



# Dilemma of Research

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It takes few months to publish wrong data

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It takes 10 years to correct it



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“You can always count on the Americans to do the right thing, after they have tried everything else”

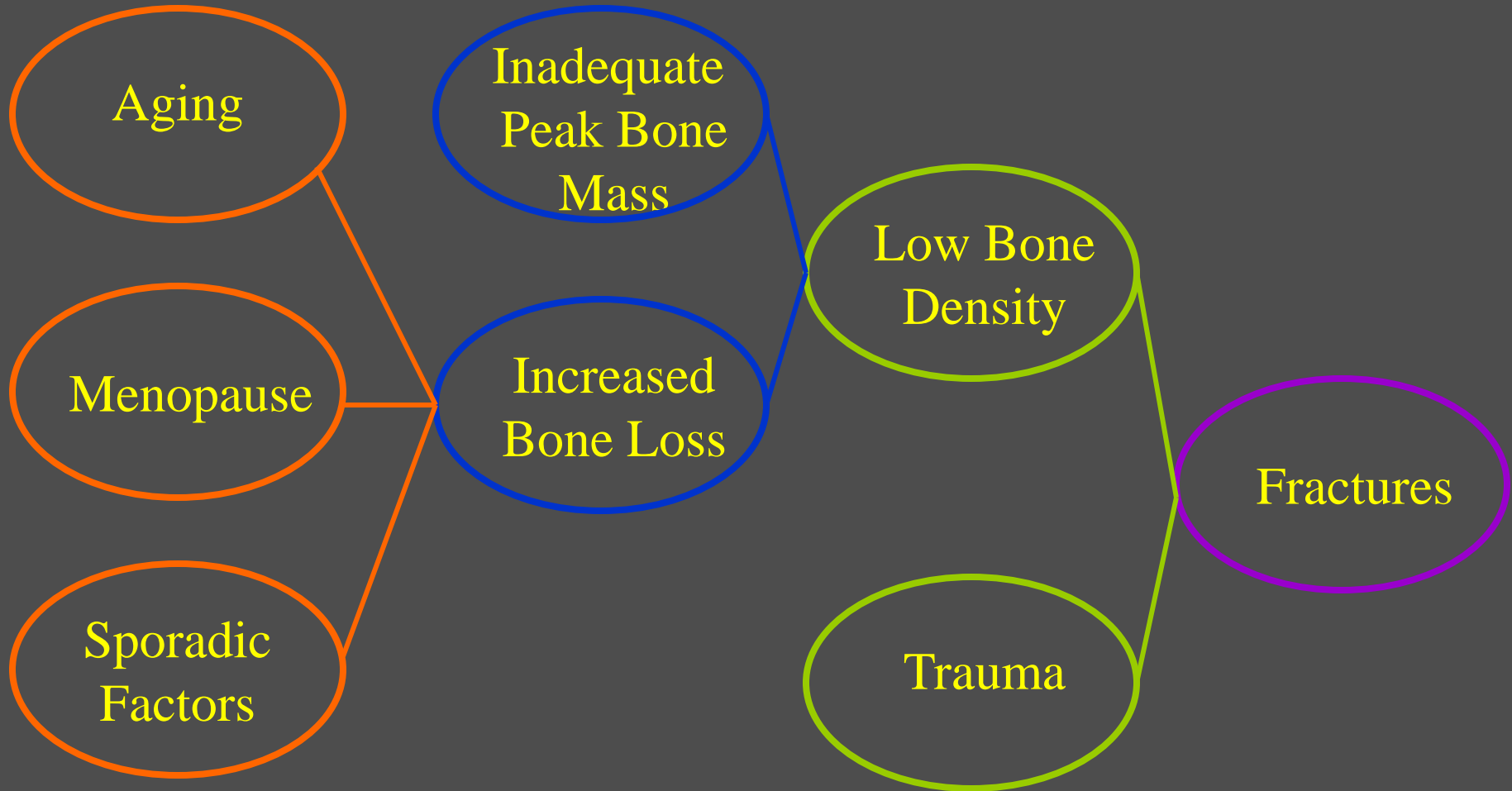
**Churchill WS**



Having nine lives is cool,  
but if you have to go through  
menopause nine times  
- forget it !



