UNIVERSITEIT GENT

FACULTY OF MEDICINE AND HEALTH SCIENCES

Hypoandrogenism in the elderly: to treat or not to treat?
12th Italian AME Meeting; 6th joint Meeting with AAC
Bari november 10th

Update on diagnosis and complications of adult and elderly male hypogonadism

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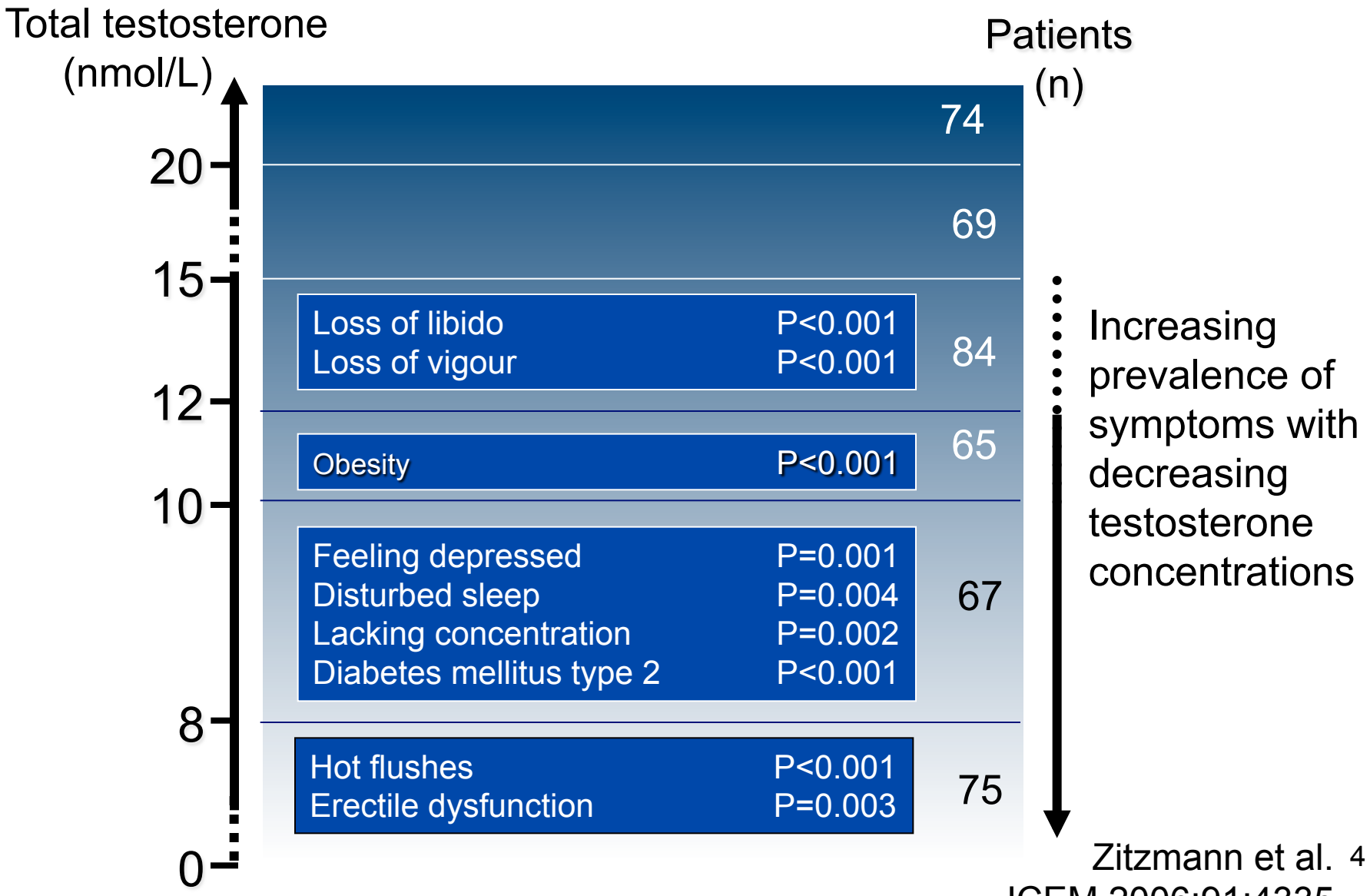
Clinical manifestations of male senescence *possibly* related to hypo-androgenism

- Decreased “general well-being” and “energy level”
- Decreased libido and increased frequency of erectile dysfunction
- Decreased sexual pilosity and skin thickness
- Decreased muscle mass and strength
- Increased fat mass (+altered distribution)

Clinical manifestations of male senescence *possibly* related to hypo-androgenism

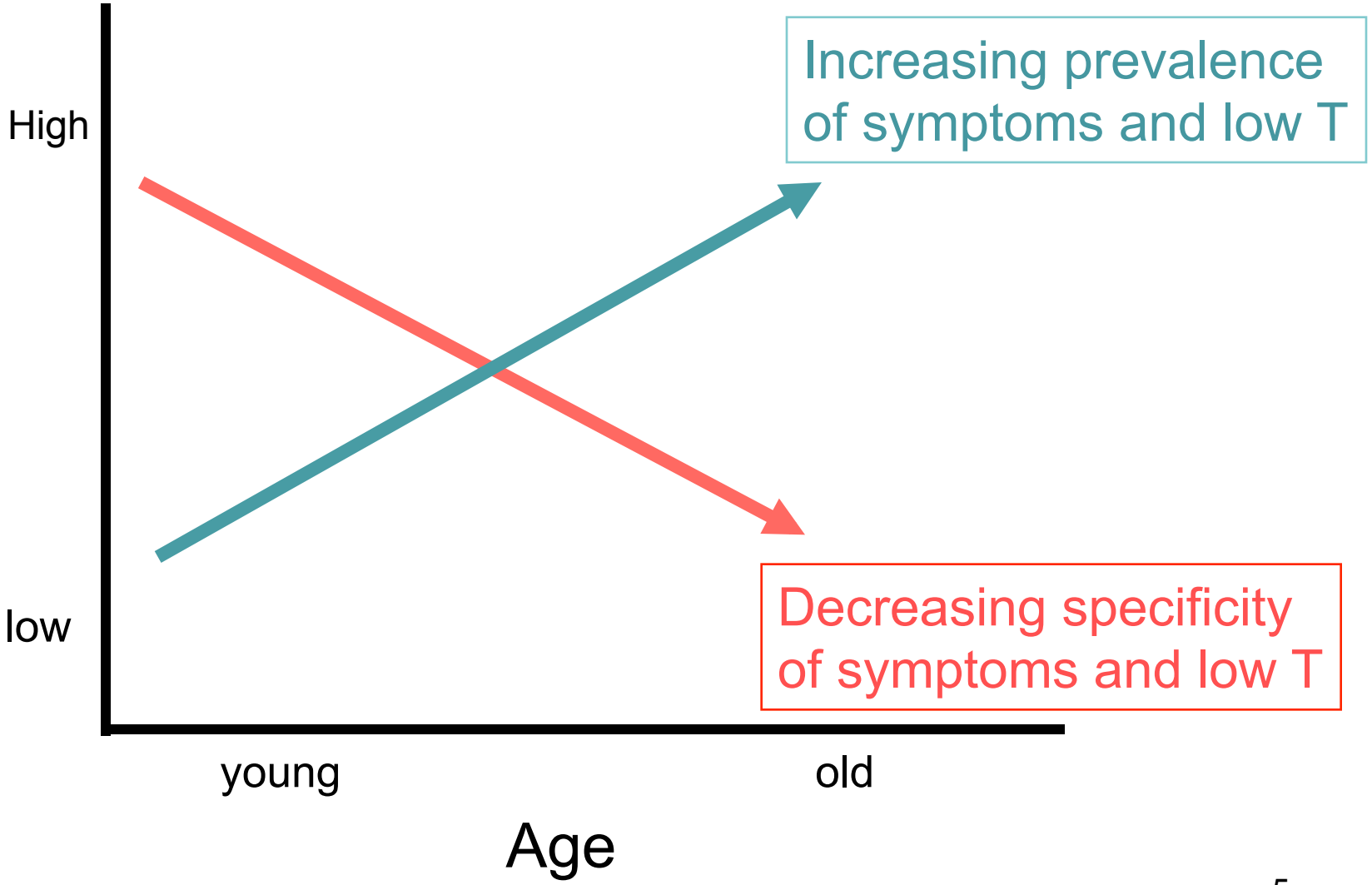
- Osteopenia
- Easy sweating; hot flushes
- Decreased red blood cell volume
- *Decreased immunocompetence*
- *Increased cardiovascular risk*
- *Regression cognitive functions*

Symptom-specific threshold testosterone levels for observed increase of prevalence in patients attending an andrology clinic

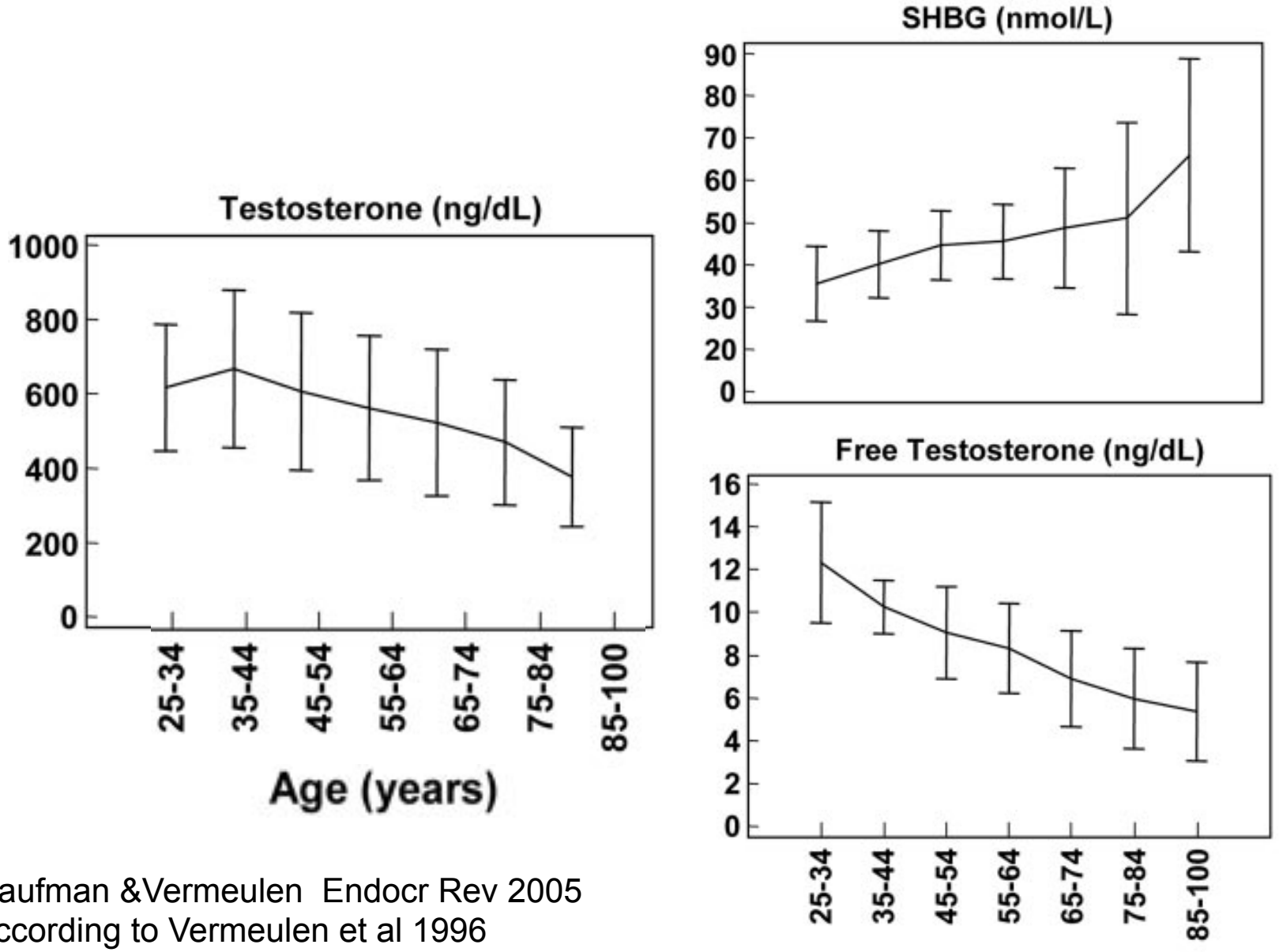


Zitzmann et al. [4]
JCEM 2006;91:4335

Symptoms of hypoandrogenism and low serumtestosteron(T)

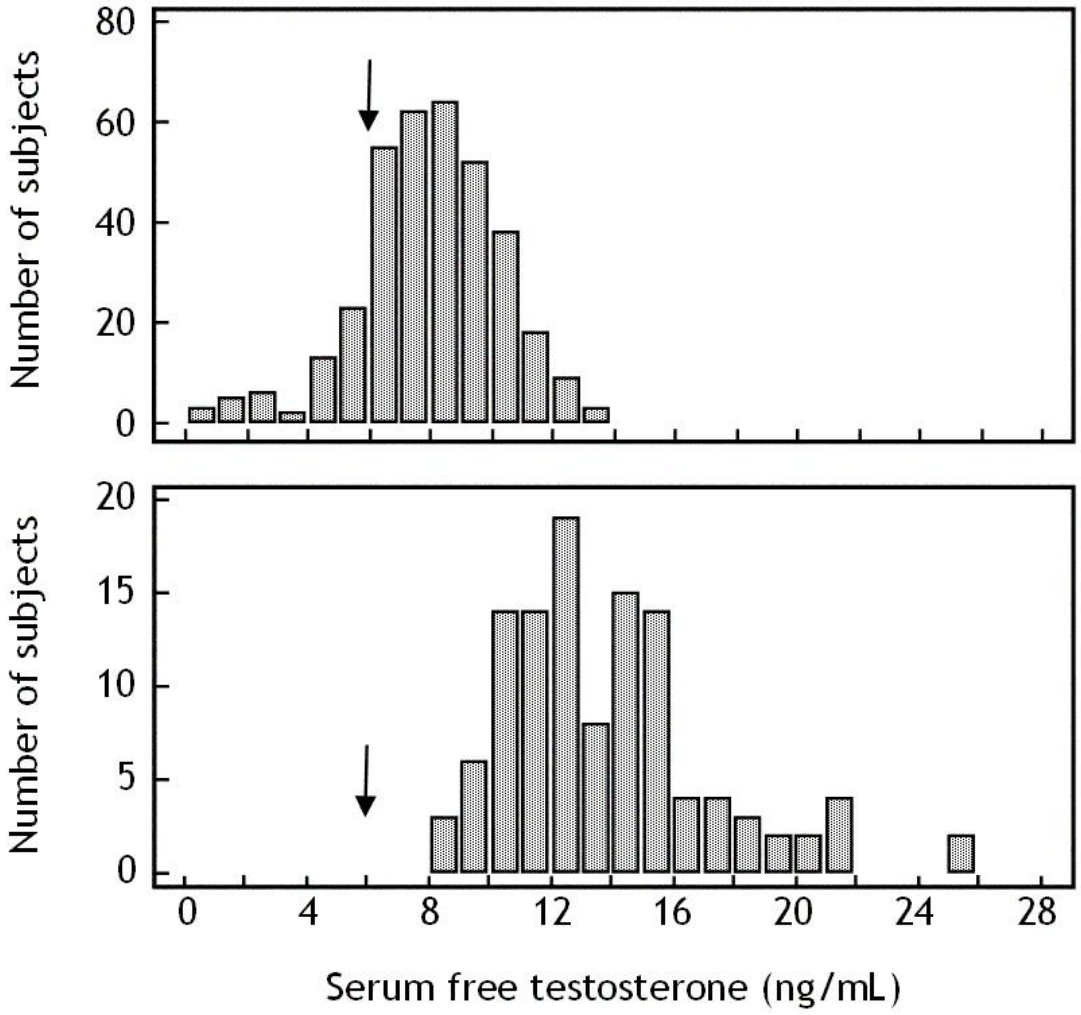


Serum testosterone and SHBG *vs* age (RIA)

