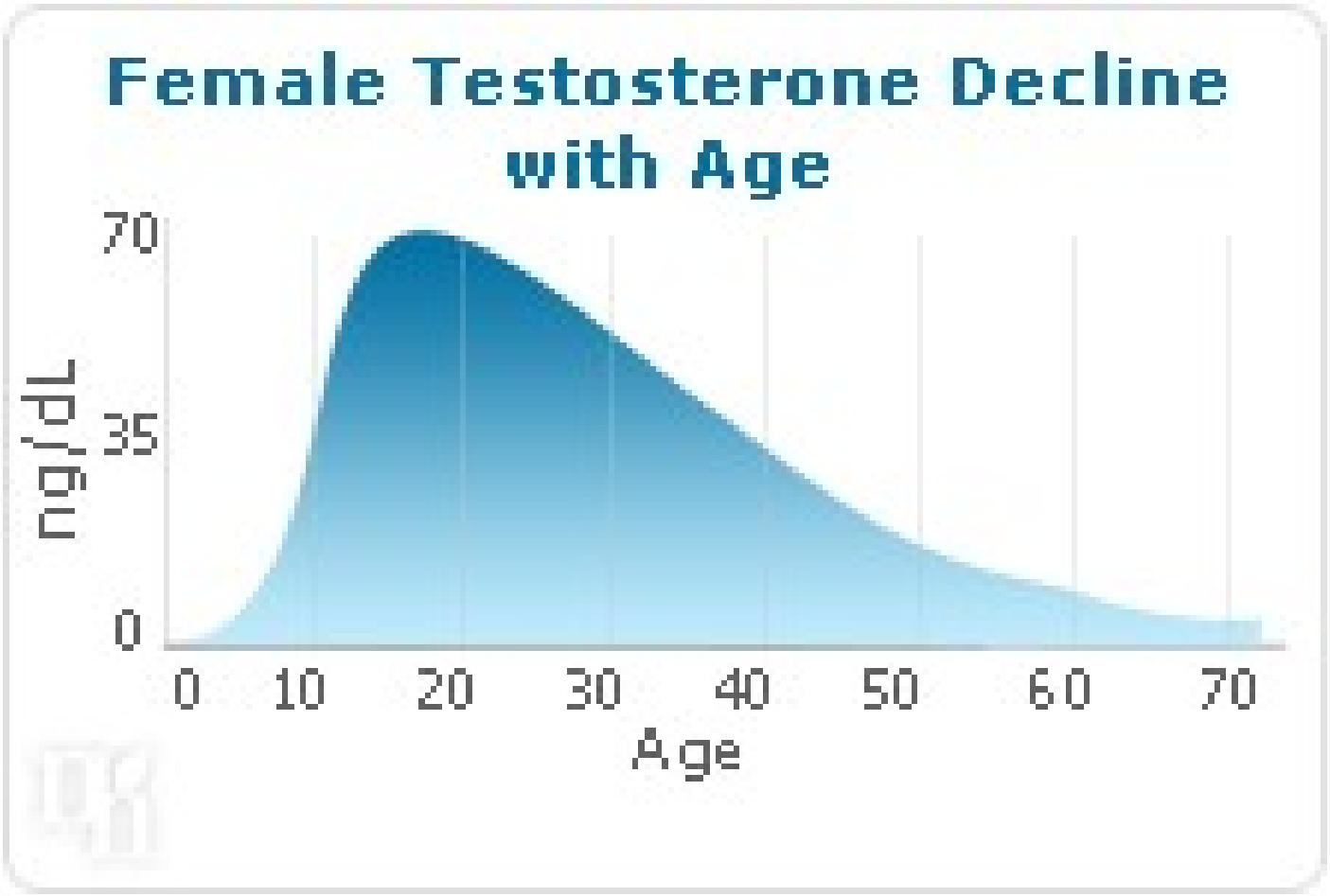


Follicle Stimulating Hormone (FSH)