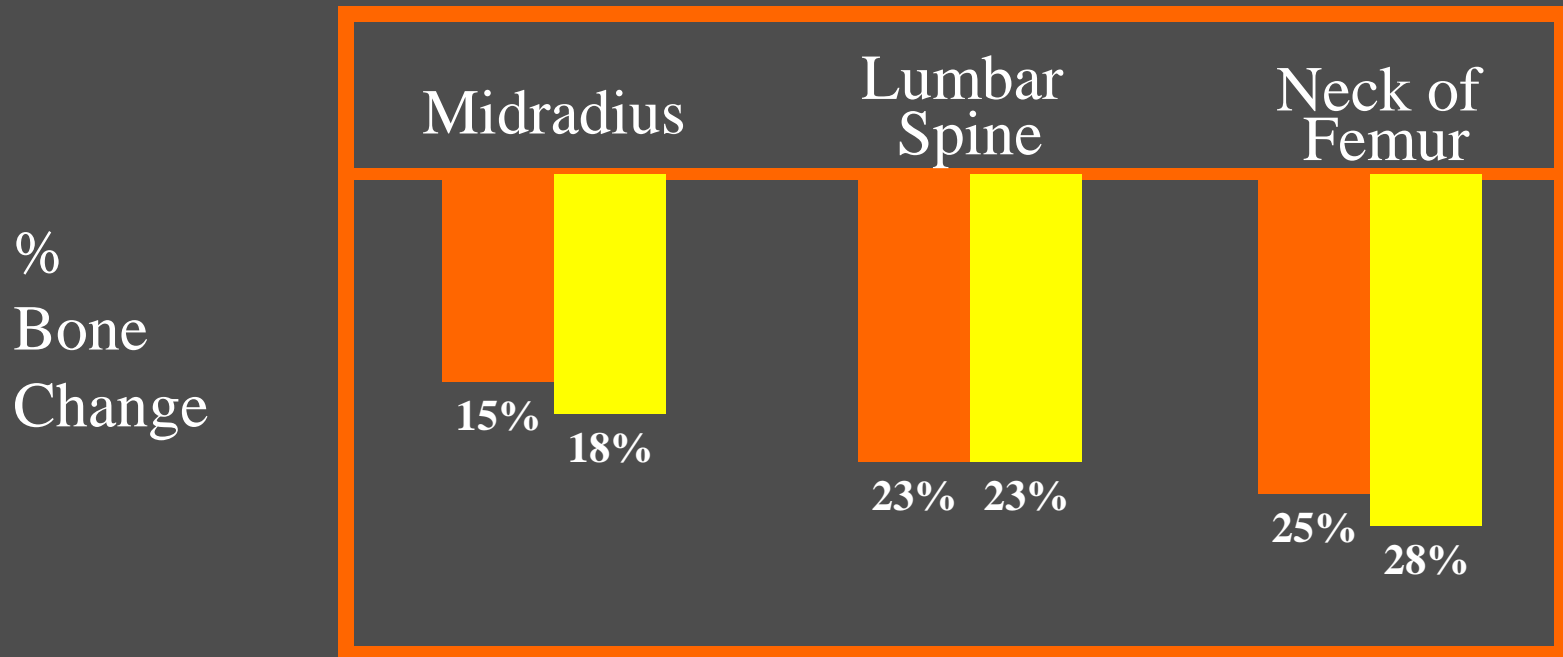
# Pathogenesis of Osteoporosis

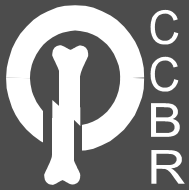




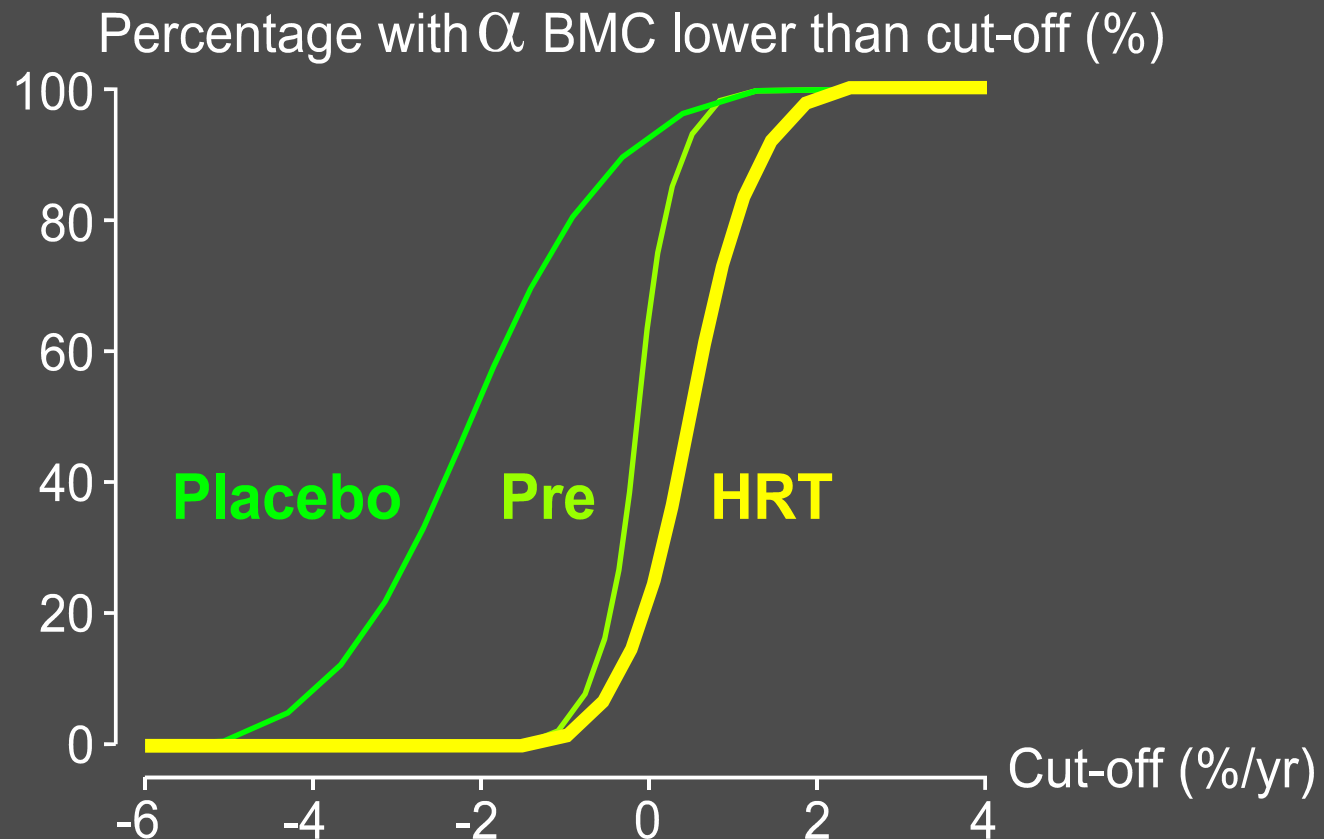
# Effects of Age and Menopause on Bone Mass

- Oophorectomized Cases
- Postmenopausal Controls





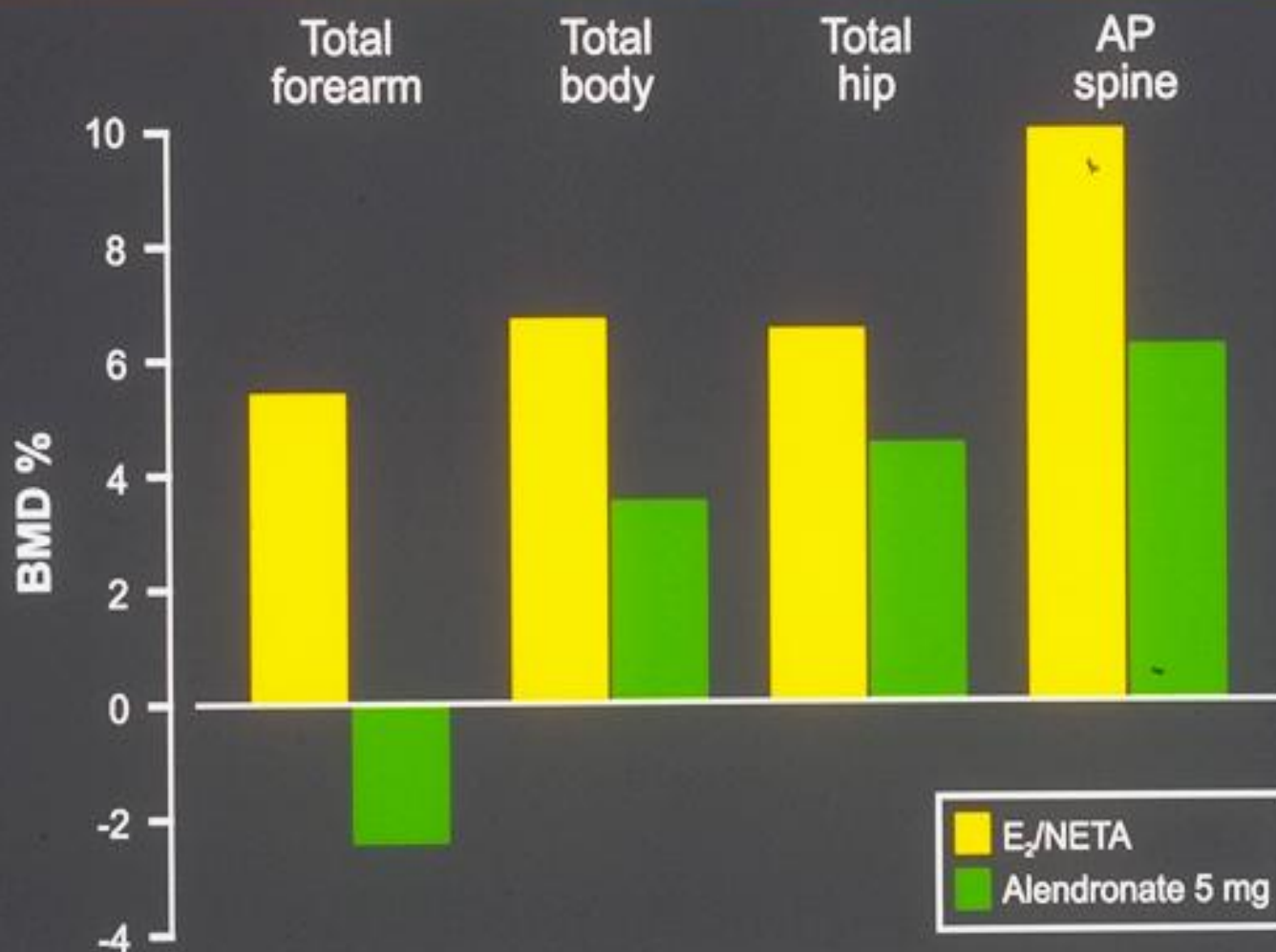
# Fraction of Non-responders to HRT as a Function of Cut-off Level

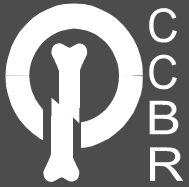


Non-responders : Women with an  $\alpha$  BMC below the cut-off level while receiving HRT.



# The Effect of E<sub>2</sub>/NETA and Alendronate (5 mg). Placebo corrected - 4 years.





# Effect of HRT on Fracture Risk

Fracture	Study	Author	Relative Risk
Hip	Case-control	Weiss (1980)	0.43
	Case-control	Johnson (1981)	0.72
	Case-control	Paganini-Hill (1981)	0.42
	Case-control	Krieger (1982)	0.56
	Case-control	Ross (1984)	0.44
	Cohort	Kiel (1987)	0.63
Spine	Cohort	Naessen (1990)	0.70
	Cohort	Wasnich (1986)	0.50
Wrist	Trial	Ettinger (1985)	0.30
	Trial	Ettinger (1985)	0.60



# Conclusion

**Estrogen therapy + appropriate doses of progestogens results in:**

- **Increase in HDL cholesterol**
- **Decrease in LDL cholesterol**
- **Decrease in total cholesterol**
- **No change in triglycerides (and VLDL cholesterol)**



## Effects on other risk factors

**HRT – with or without  
progestogen – results in:**

- **Decrease in diastolic blood pressure**
- **Reduction in body weight**
- **Changes in body composition;  
LBM $\uparrow$ , FAT MASS $\downarrow$**
- **Redistribution in body fat from  
android to gynecoid pattern**