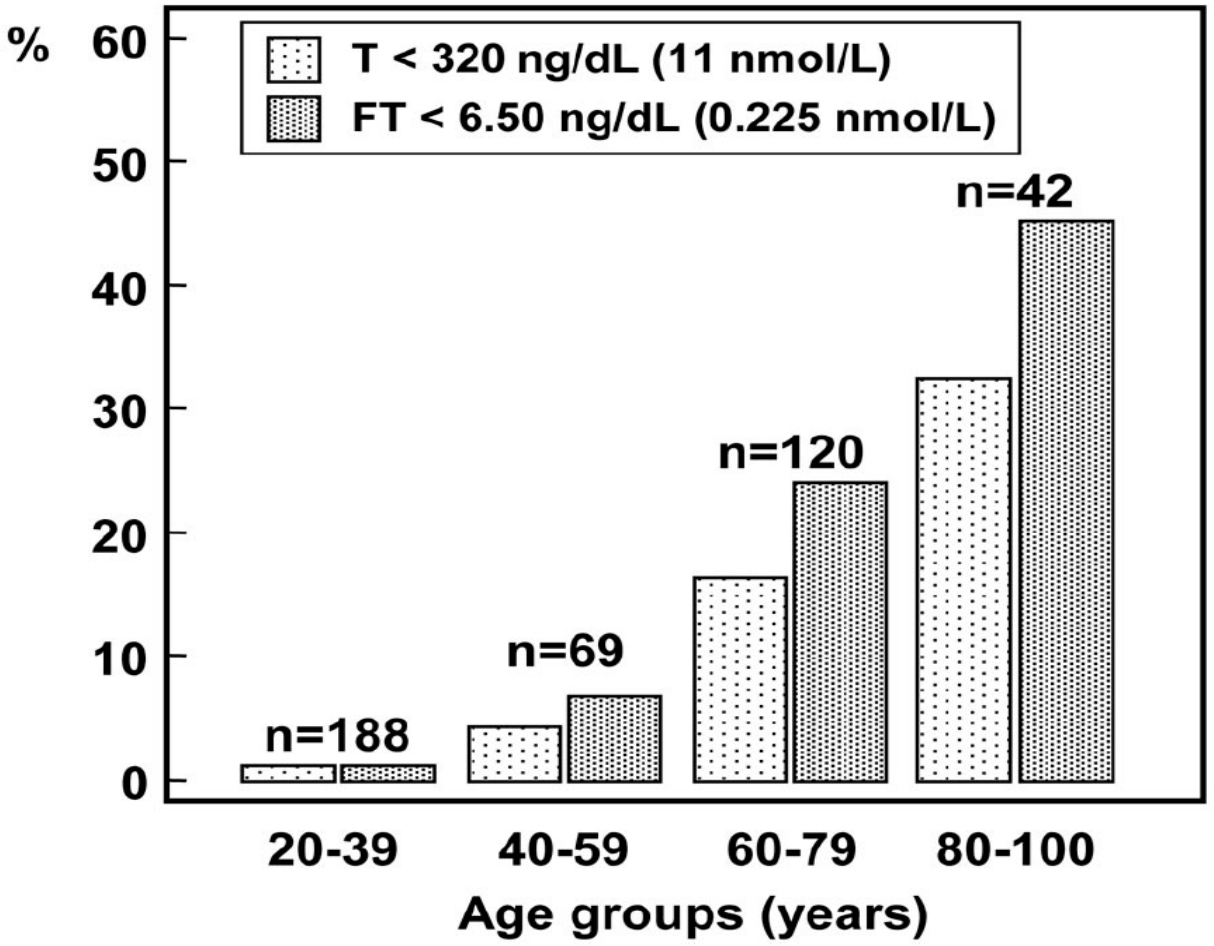


Kaufman &Vermeulen Endocr Rev 2005
according to Vermeulen et al 1996

Changes in free T distribution with age

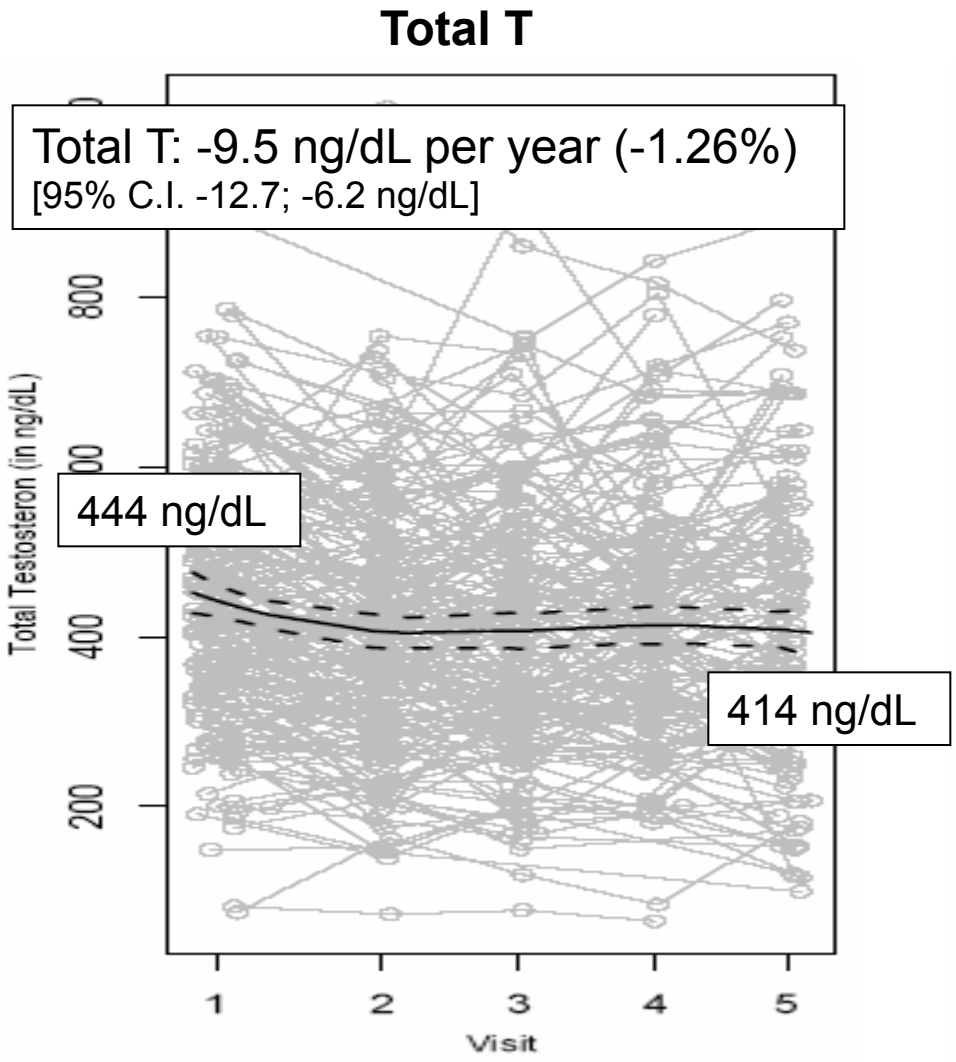


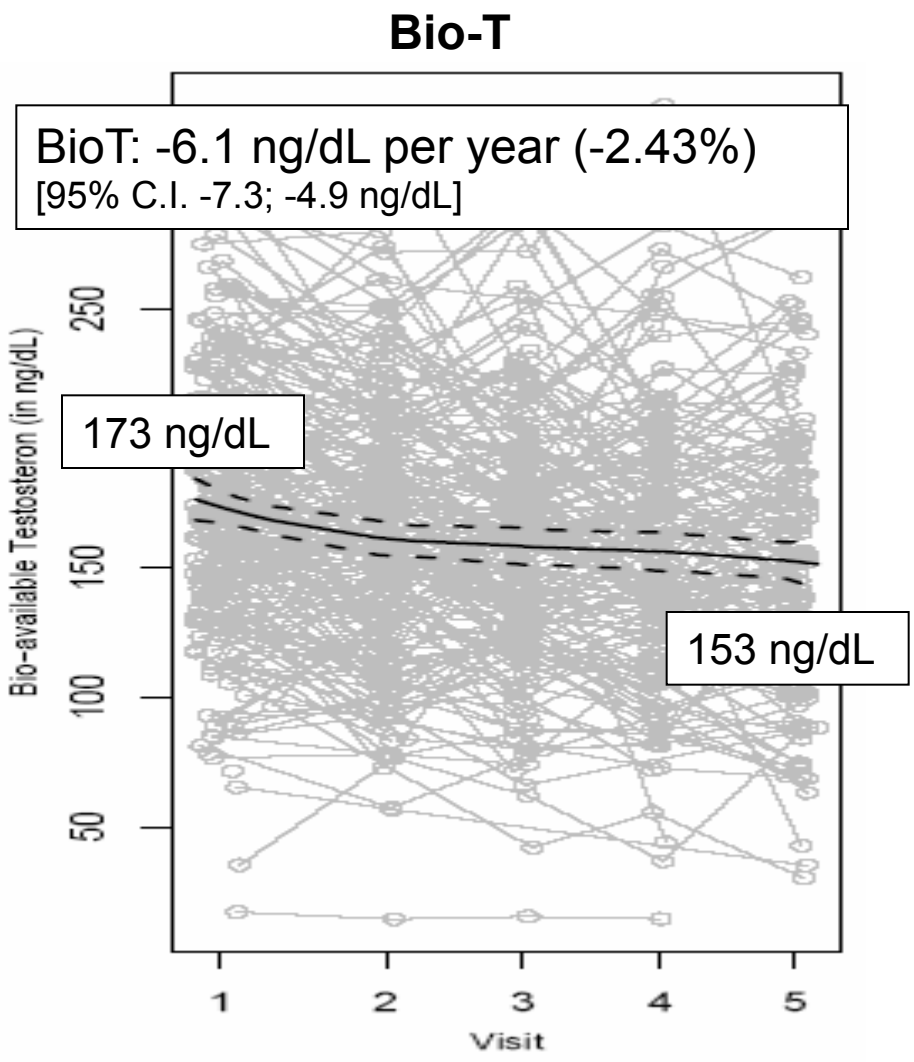
Prevalence in function of age of men with low (F)T



Kaufman &Vermeulen Endocr Rev 2005
according to Vermeulen et al 1996

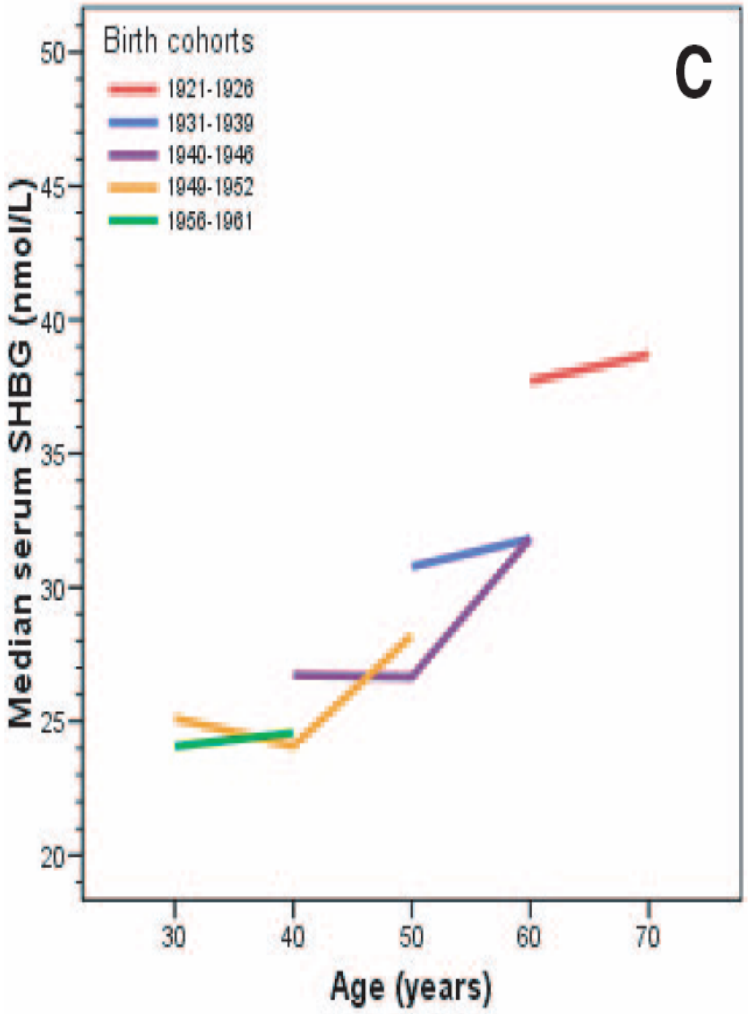
Evolution serum testosterone over 4yrs in community-dwelling men >70yrs (n=221)