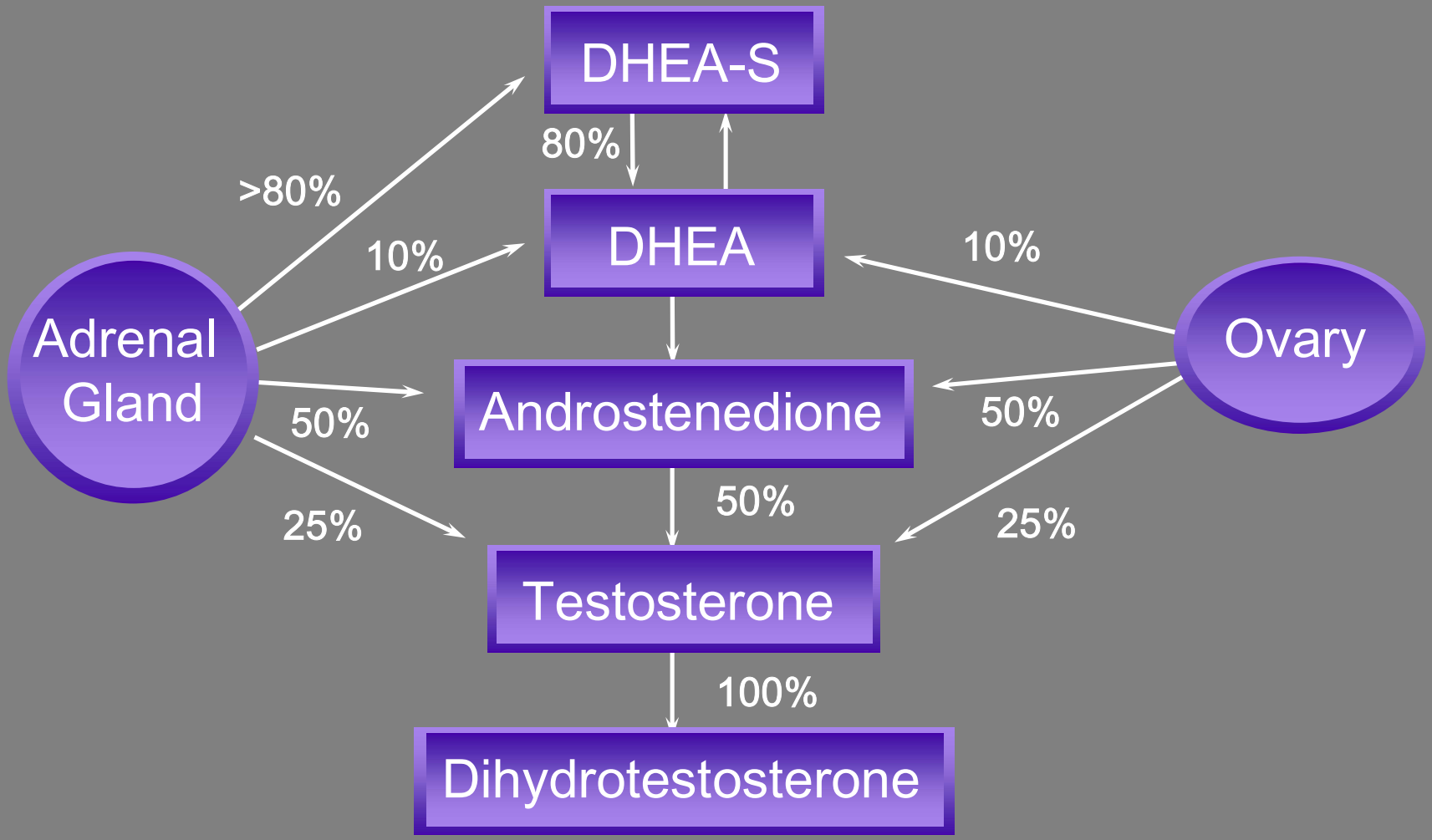
- Bone loss
  - FSH directly regulates osteoclasts and bone resorption.
- Weightgain
- Loss of libido
- Silent Inflammation

Androgens, Menopause and Aging

IS THERE A PLACE FOR REPLACEMENT THERAPY?