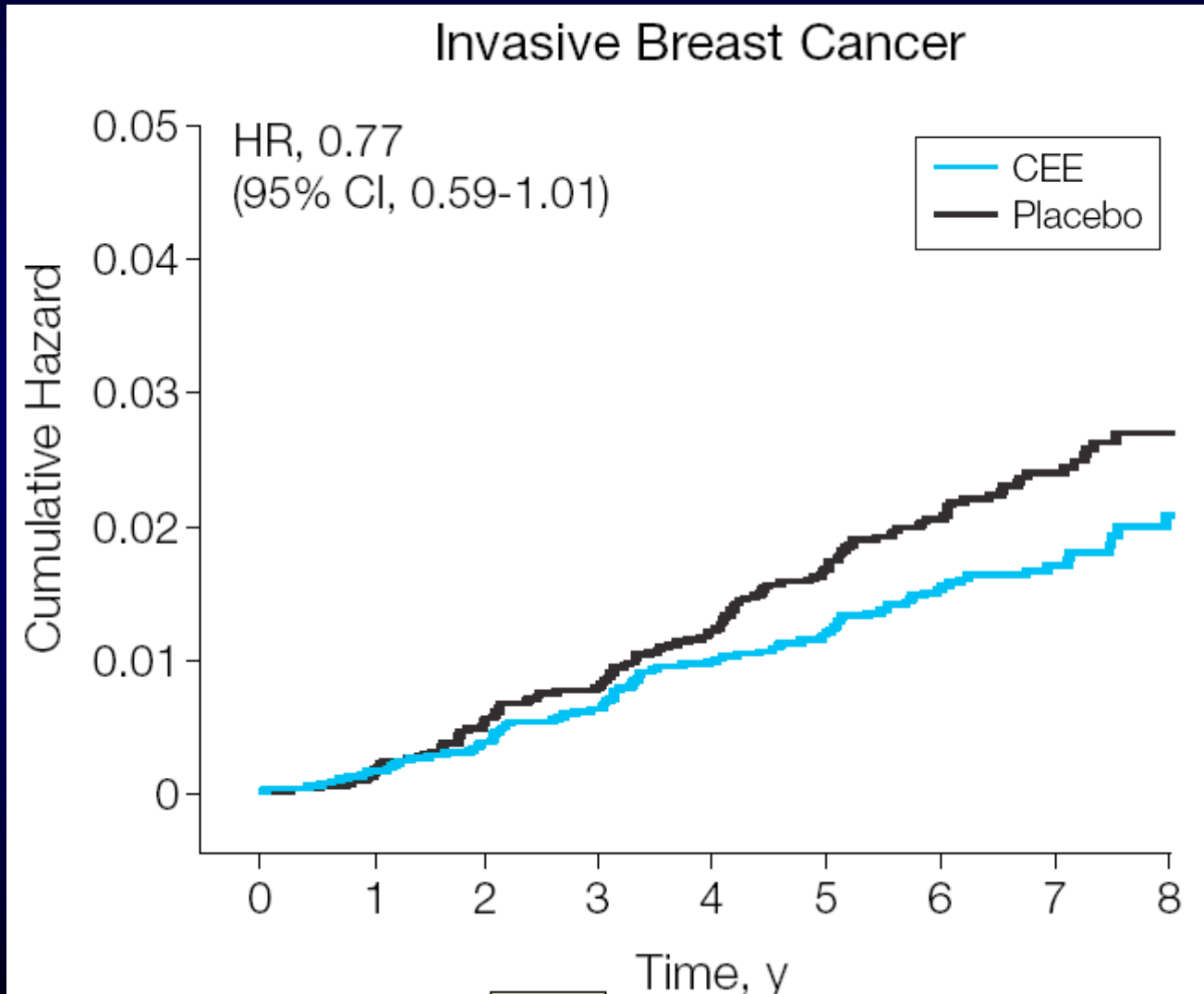
## HRT – time to consider WHI

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- Mean age was 63 at baseline
- 2/3 were overweight/obese
- 3 years HRT did not pose any health hazards
- Previous HRT users had decreased breast cancer risk

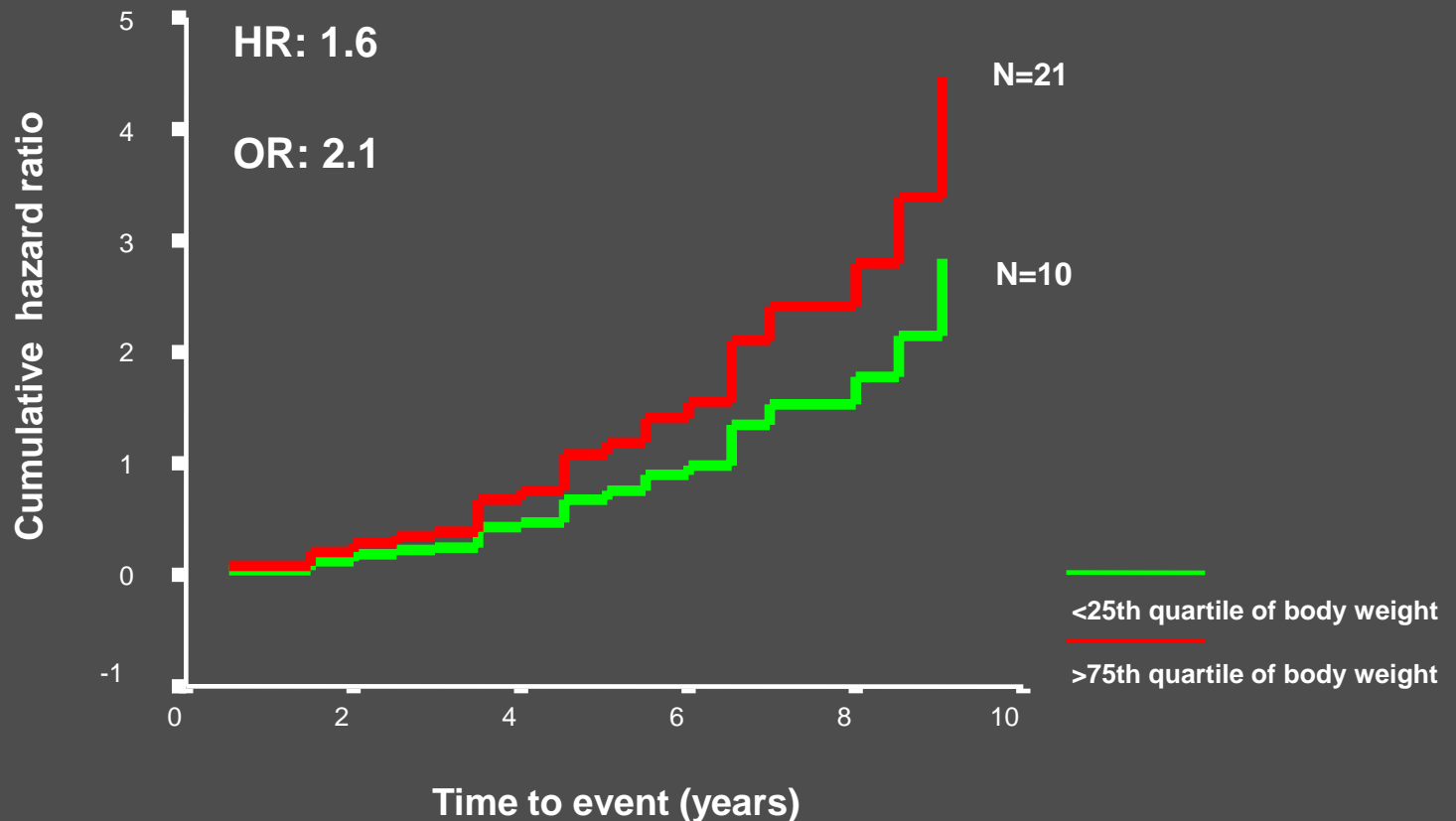
**? What are the long term effect of short term HRT**