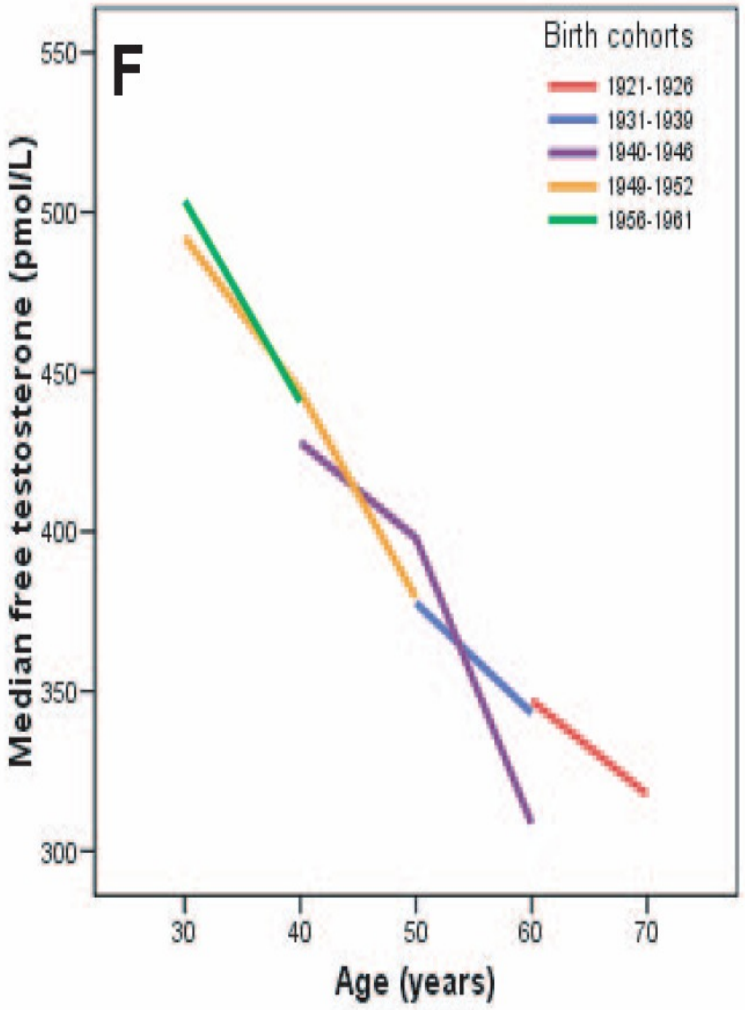


SHBG & free testosterone vs age and cohort effects

SHBG



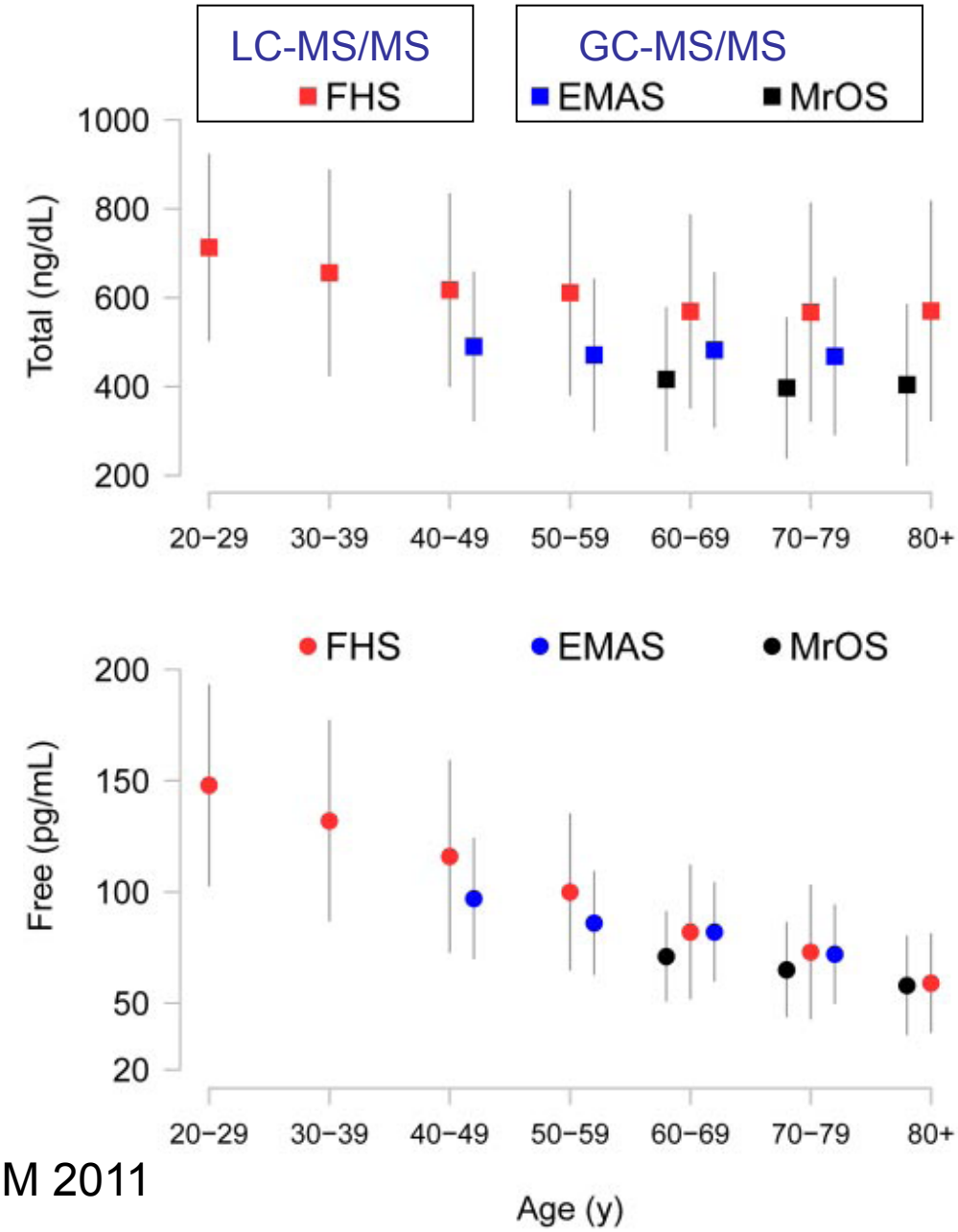
Free Testosterone



MONICA Denmark study population

Andersson et al J Clin Endocrinol Metab 92: 4696-4705; 2007

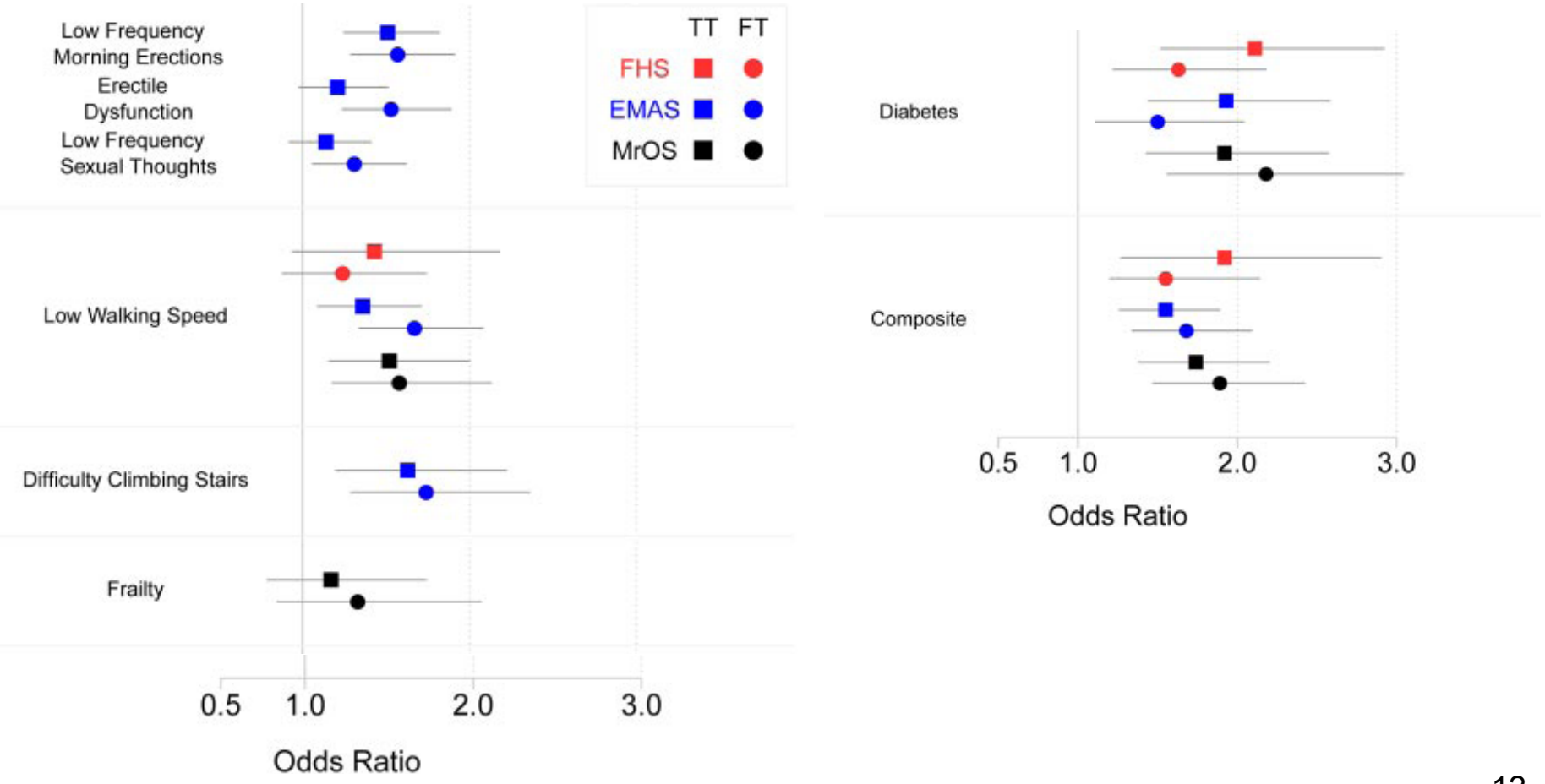
Serum testosterone *vs* age (LC-MS/MS & GC-MS/MS)



Bhasin et al JCEM 2011

Lower cut-off (percentile 2.5) for T by LC-S/MS in reference group of healthy young nonobese men (from FHS) applied to three cohorts:FHS; MrOS; EMAS

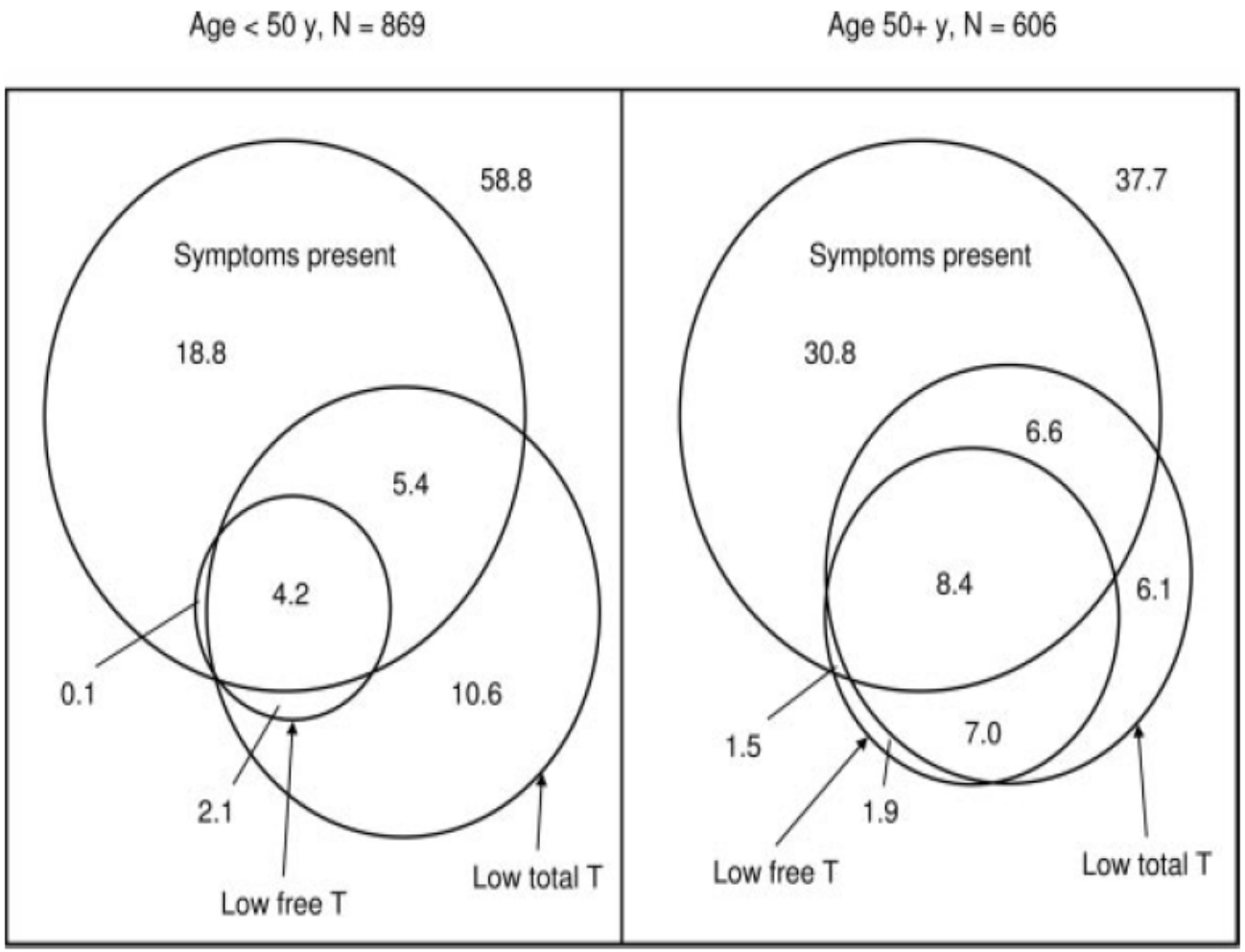
TT<348.3 ng/dl; FT<70pg/ml



Prevalence of symptomatic androgen deficiency in men
Boston Area Community Health (BACH) Survey

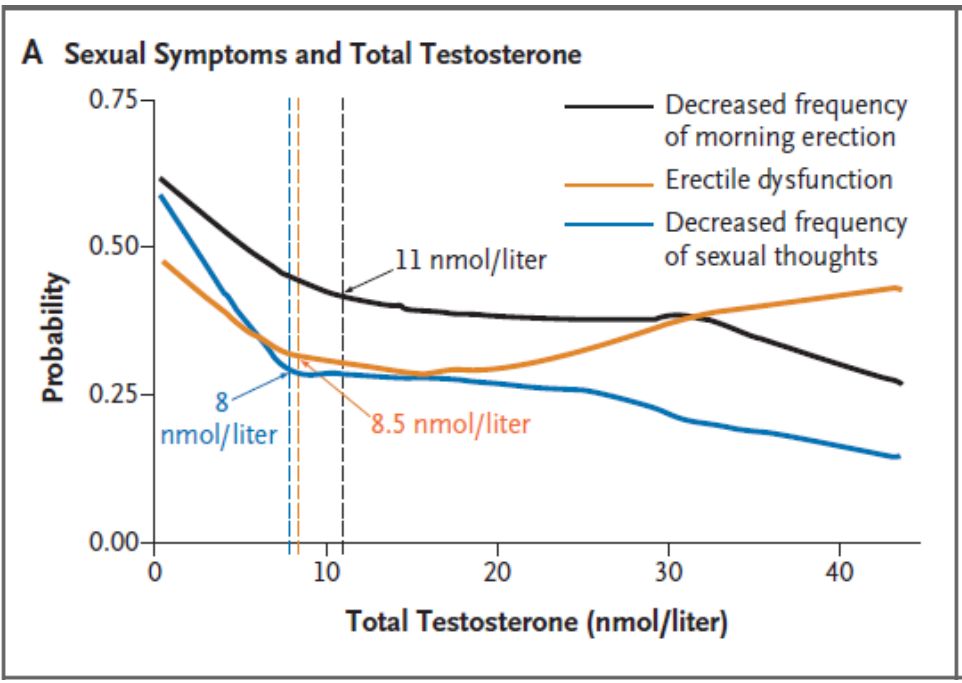
Low TT= <300ng/dl (10.4 nmol/L)

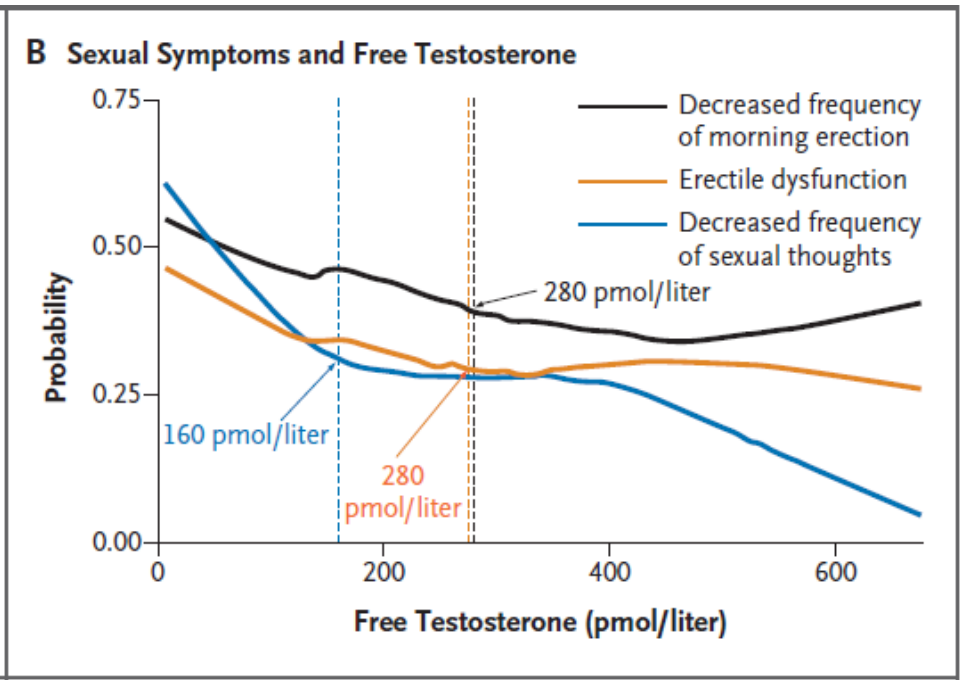
Low FT= <5ng/dl (0.17nmol/l)



Araujo et al JCEM 92:4241-4247; 2007

Identification of late onset hypogonadism (EMAS)



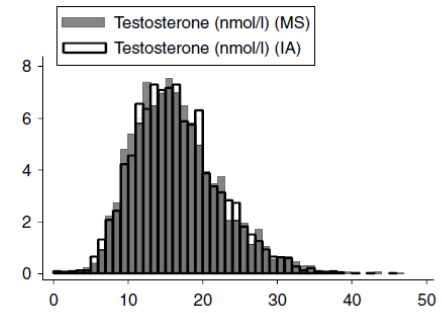


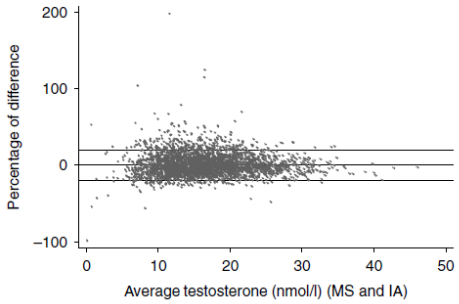
Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per liter (3.2 ng per milliliter) and a free testosterone level of less than 220 pmol per liter (64 pg per milliliter).