Female Testosterone Decline with Age
70
35
0
ng/dL
0
10
20
30
40
50
60
70
Age

Source of circulating Androgens in Premenopausal Women



Buster and Casson, 1999

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Androgen therapy in women

Key points

- Androgen levels decline with age in women with no significant change associated with the natural menopause [A]
- There is strong evidence that androgens influence female sexual function and that testosterone therapy may be useful for women with arousal or desire disorders [A]

2016 IMS Recommendations. *Climacteric* 2016;19:109–50


EVEN WOMEN MAY
EXPERIENCE A CONDITION
KNOWN AS LOW T

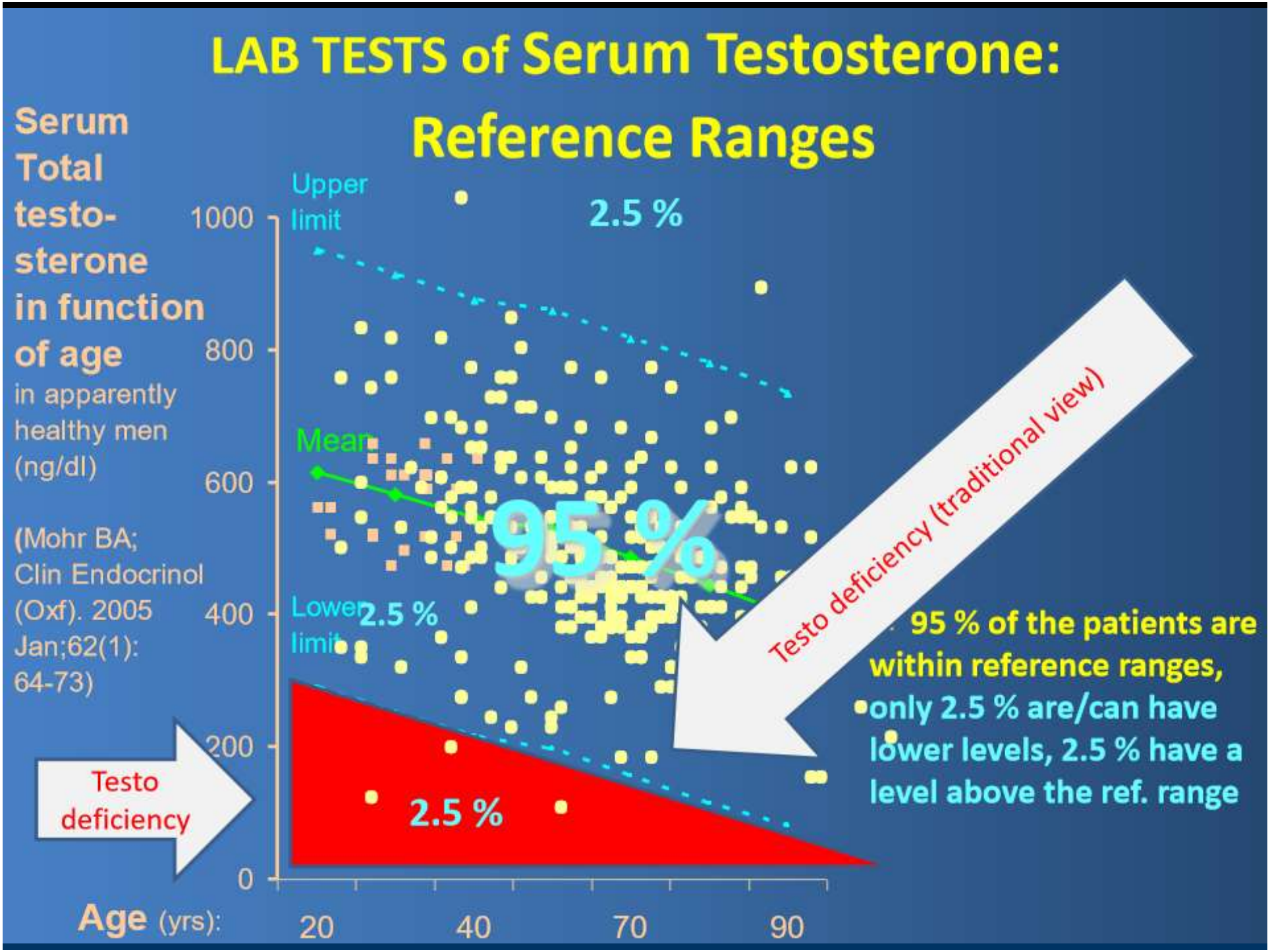
Total Testosterone: Reference Values

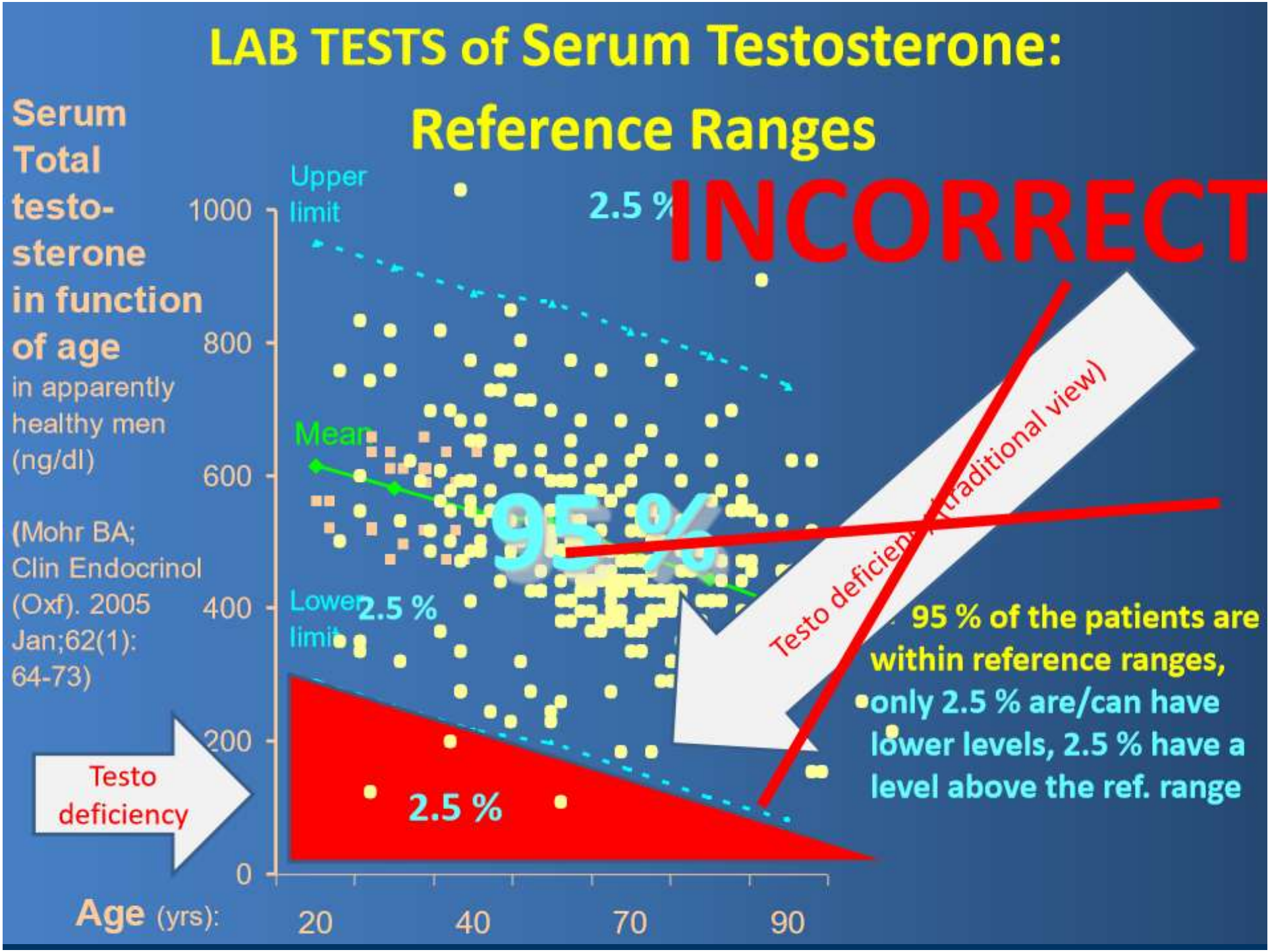
0,7 – 2,8 nmol /ml

0,2 - 0,8 ng/ml

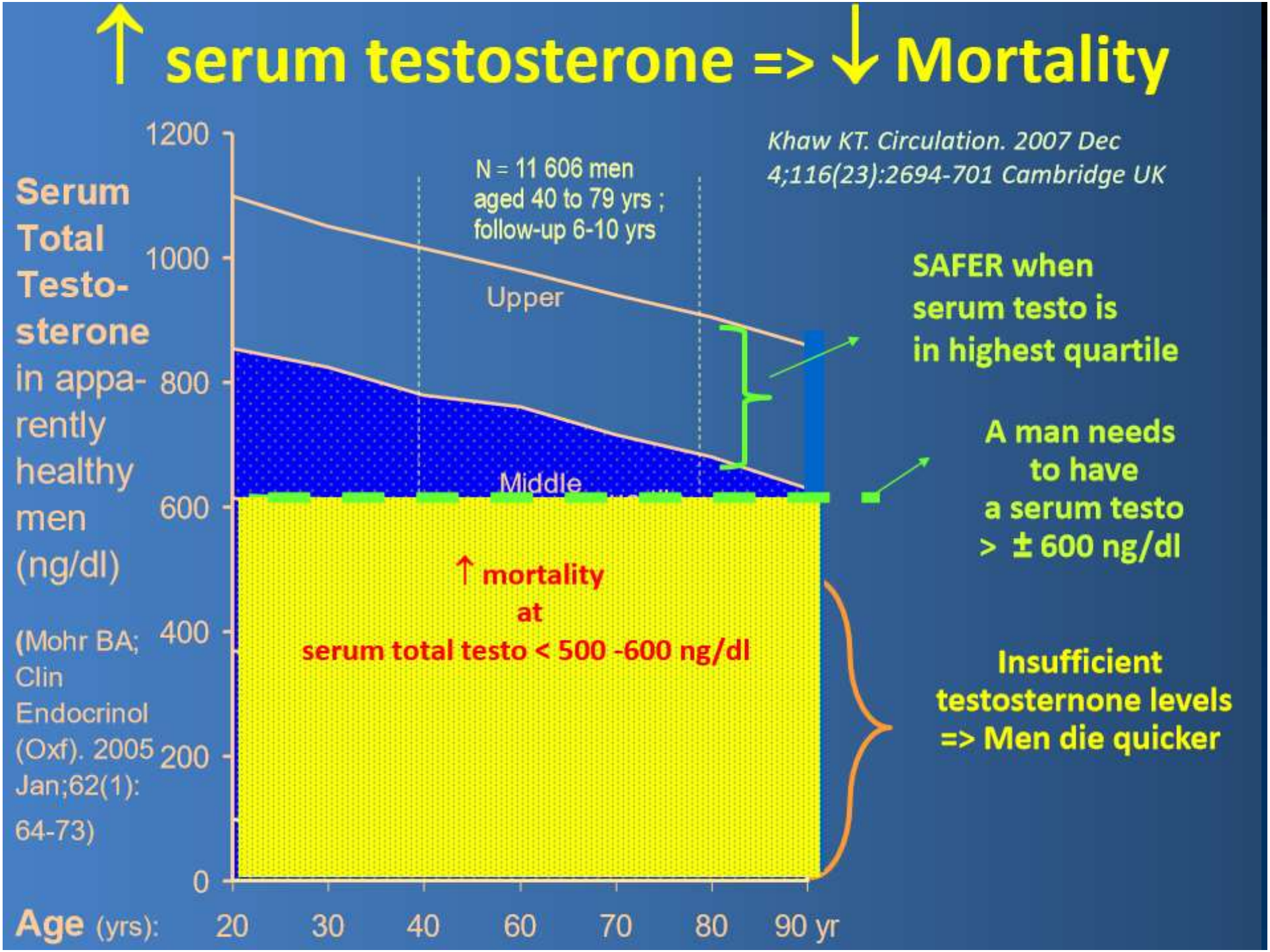
- Woman between 40 and 60 years
- x10 in men