# WHI: CEE-ALONE





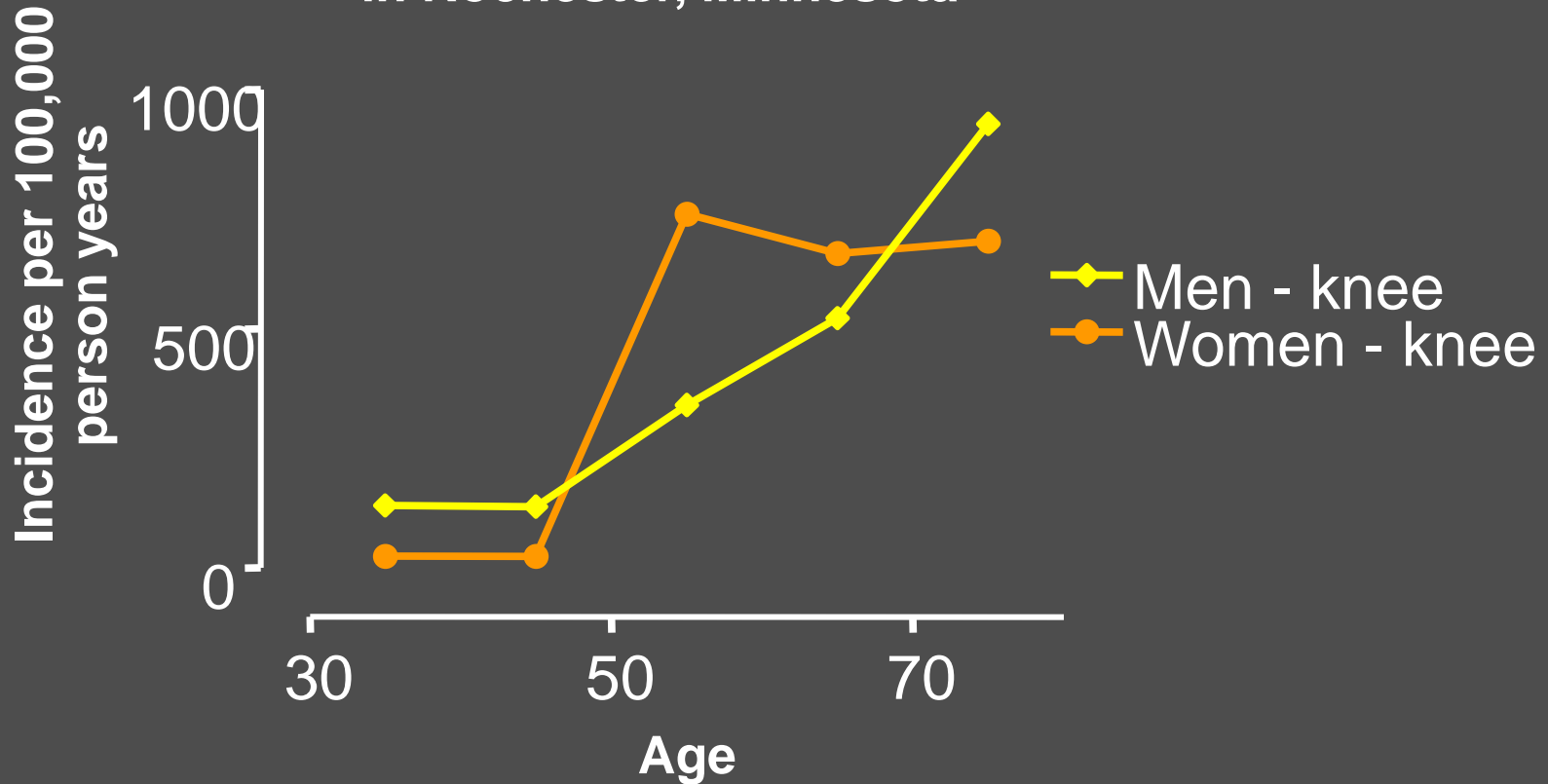
# Relative risk of estrogen-related cancers in overweight versus lean women





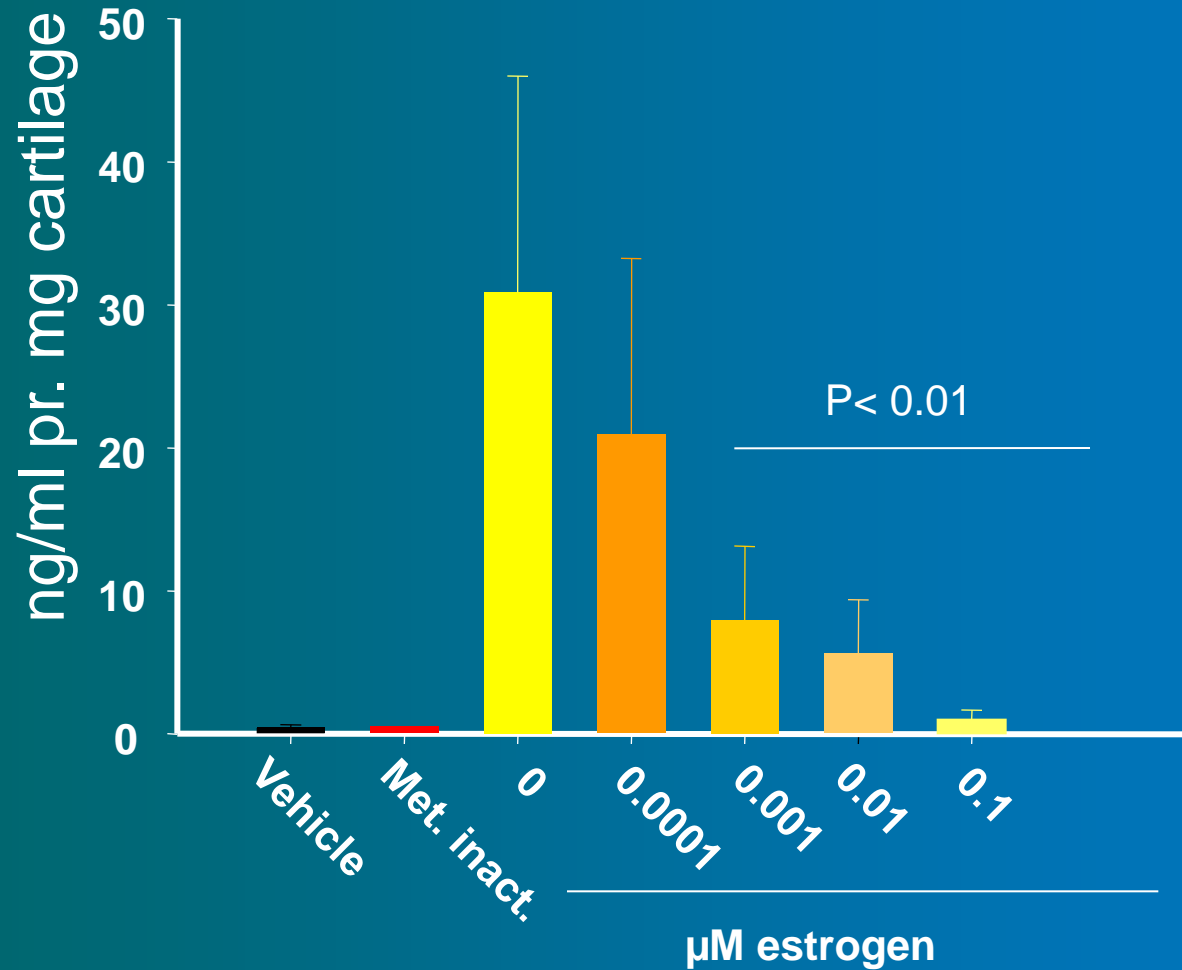
# OA and Cartilage Degradation Increases after the Menopause

Incidence of hip and knee OA  
in Rochester, Minnesota



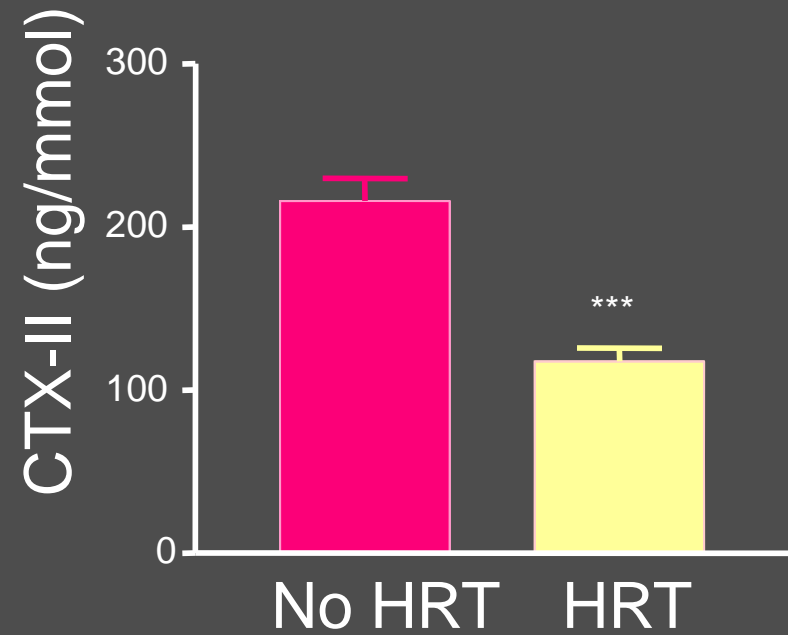
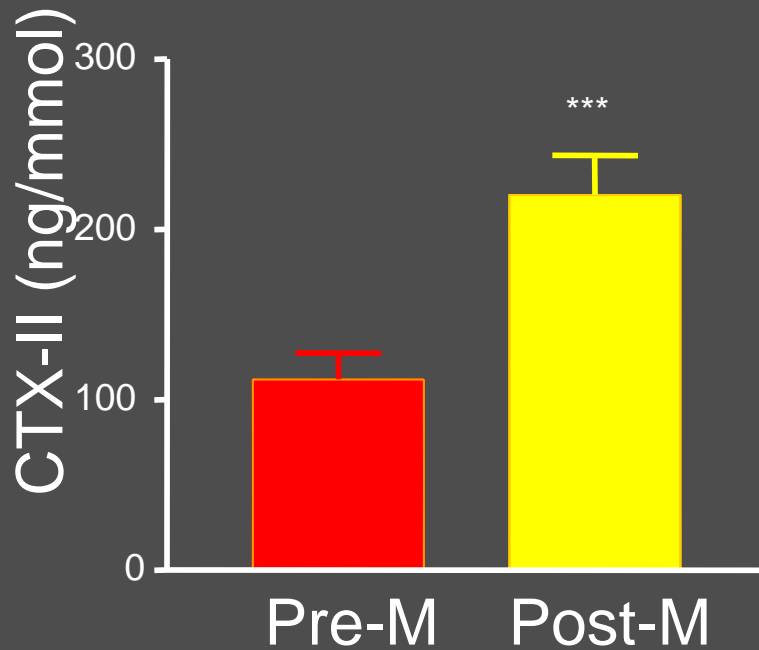
# The Cartilage Explant Culture System