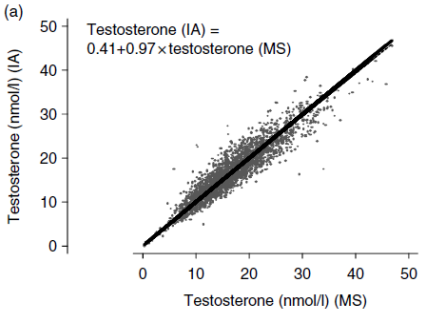
Prevalence: 0.1% 40-49y
0.6% 50-59y
3.2% 60-69y
5.1% 70-79y

Wu et al NEJM 363:123-35; 2010

Comparison serum testosterone in EMAS by immunoassay versus mass spectroscopy





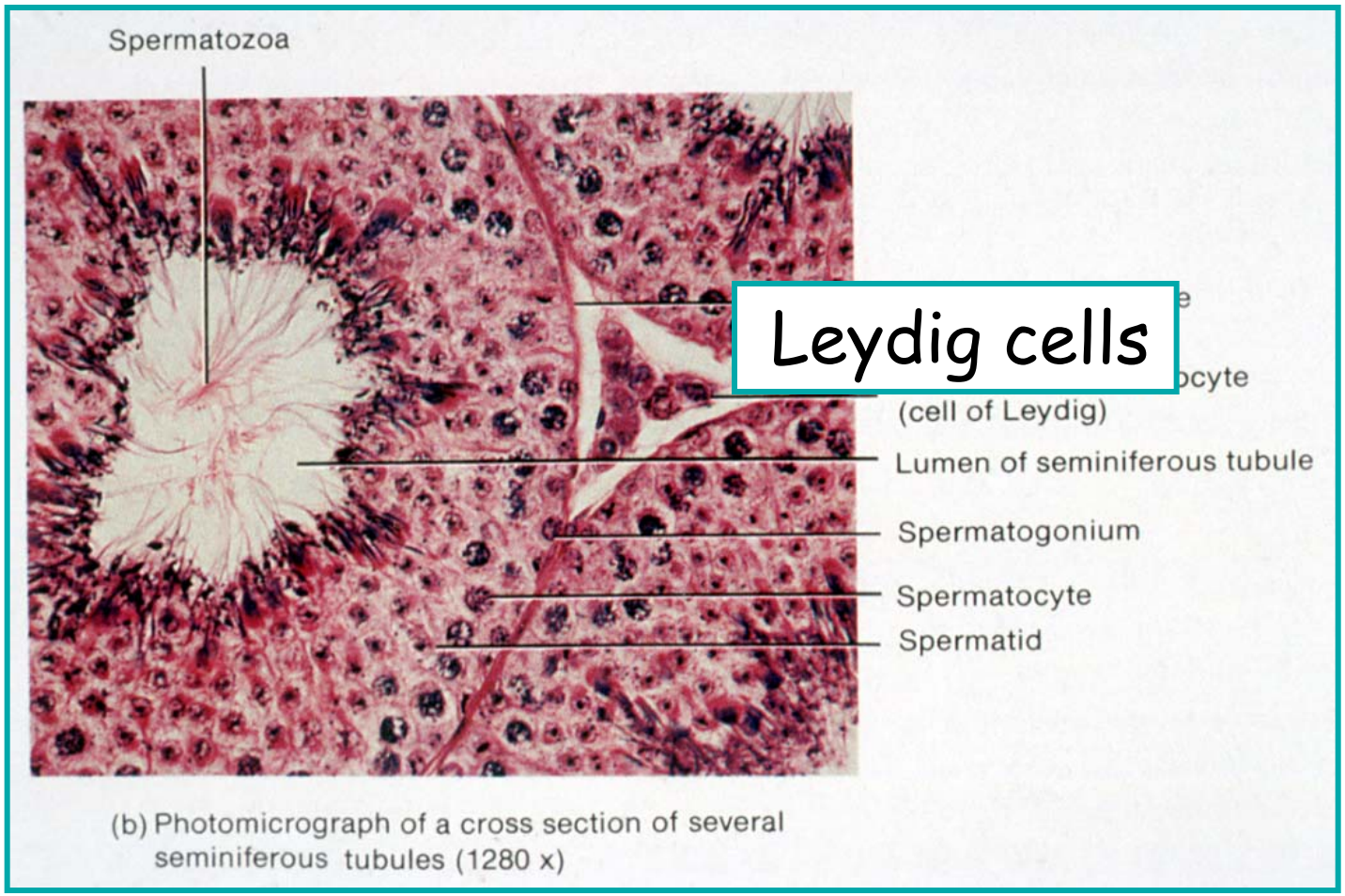


- Detection of low T (<11nmol/L):
  75% sensitivity
  96% specificity

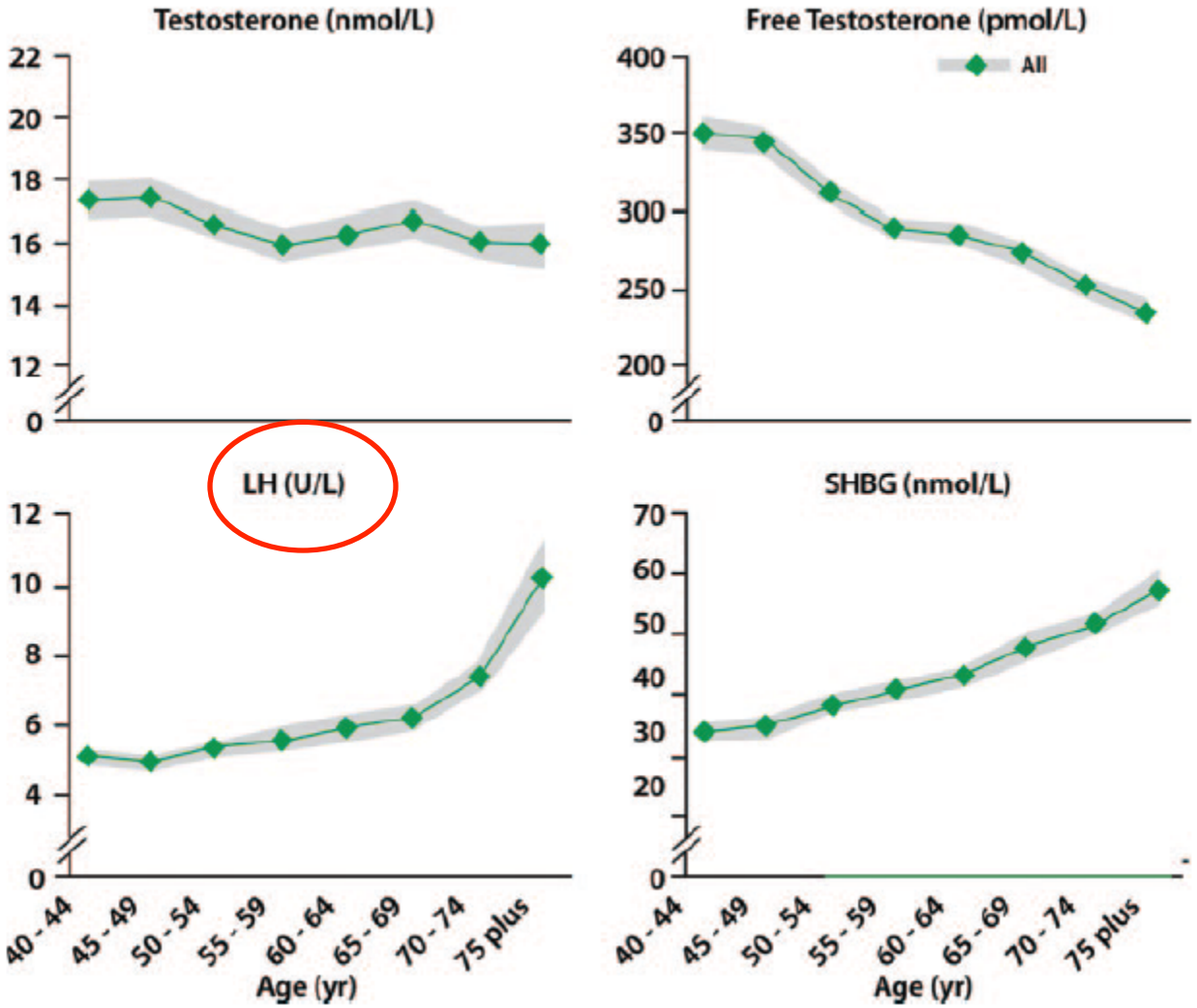
- Diagnosis of hypogonadism (T<11nmol/L + FT< 0.220nmol/L + 3 sexual symptoms):
  86% sensitivity
  9% specificity

Huhtaniemi et al EJE 203;166:983-991

Mixed testicular and hypothalamic factors in Late Onset Hypogonadism

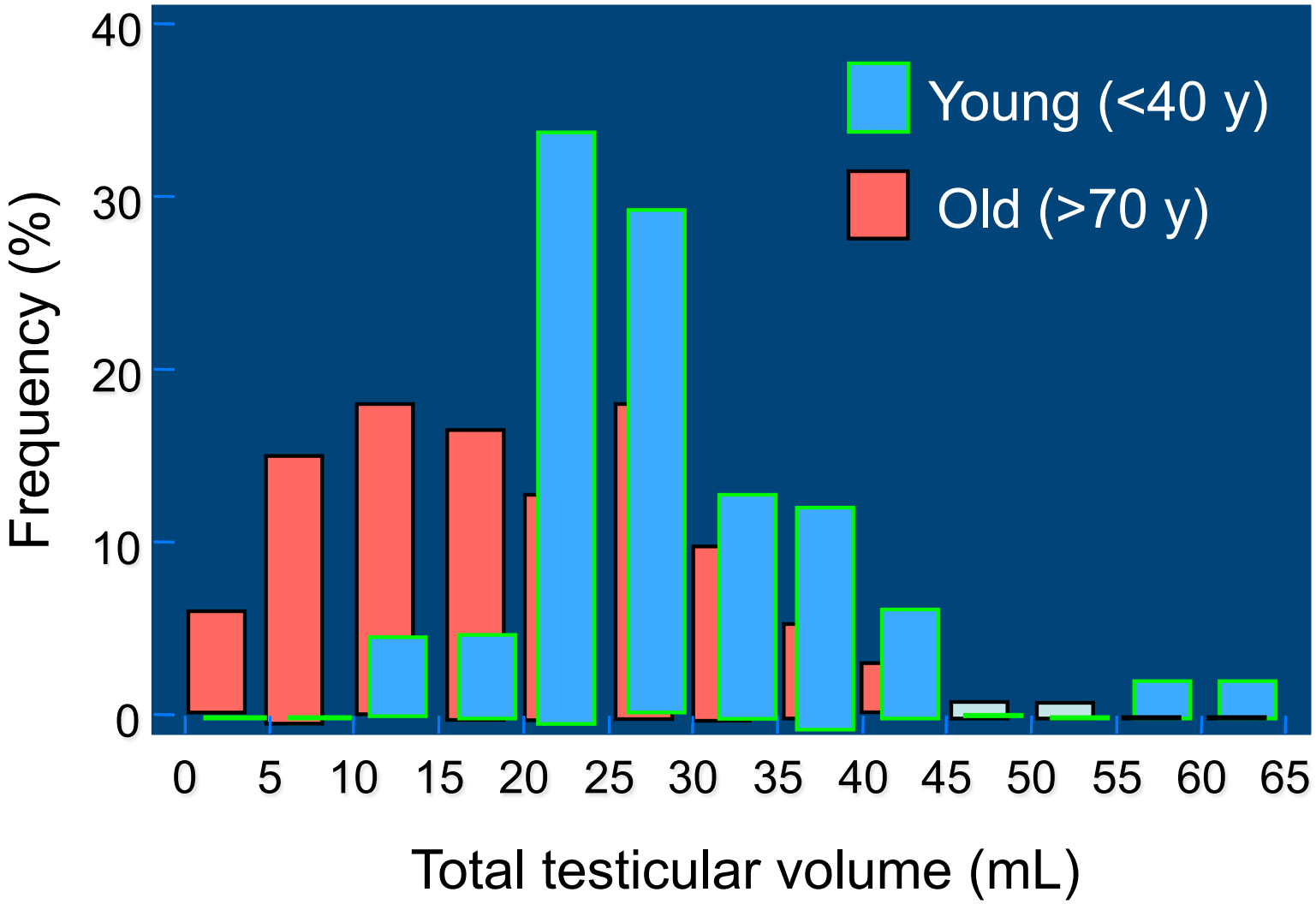


Age-related changes and modifiable risk factors EMAS stuy population



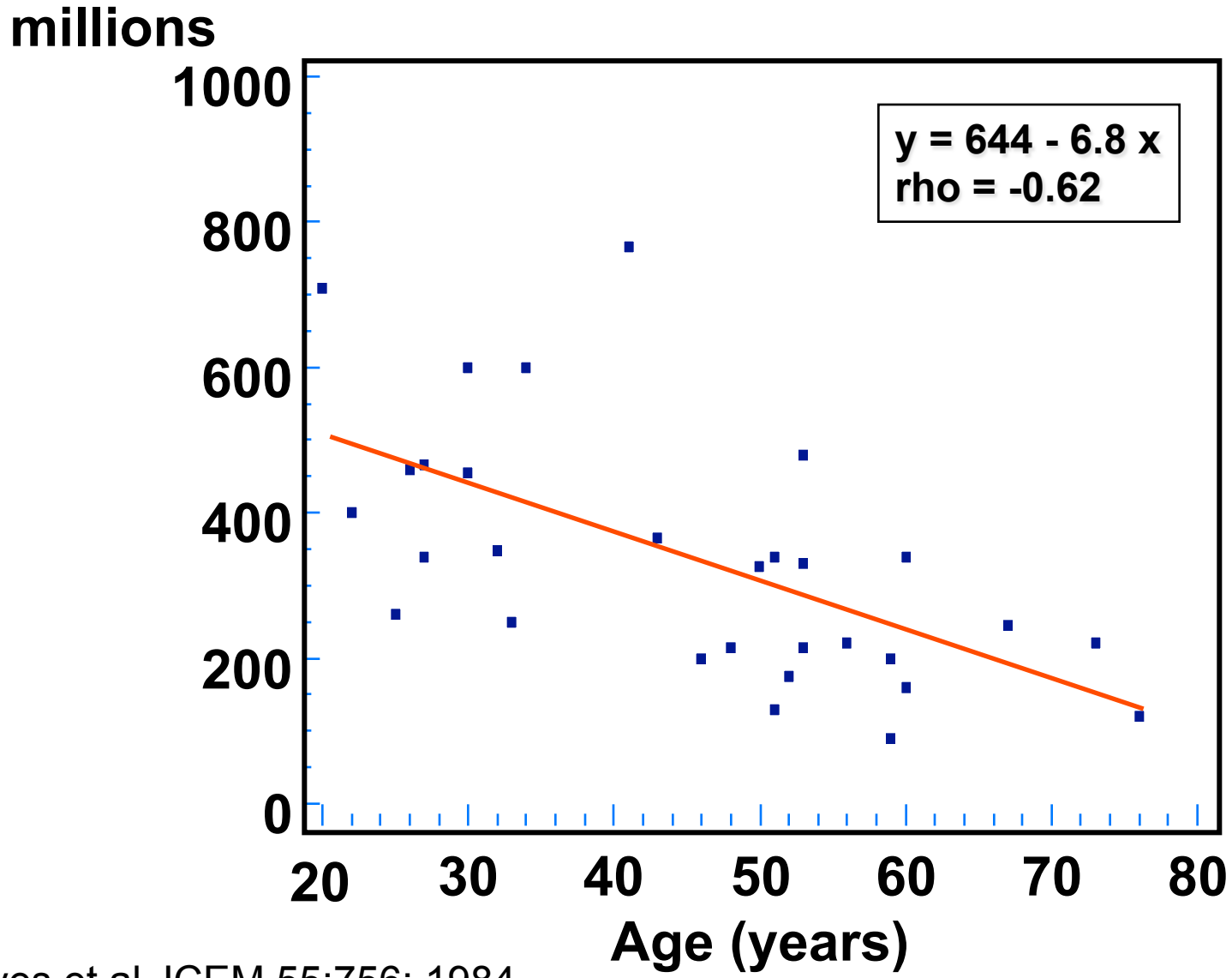
Wu et al J ClinEndocrinol Metab 93:2737; 2008