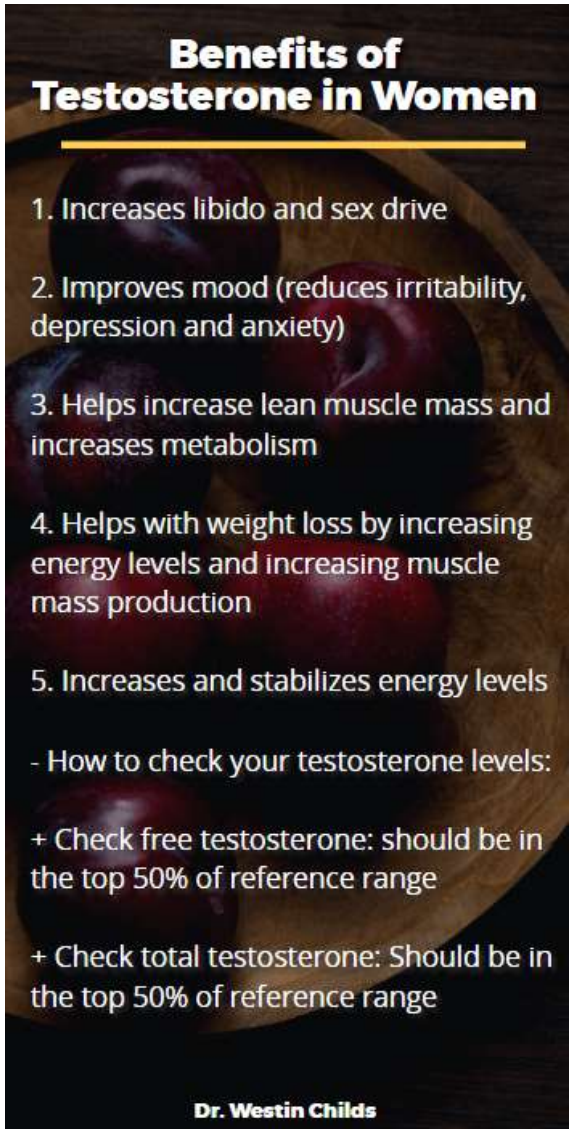
LAB TESTS of Serum Testosterone: Reference Ranges




LAB TESTS of Serum Testosterone:
Reference Ranges
Serum Total testo-sterone in function of age
in apparently healthy men (ng/dl)
(Mohr BA; Clin Endocrinol (Oxf). 2005 Jan;62(1): 64-73)
Upper limit
2.5 %
INCORRECT
Mean
95 %
Lower limit
2.5 %
Testo deficiency (traditional view)
95 % of the patients are within reference ranges,
only 2.5 % are/can have lower levels, 2.5 % have a level above the ref. range
Testo deficiency
2.5 %
1000
800
600
400
200
0
Age (yrs):
20
40
70
90

↑ serum testosterone => ↓ Mortality




Benefits of Testosterone in Women
1. Increases libido and sex drive
2. Improves mood (reduces irritability, depression and anxiety)
3. Helps increase lean muscle mass and increases metabolism
4. Helps with weight loss by increasing energy levels and increasing muscle mass production
5. Increases and stabilizes energy levels
- How to check your testosterone levels:
+ Check free testosterone: should be in the top 50% of reference range
+ Check total testosterone: Should be in the top 50% of reference range
Dr. Westin Childs

DHEAS levels and Cognitive Function

Cross-Sectional Study (295 women aged 55±12)

Higher endogenous DHEAS levels are independently and favorably associated with:

- Brain executive function
- Simple concentration
- Working memory
- General better cognitive performance
- Living with other people, doing crosswords, playing a musical instrument

Davis SR, JCEM Dec 2007

Conclusions

- The safety of HT largely depends on age
- Women younger than 60 years should not be concerned about the safety profile of HT
- New data and re-analyses of older studies by women's age show that, for most women, the potential benefits of HT given for a clear indication are many and the risks are few when initiated within a few years of menopause

Thank you for your attention!

H·E·A·T

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Luxembourg