## Estrogen has direct chondroprotective Effects





# Cartilage, an Estrogen Responsive Tissue



# WHI – Unopposed-estrogen

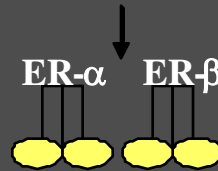
	Estrogen N=5076	Placebo n=5196	HR (95% CI)	P
Total Joint Replacement	119	169	0.73 (0.58-0.93)	0.01
Hip Joint Replacement	28	53	0.55 (0.35-0.88)	0.01
Knee Joint Replacement	93	121	0.8 (0.61-1.05)	0.11

Compliance more than 80%



# Mechanisms by which estrogen is believed to convey chondroprotective effects

## Estradiol



### Anabolic

TGF, IGF-1

↑ Chondrocyte proliferation  
↑ Chondrocyte maturation

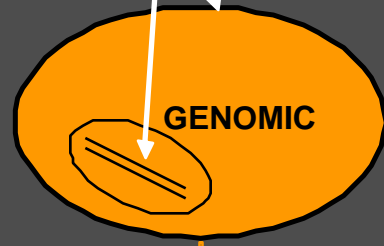
↑ Proteoglycan synthesis  
↑ Collagen synthesis

### Catabolic

IL-1, IL-6

MMP-1, MMP-3, MMP-13 ↓  
TIMP-1 ↑

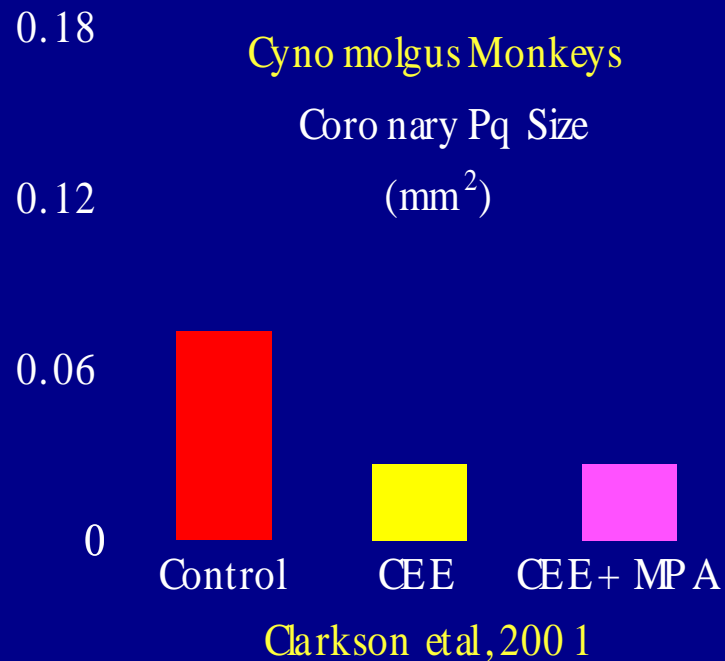
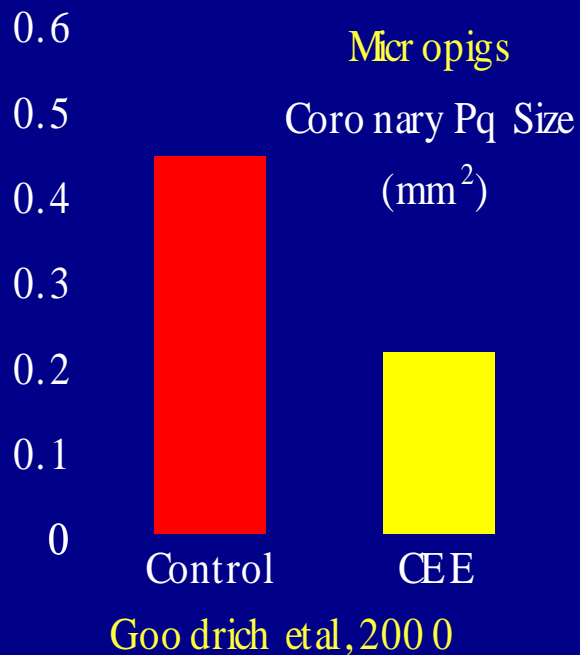
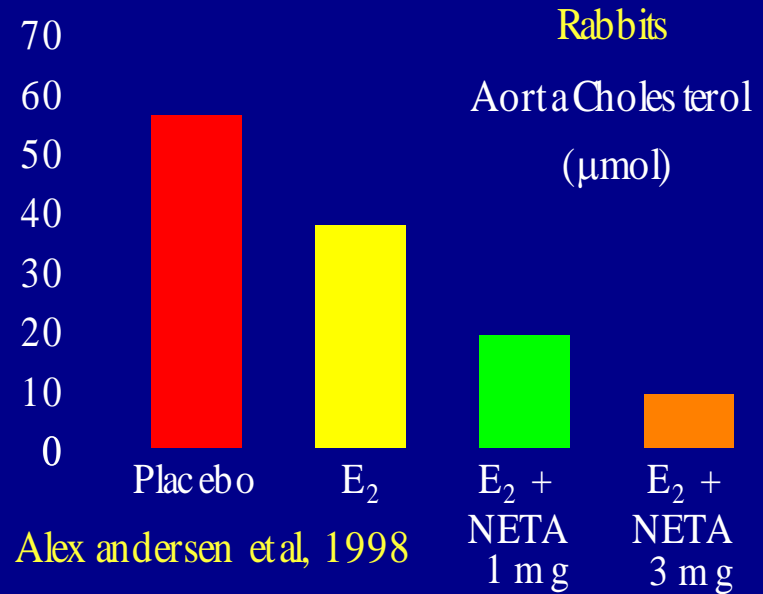
Proteoglycan degradation ↓  
Collagen degradation ↓↓



Decreased collagenolytic activity  
Increased cartilage matrix synthesis

Improved cartilage health?

# "Primary Prevention" of Atherosclerosis Progression of Relevant Animal Models



# Isolation of groups with different forms of body fat distribution from 1356 elderly women



QTR of Central fat%





1/4	2/4	3/4	4/4
1/3	2/3	3/3	4/3
1/2	2/2	3/2	4/2
1/1	2/1	3/1	4/1

QTR of Peripheral fat%





# Estradiol metabolism in elderly women with different forms of body fat distribution

					
E2 pmol/l	45,8	48,08	58,06 +	53,3	P<0.00 1
SHBG nmol/l	84,39	86,87	47,62 *	62,34	P<0.00 1
Free E2	68,13	63,00	155,0 *	98,7	P<0.00 1