Decreased mean testicular volume (by 31%)



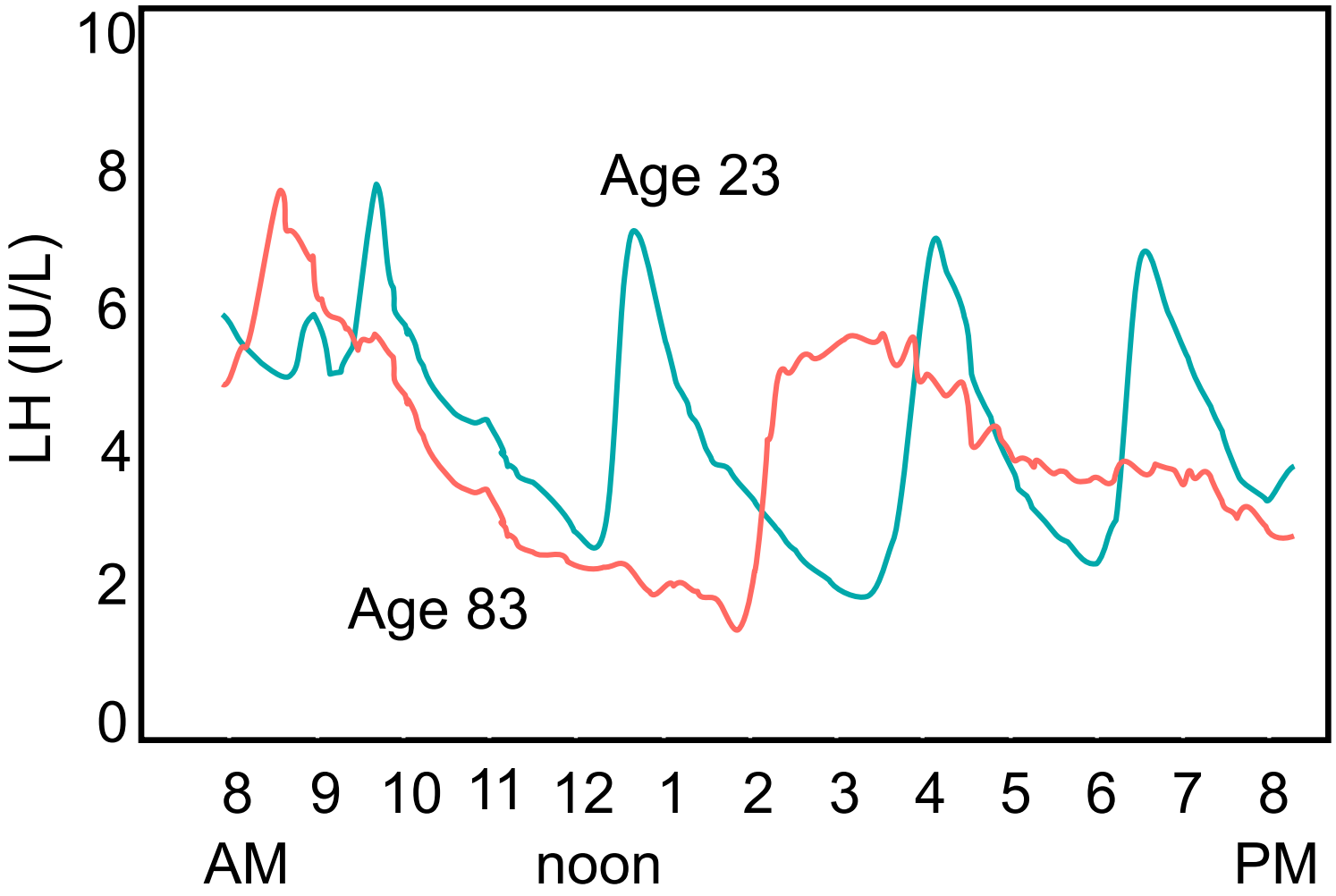
Mahmoed et al.
JCEM 2003;88:179

Decreased number of Leydig cells

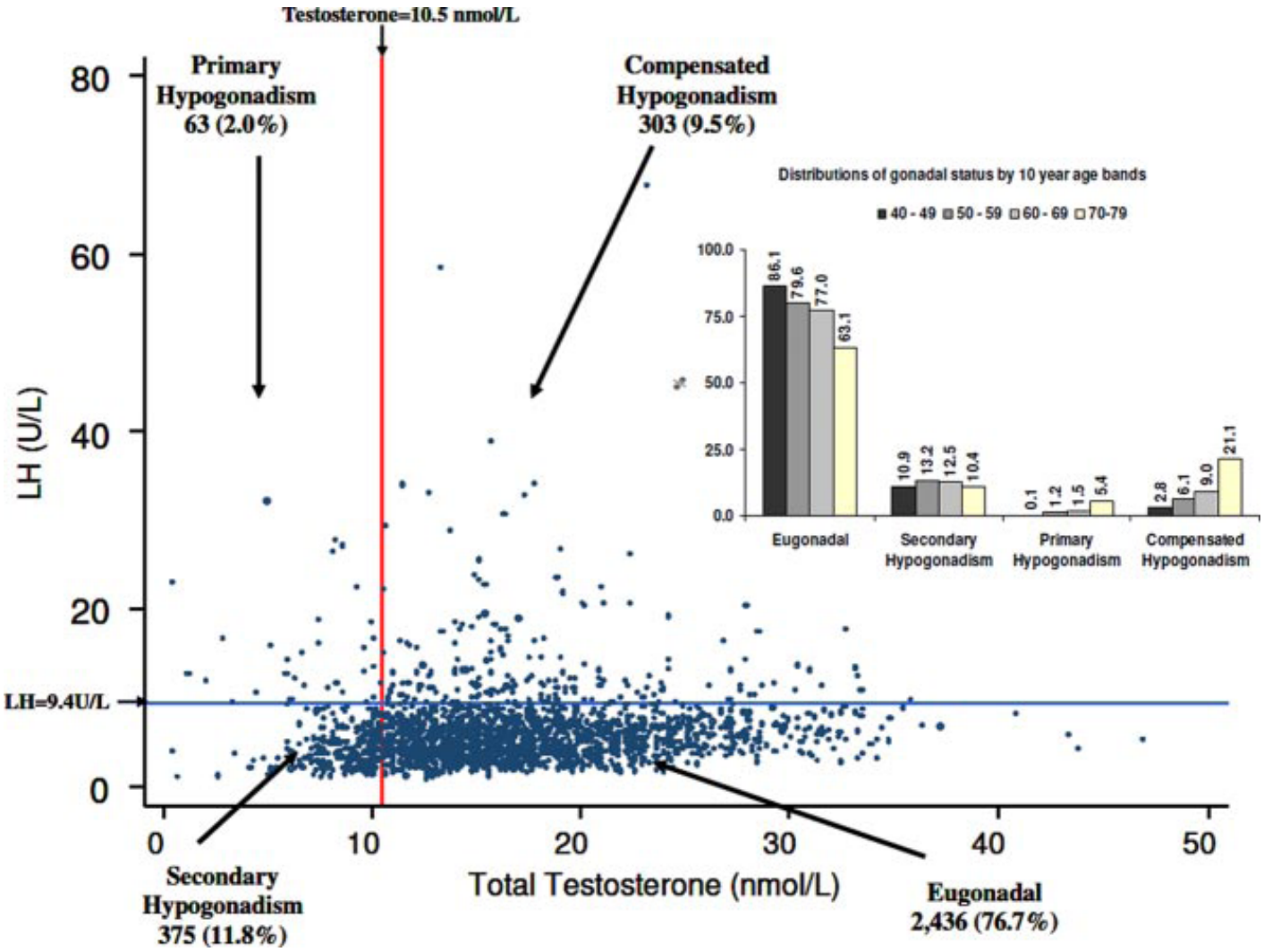


Neaves et al JCEM 55:756; 1984

LH pulsatility in young and elderly men (representative profiles)

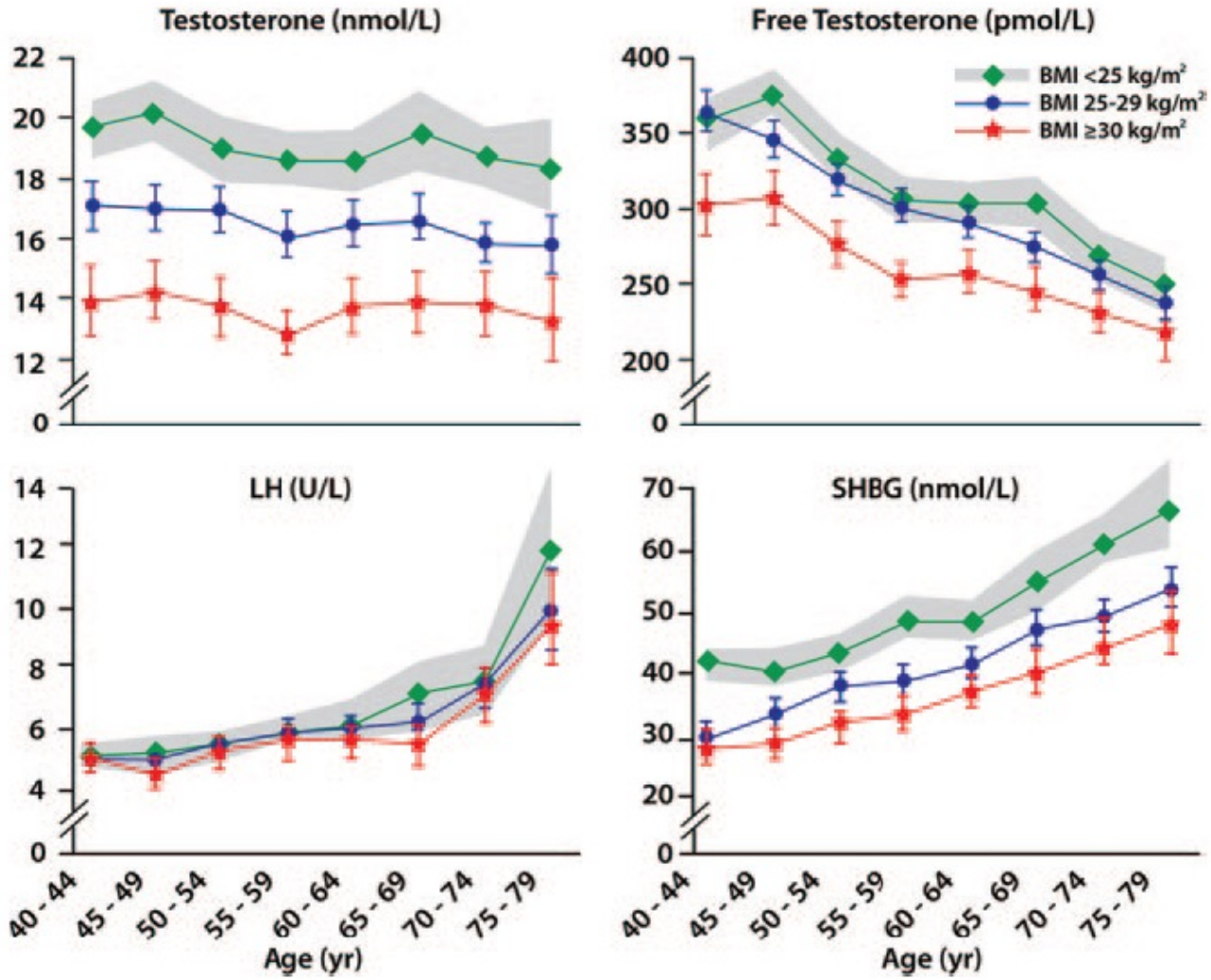


Presentation of hypogonadism in EMAS



Tajar et al JCEM 2010

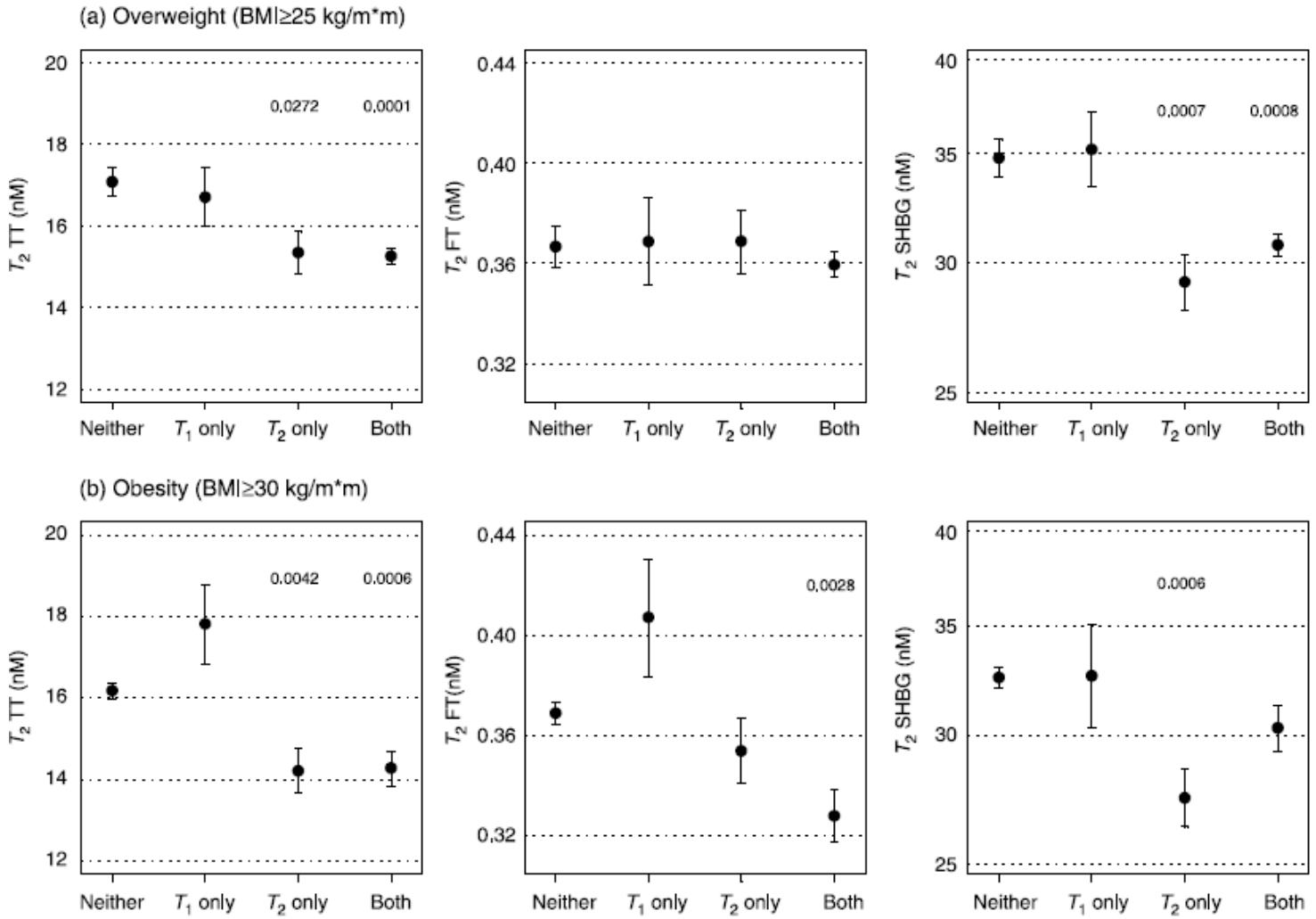
Age-related changes and modifiable risk factors EMAS stuy population



Wu et al J ClinEndocrinol Metab 93:2737; 2008

Effect of obesity on serum testosterone

MMAS study population



Mohr et al EJE155:443-452;2006

Summary diagnosis of hypogonadism: well established low T?