Bound-E2



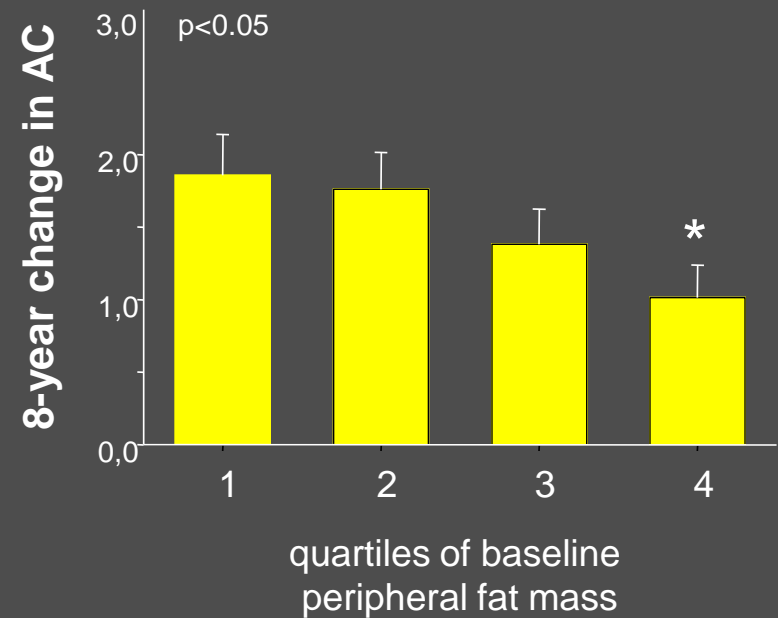
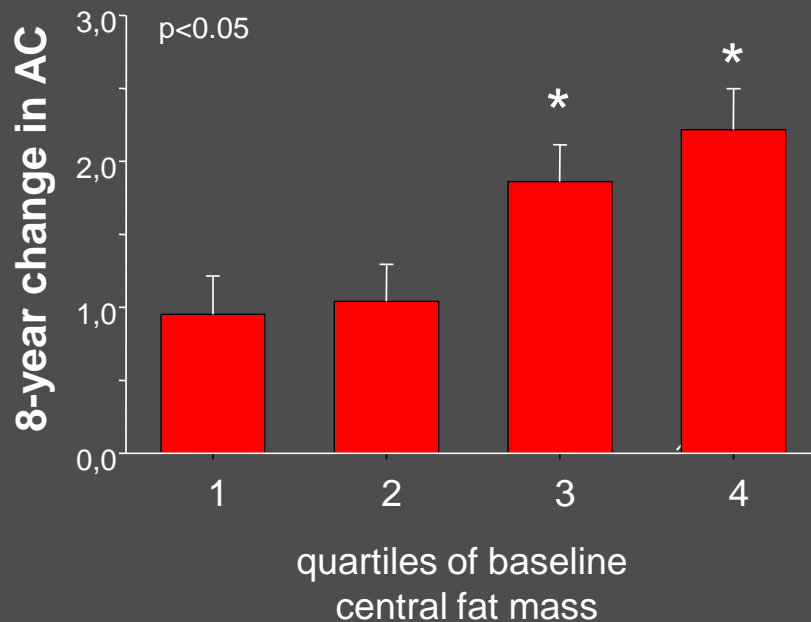
  