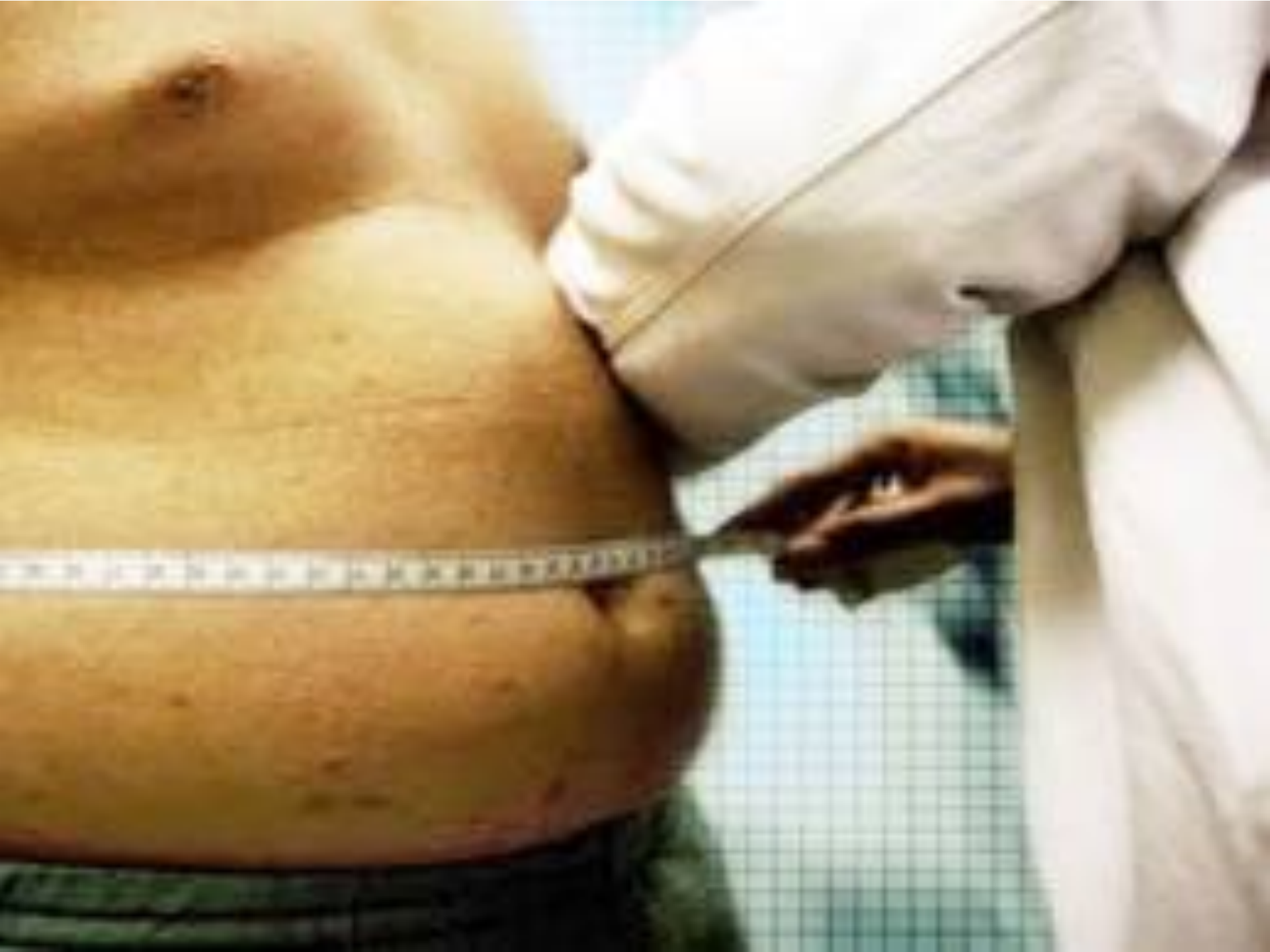
- Cut-off around <11nmol/L (= 320ng/dl) for total T & <0.225nmol/L (= 6.5 ng/dl) for freeT
- Well validated immunoassay acceptable for clinic
- Blood sampling before 10 a.m
- Consider freeT when factors affecting SHBG (e.g. obesity;glucocorticoids,….) and when borderline total T
- Elevated gonadotropins, if present can help establish diagnosis
- Low (free)T to be confirmed on second occasion, ideally with few weeks interval (cfr possible transient reversible cause)

Summary diagnosis of hypogonadism: signs/symptoms?

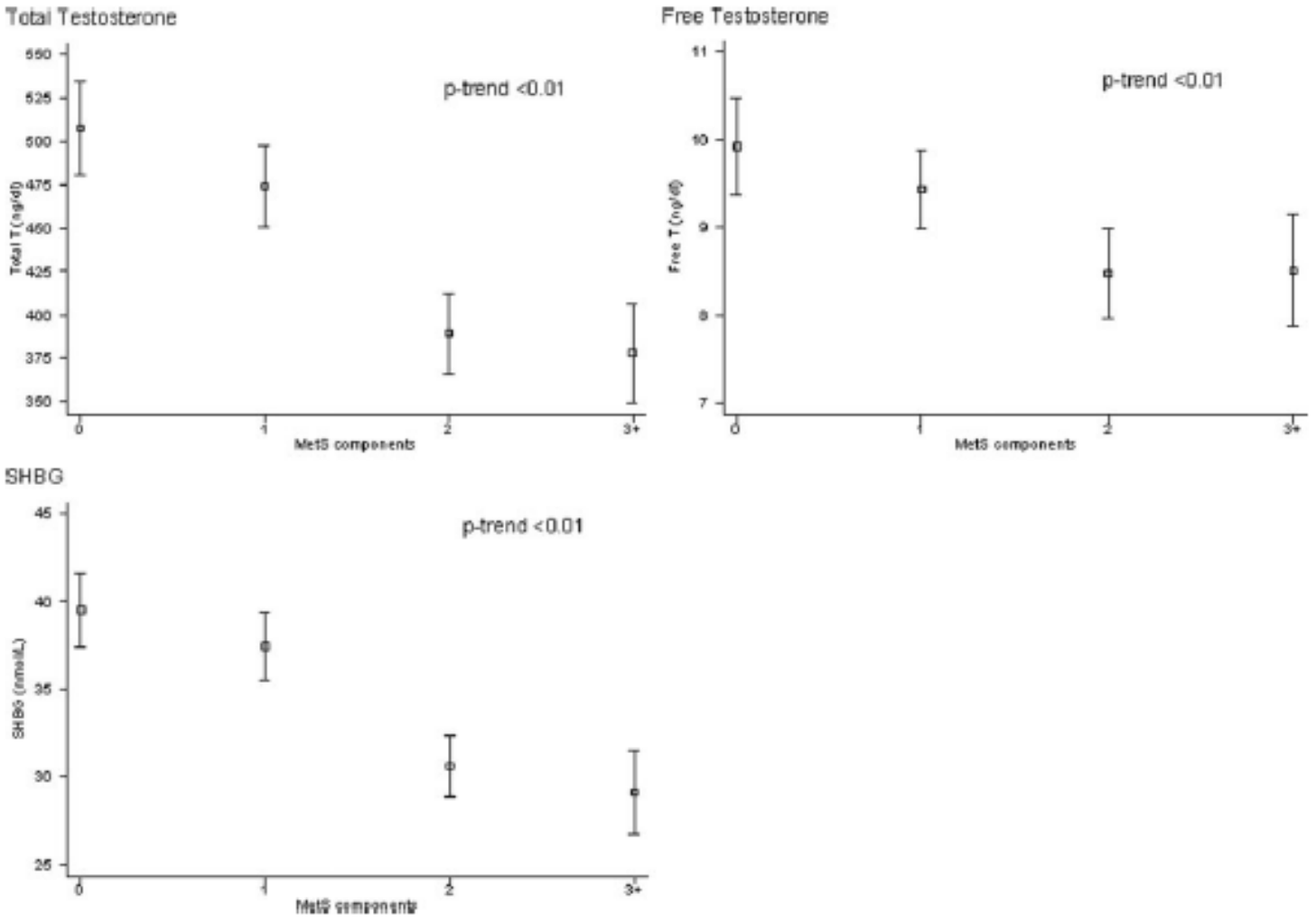
- Spontaneously reported symptoms (= reason for consultation) more reliable than ‘sollicited’ by questionning: avoid to use for diagnostic purpose screening questionnaires with poor specificity
- Cluster of symptoms more reliable
- more specific significance of sexual symptoms (?)
- consider alternative causes for reported symptoms

Consequences of hypogonadism

- Adiposity, insulin resistance, metabolic sy, type2 diabetes
- Sexual function
- Bone
- Muscle, mobility
- Cardiovascular disease , mortality



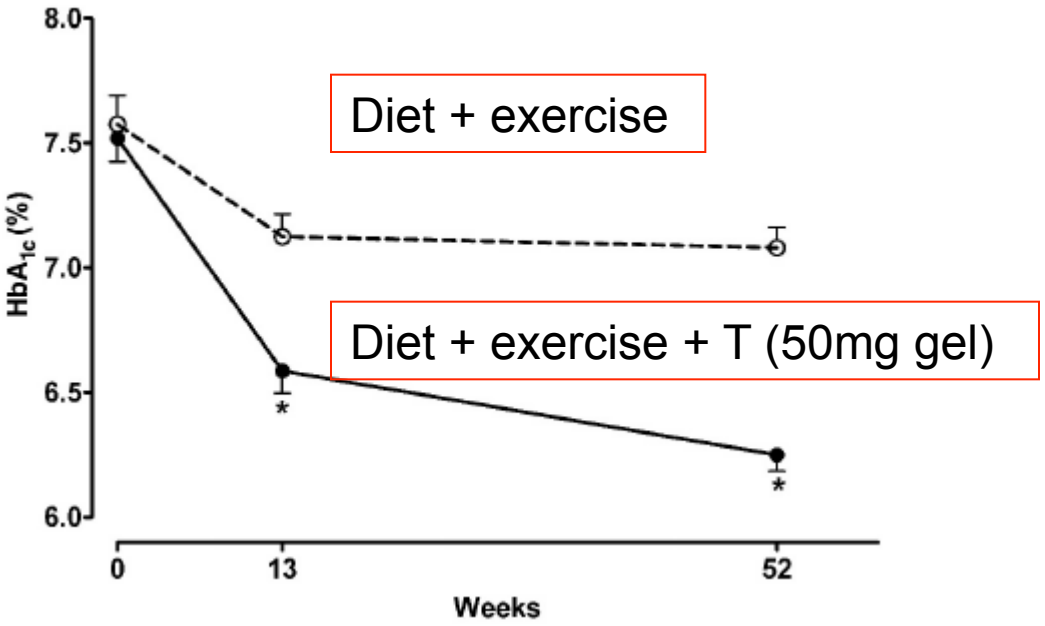
Association of SHBG and T with the metabolic syndrome

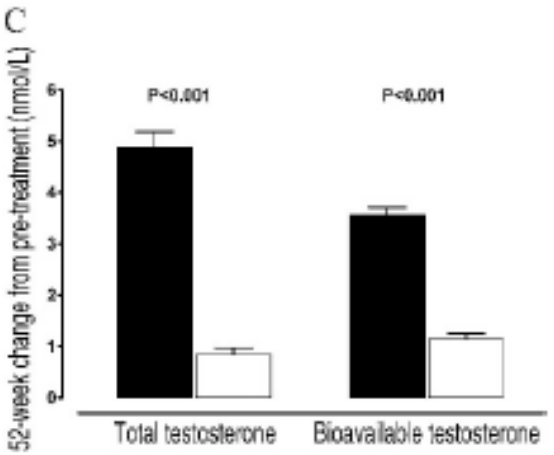


Kupelian et al J Clin Endocrinol Metab 2008;93:3403-10

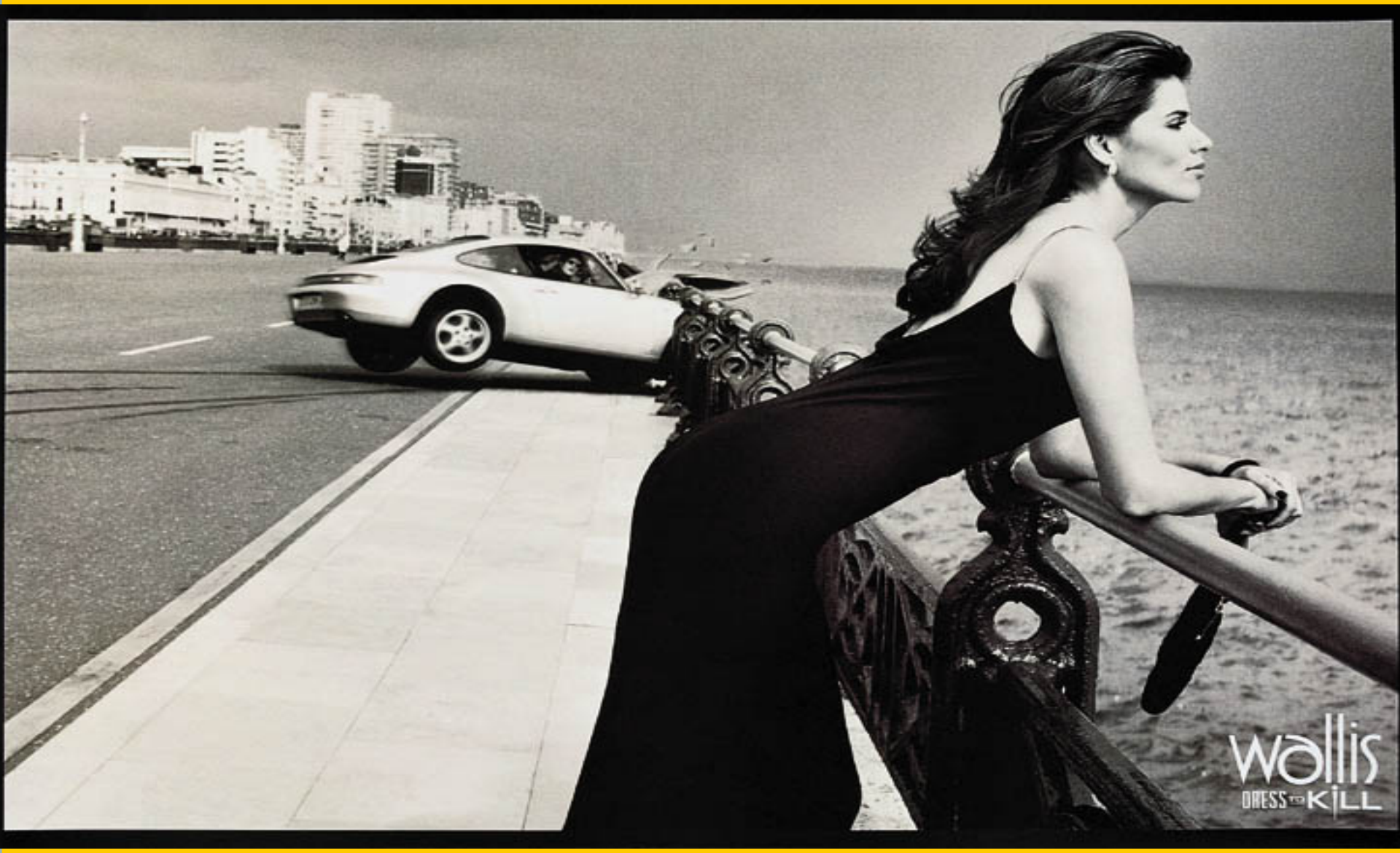
Fifty-two–Week Treatment With Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycemic Control in Men With Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone

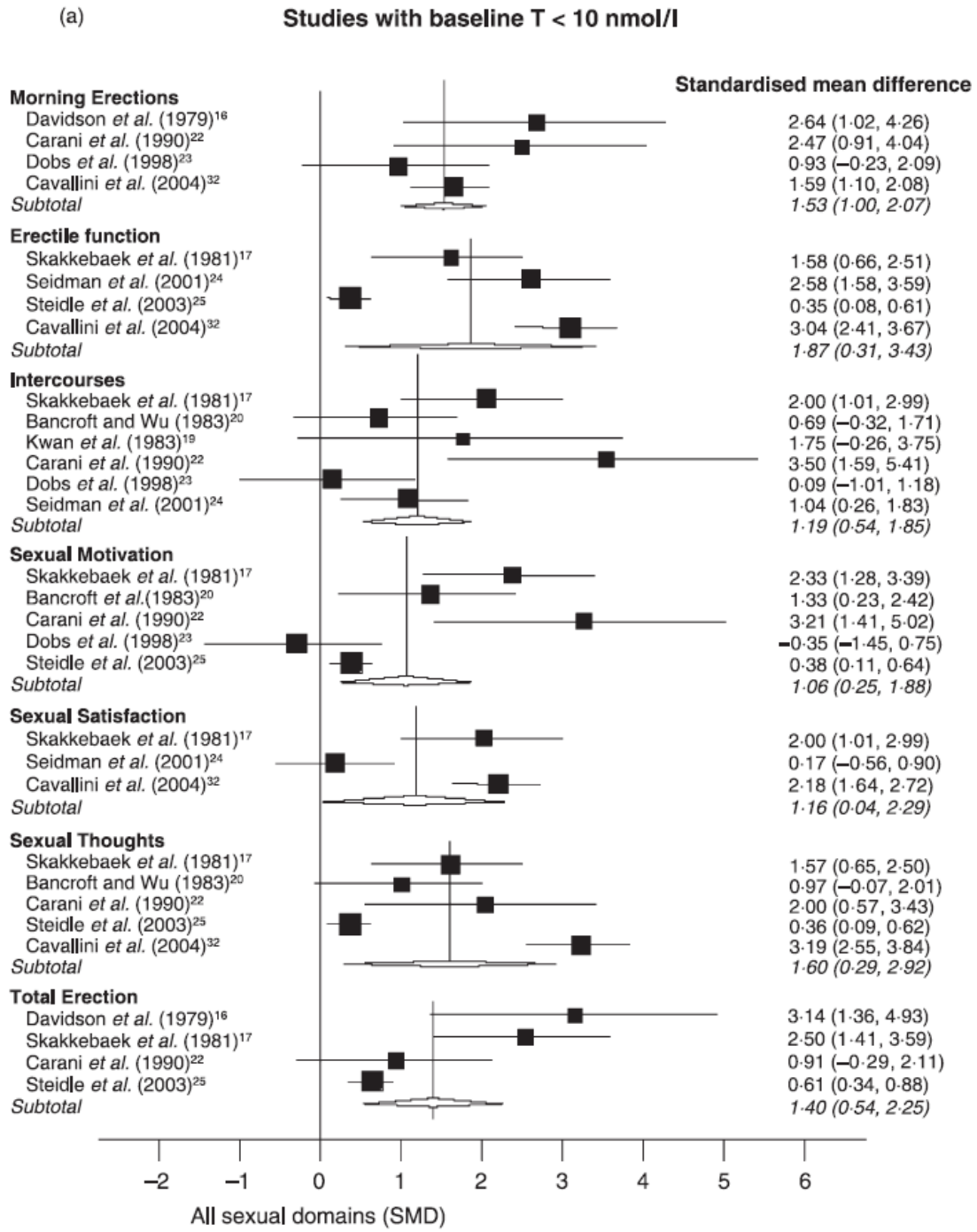
ARMIN E. HEUFELDER,* FARID SAAD,†‡ MATHIJS C. BUNCK,§ AND LOUIS GOOREN§





J Andrology 2009;30:726-36

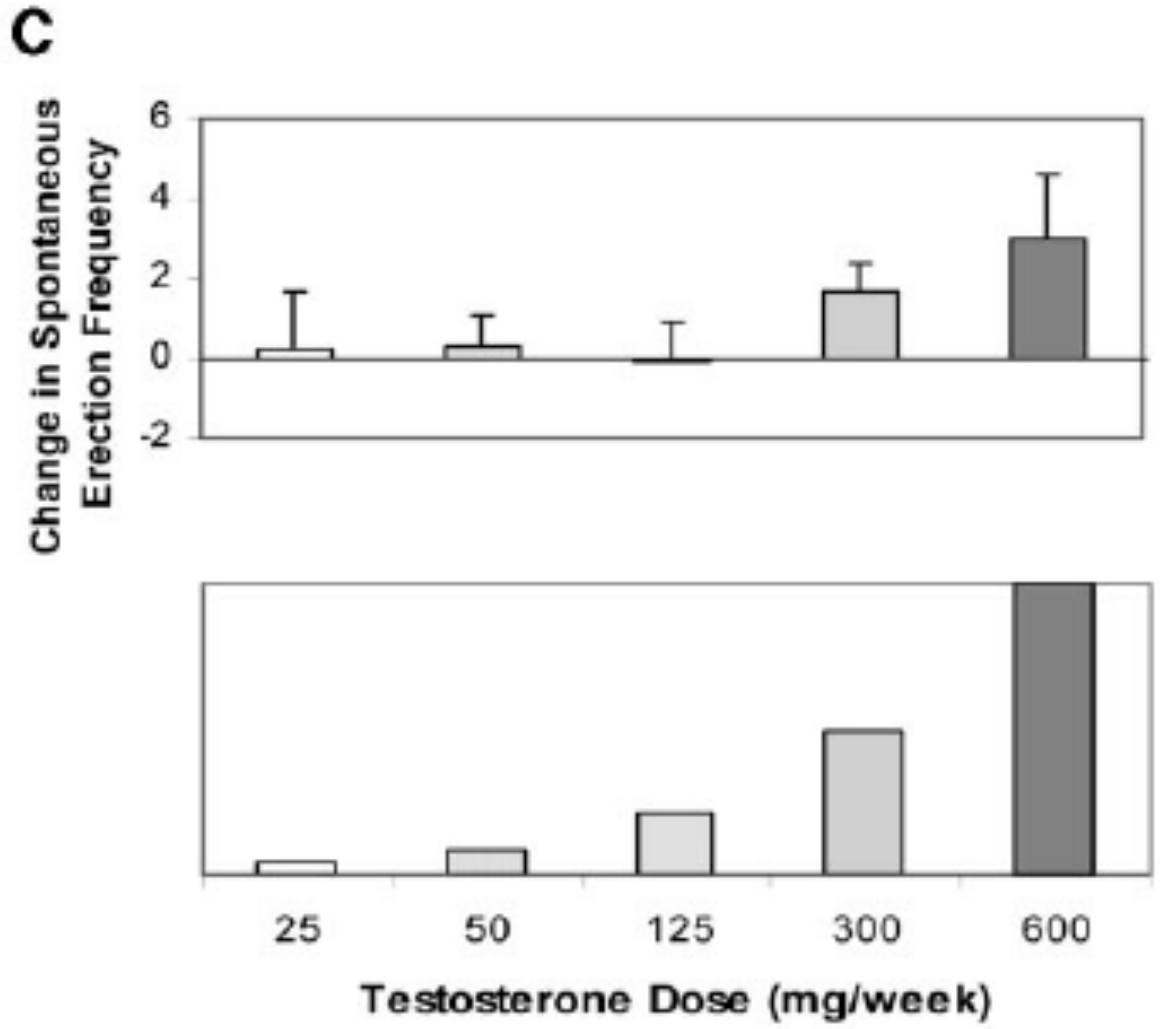

wallis
DRESS TO KILL

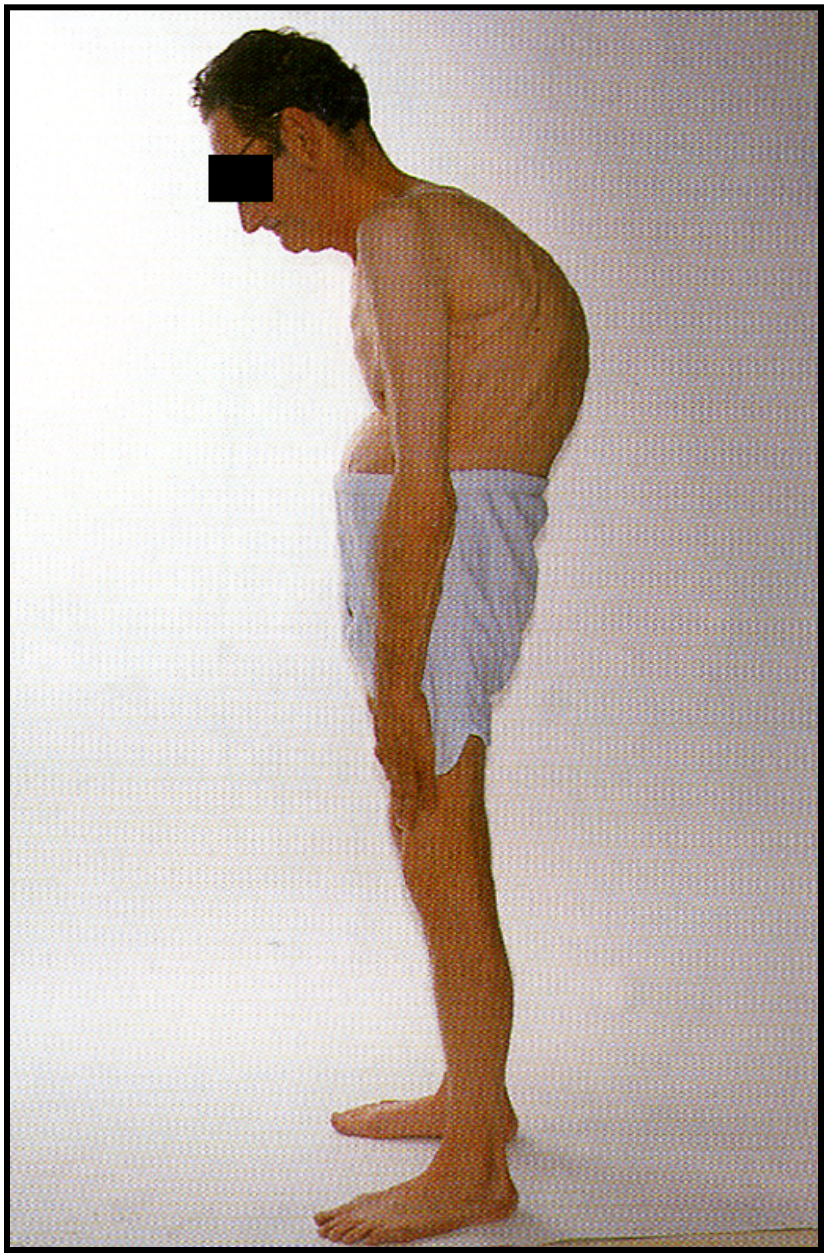


Meta-analysis treatment effects on sexual function
Isidori et al 2005
Clin Endo 63:381

Dose-Dependent Effects of Testosterone on Sexual Function, Mood, and Visuospatial Cognition in Older Men