Free-E2

+ vs lean; \* vs all

Tankó et al *Circulation* 2004, in press



# Independent contribution of fat depots to the 8-year progression of aortic calcification in elderly women

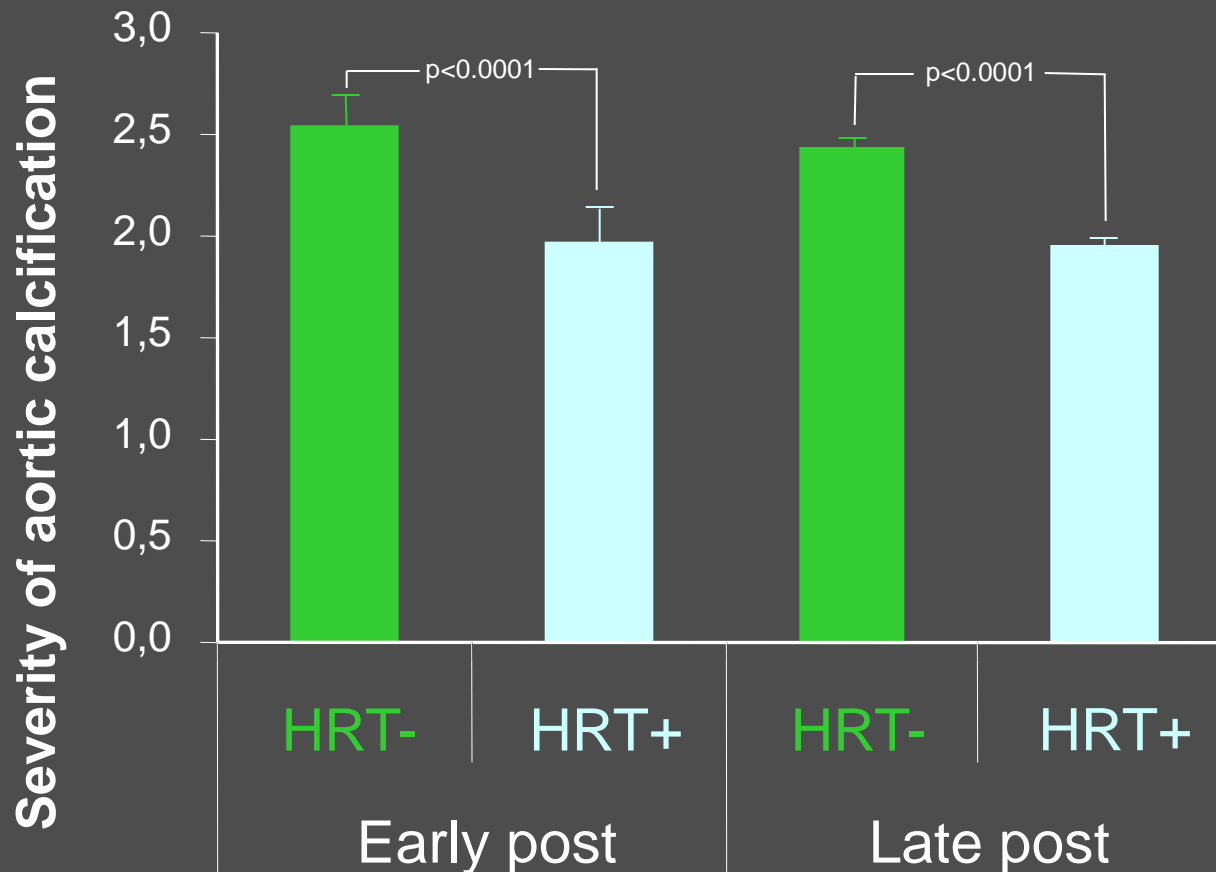


\* vs. 1st quartile

# HRT and aortic calcification

N = 1280

Adjusted for age and BMI

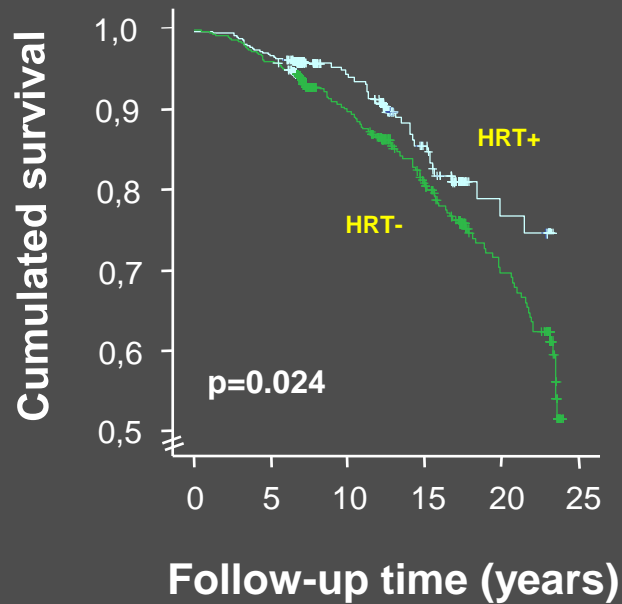




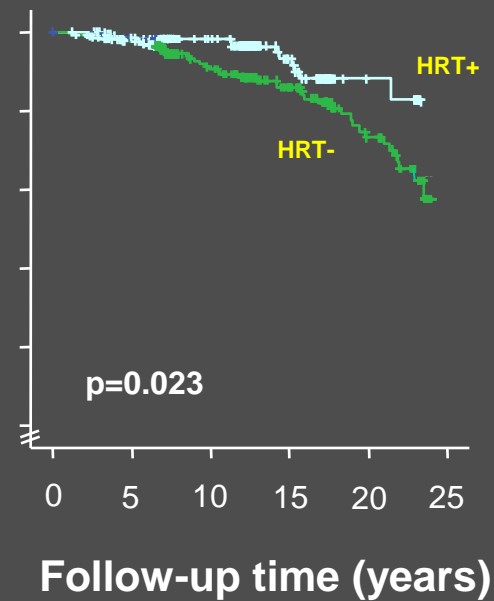
# HRT and mortality

N = 1280; No. of deaths=174  
Age at baseline =  $55.6 \pm 6.1$  years

## All-cause mortality

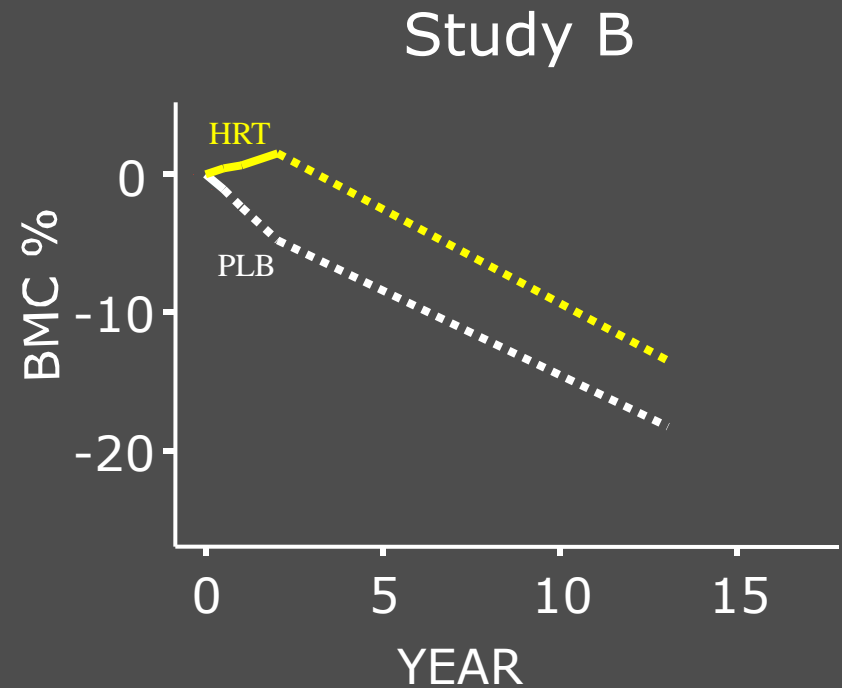
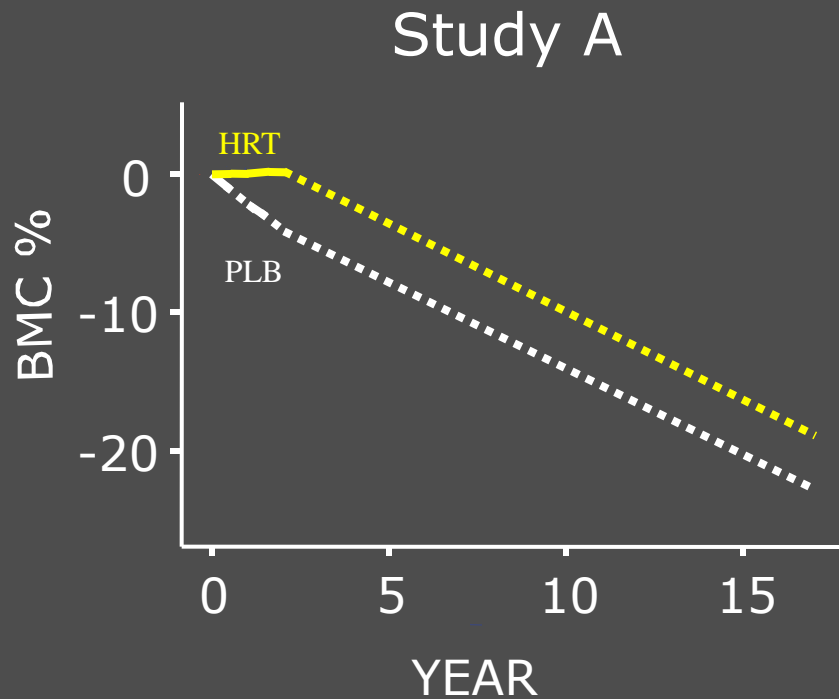


## CVD mortality



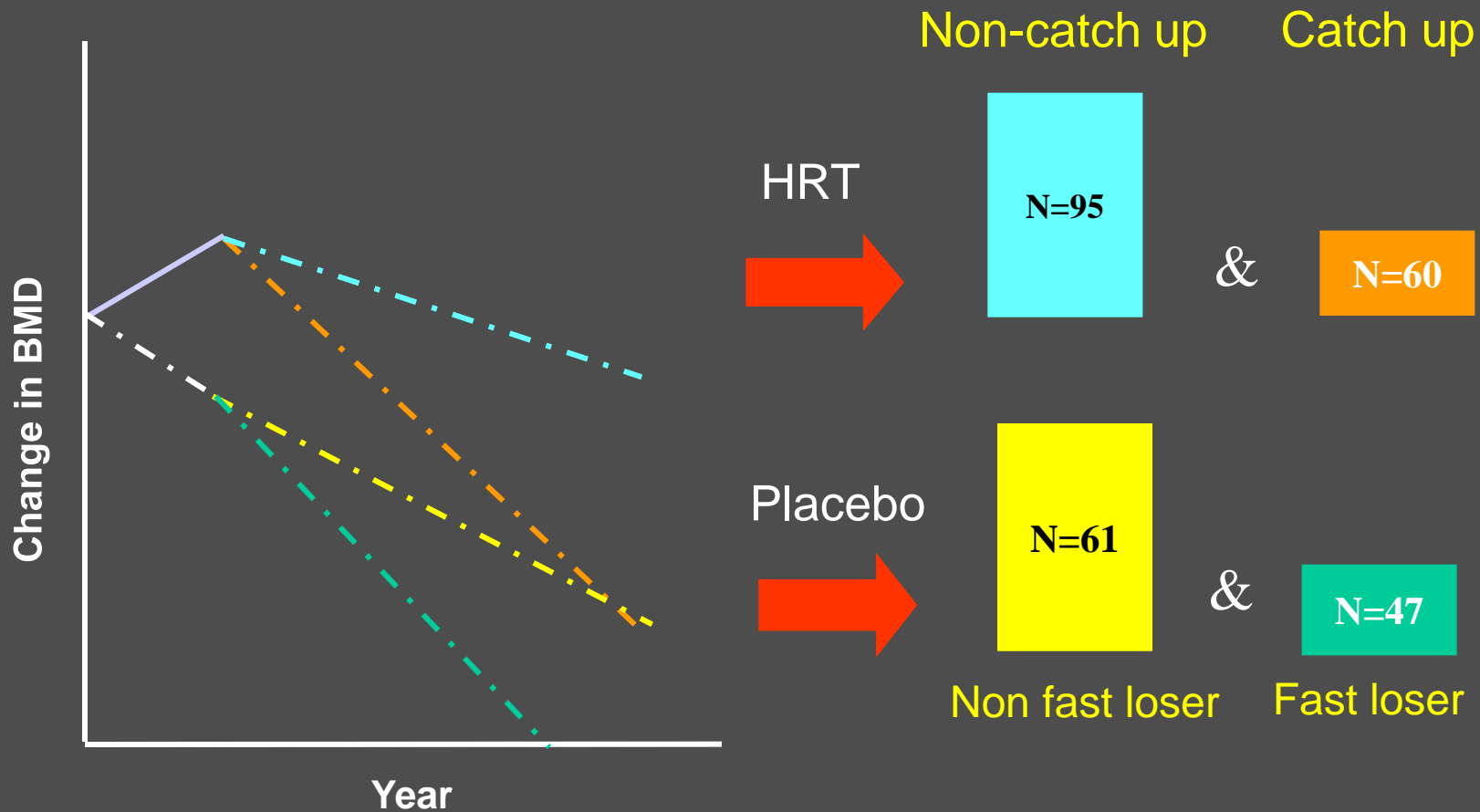


# Longitudinal Changes in Forearm BMC



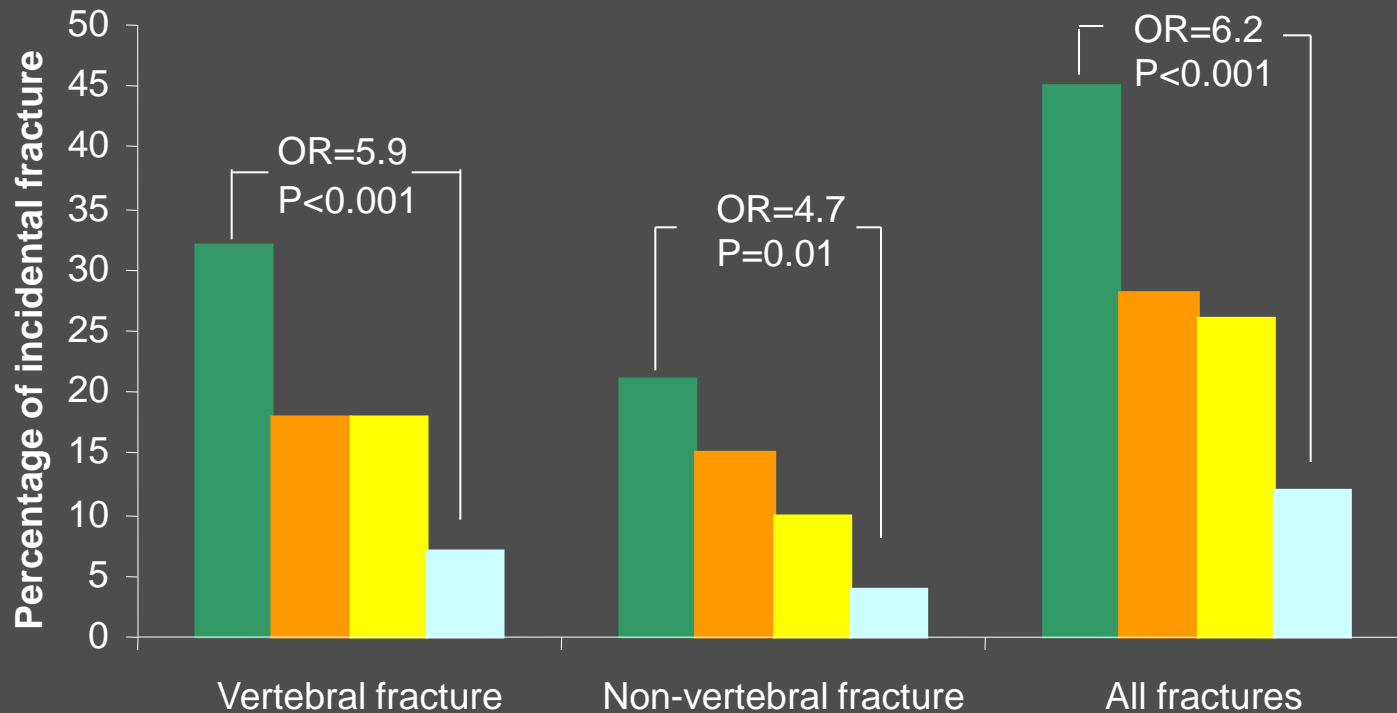


# Definition of "Catch up" bone loss and "Fast loser"





# Incidence of osteoporotic fracture between the groups



Fast loser    Catch up    Non-fast loser    Non-catch up



CCRR

# Reduction of cognitive decline after 2 years of HRT

Cognition	Placebo (n=107)	HRT (n=154)	OR (95%CI)	P value
Score $\geq$ 6	14	8	0.36 (0.15-0.90)	0.02
Score <6	93	146		



## HRT – time to consider PERF – 15 years after

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- 8% higher BMD
- 50% decreased risk of fracture
- Better cognitive function
- No increased risk of breast cancer
- Decreased atherogenesis
- Chondroprotective effects



# Treatment of Osteoporosis Yesterday, today, tomorrow

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## 1. Anti-resorptive agents

- ERT/HRT
- SERM
- Rank-L inhibitor
- Bisphosphonates

## 2. Formation stimulating agents

## 3. Combined regimens

## 4. Uncoupling agents



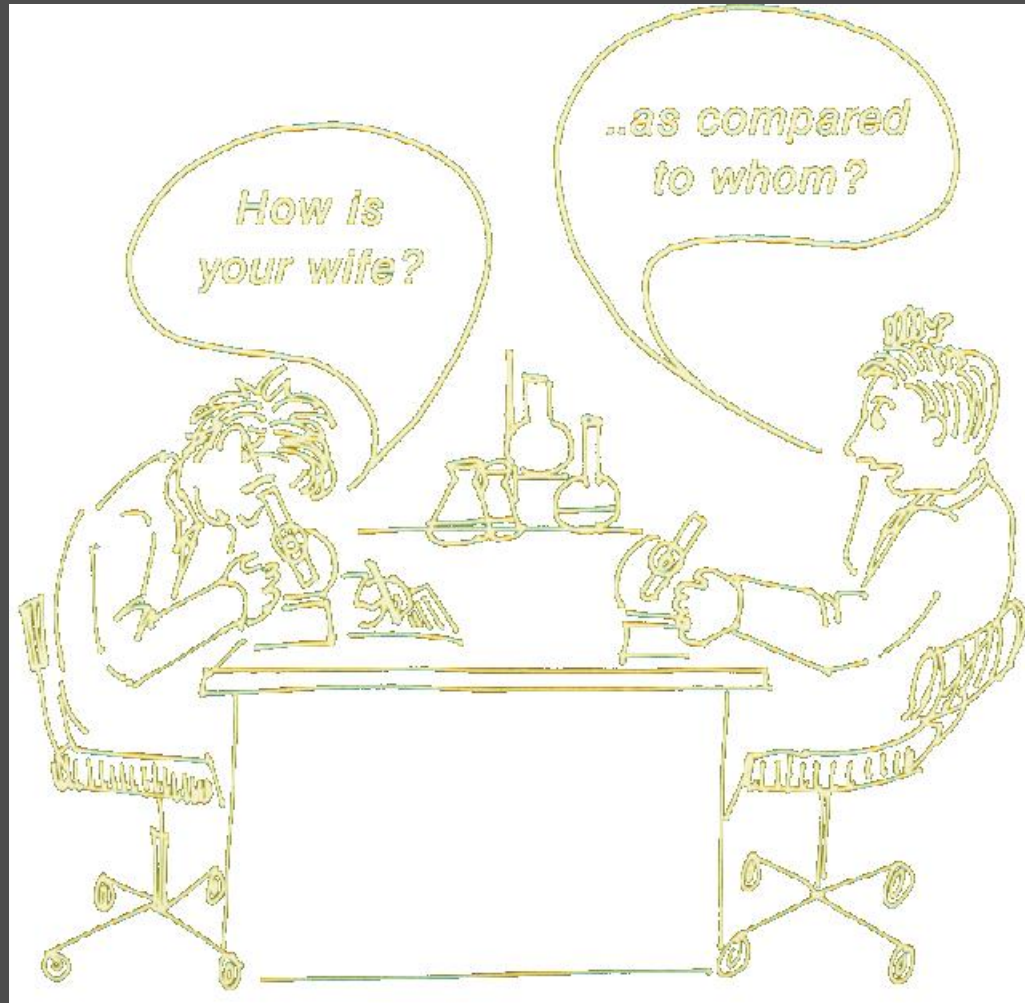
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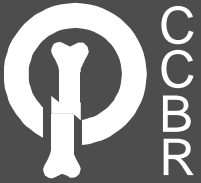
# Cost effectiveness of hormone therapy

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- The cost per QALY for a woman starting treatment with HRT at age 50 is 290-2800\$
- The acceptable cost for QALY is in the order of 30000-80000 \$
- **Fredrik Borgström**

# Scientific Approach ?



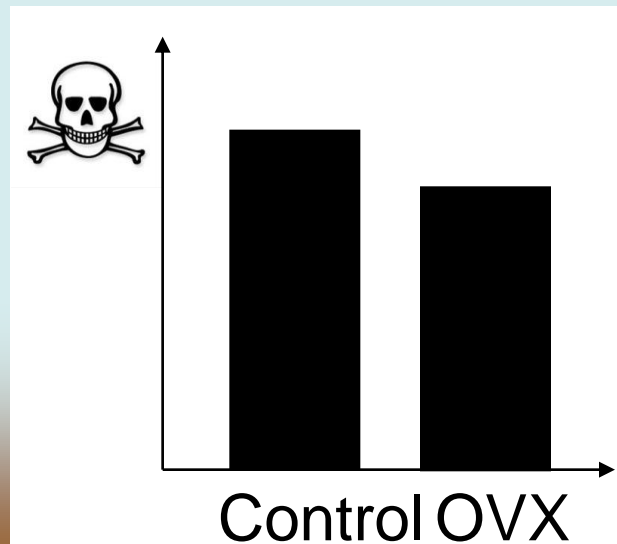


# Bisphosphonates

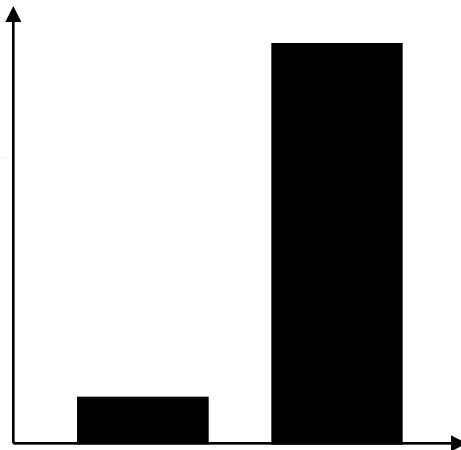
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1. Gastro intestinal side effects
2. Osteonecrosis of the jaw
3. Over suppression of bone turnover – Frozen bone
4. Musculoskeletal pain
5. Nephrotic syndrome
6. Life long half-life
7. Arterial Fibrillation
8. Others

Have you considered to get an Ovariectomy?



No, I would rather stop smoking!



Control Smoker