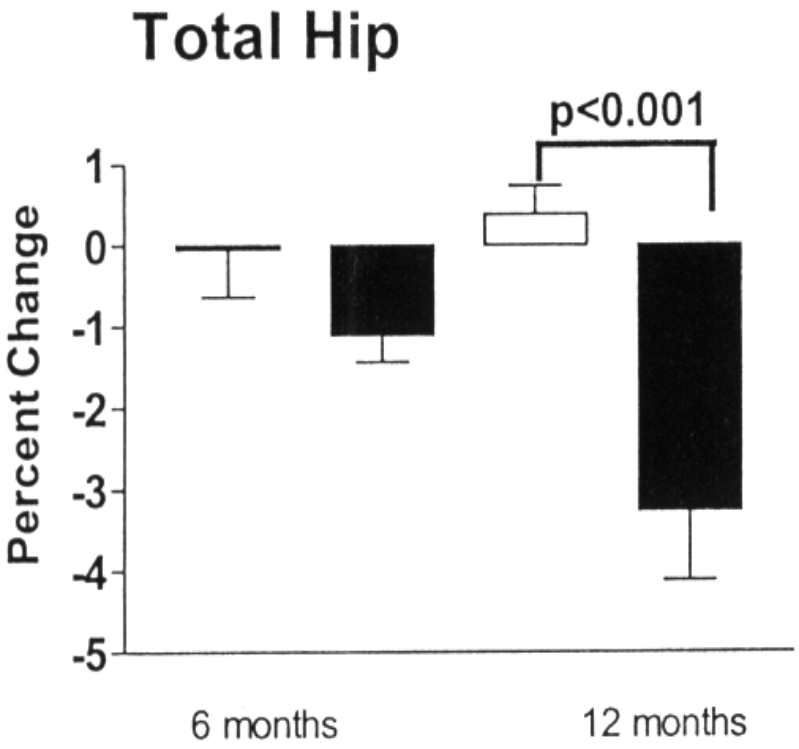
Gray et al JCEM 2005

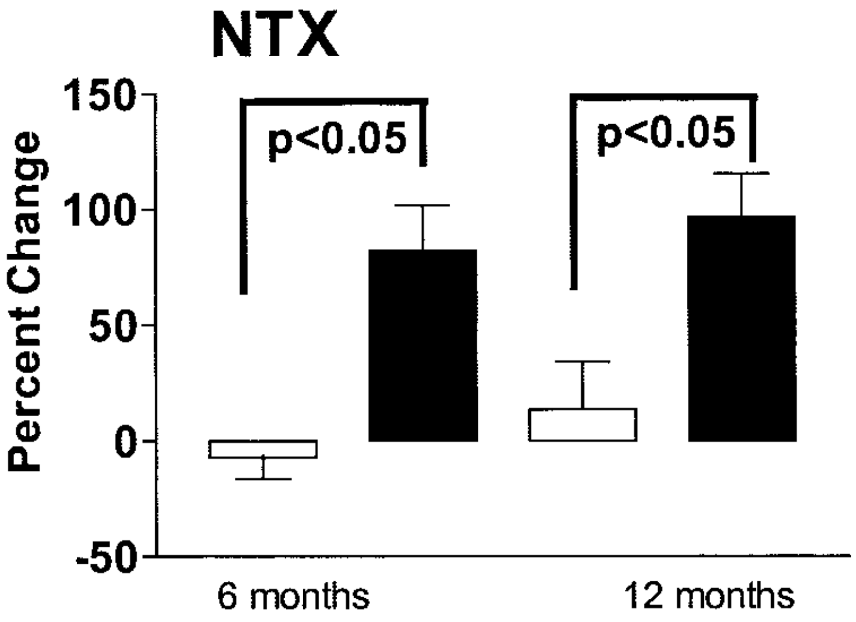




Belchetz & Hammond, 2003

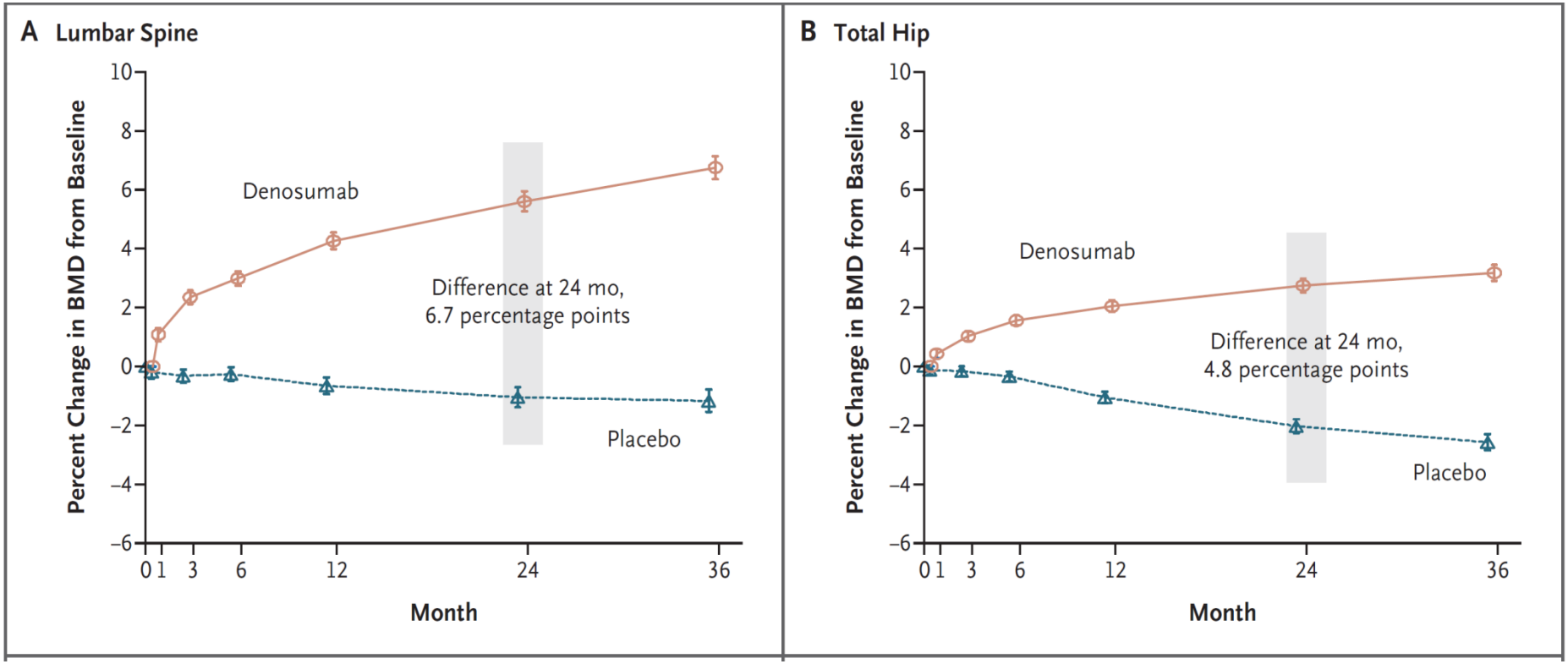
Bone loss during chemical castration with GnRH analogs in prostate cancer





Mittan et al., J Clin Endocrinol Metab 2002;87:3656

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer



Smith et al N Engl J Med 2009;361:745-55.

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

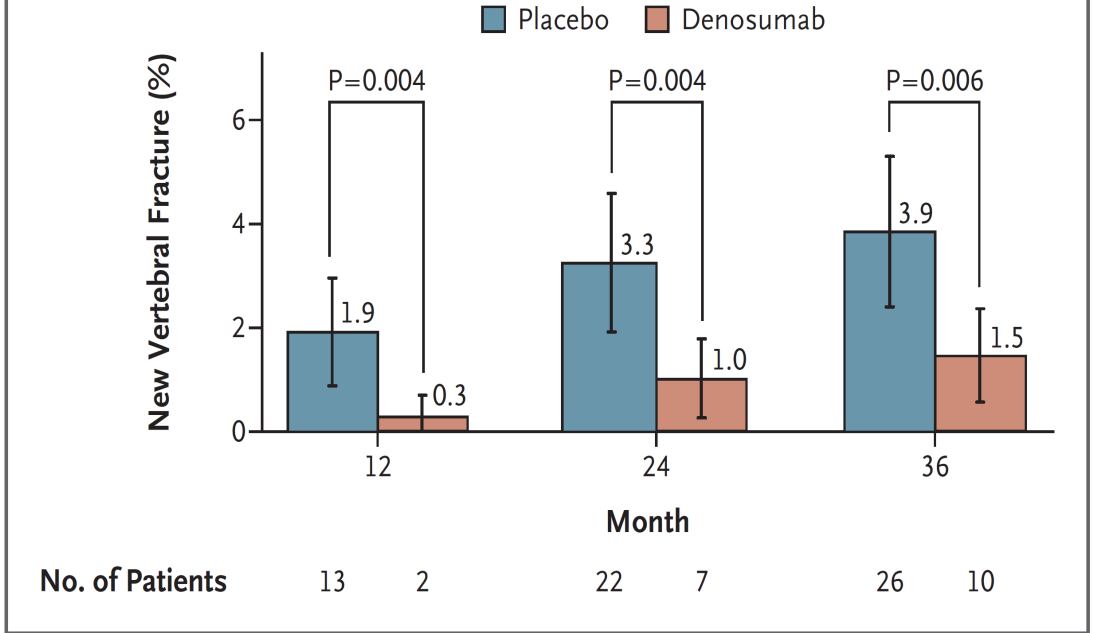
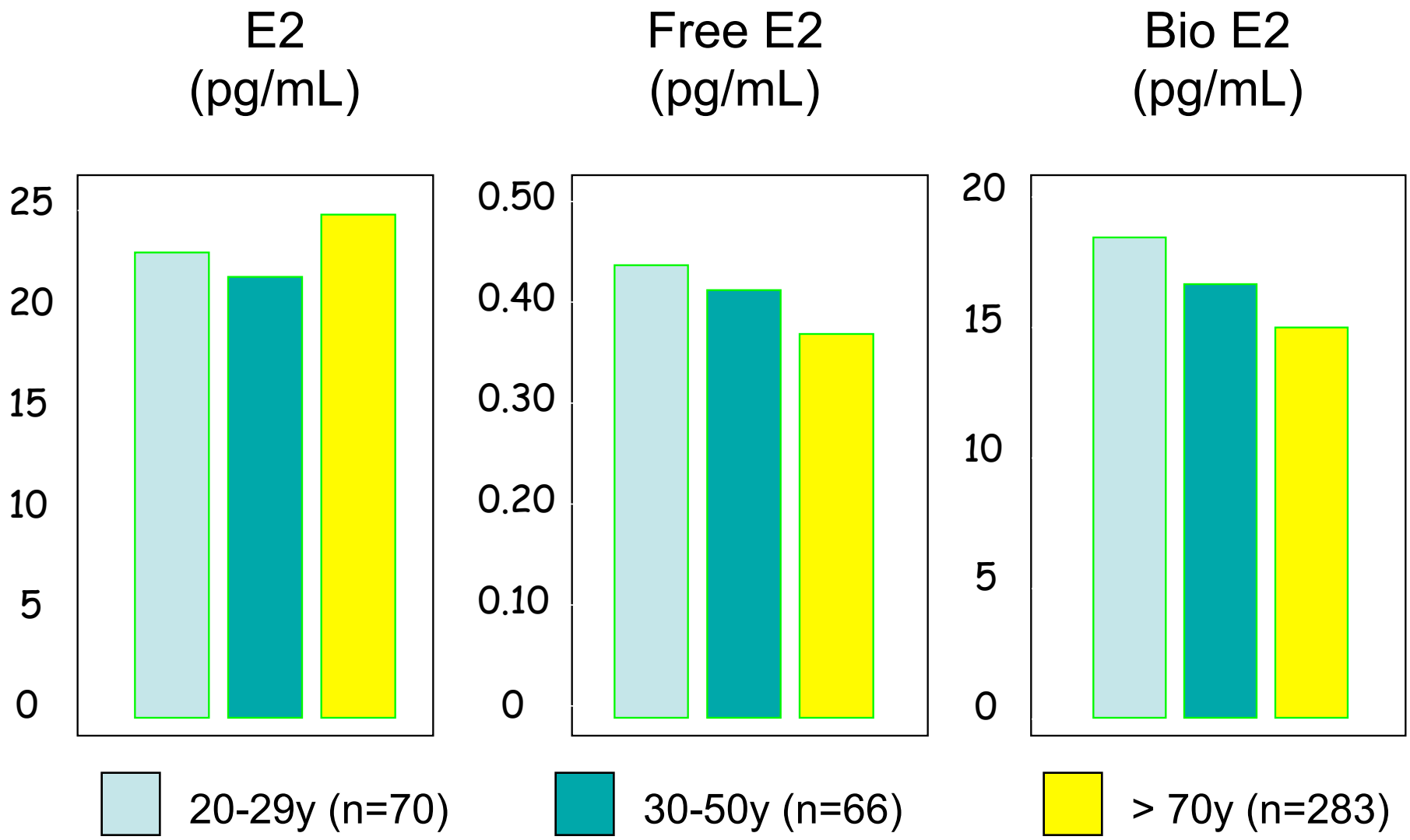


Figure 3. Cumulative Incidence of New Vertebral Fracture at 12, 24, and 36 Months, According to Study Group.

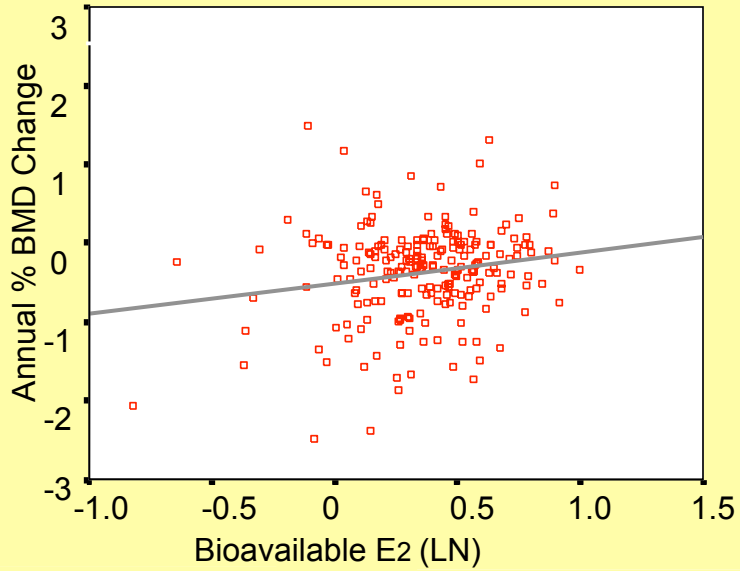
The relative risk for vertebral fracture among 679 patients in the denosumab group as compared with 673 patients in the placebo group was 0.15 at 12 months, 0.31 at 24 months, and 0.38 at 36 months.

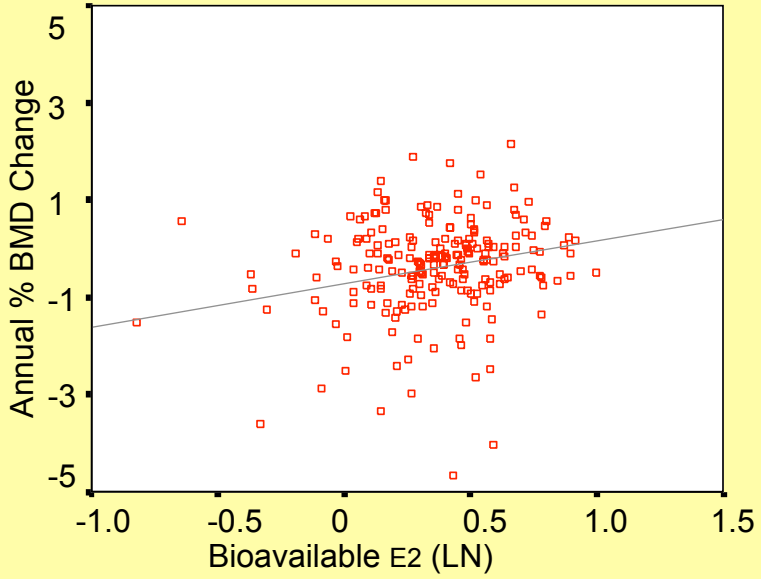
Smith et al N Engl J Med 2009;361:745-55.

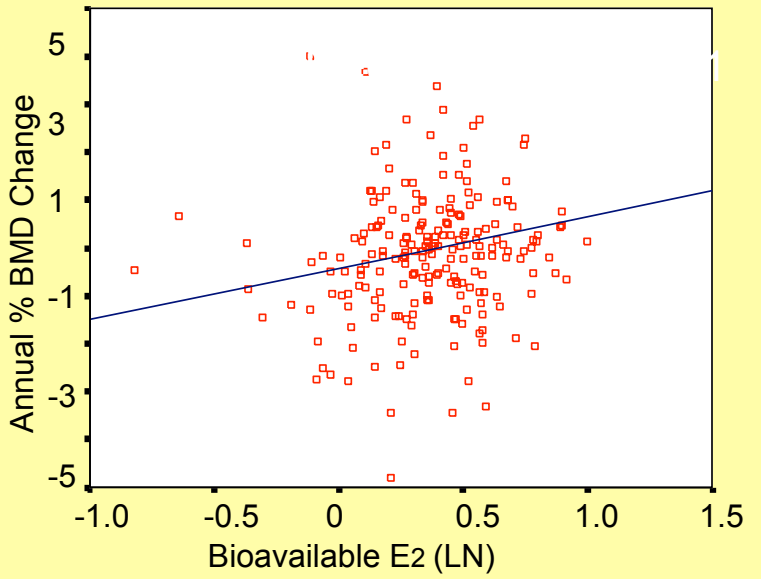

E2
(pg/mL)
25
20
15
10
5
0
Free E2
(pg/mL)
0.50
0.40
0.30
0.20
0.10
0
Bio E2
(pg/mL)
20
15
10
5
0
20-29y (n=70)
30-50y (n=66)
> 70y (n=283)

Bone loss vs Bioavailable E_2 in elderly men >70y

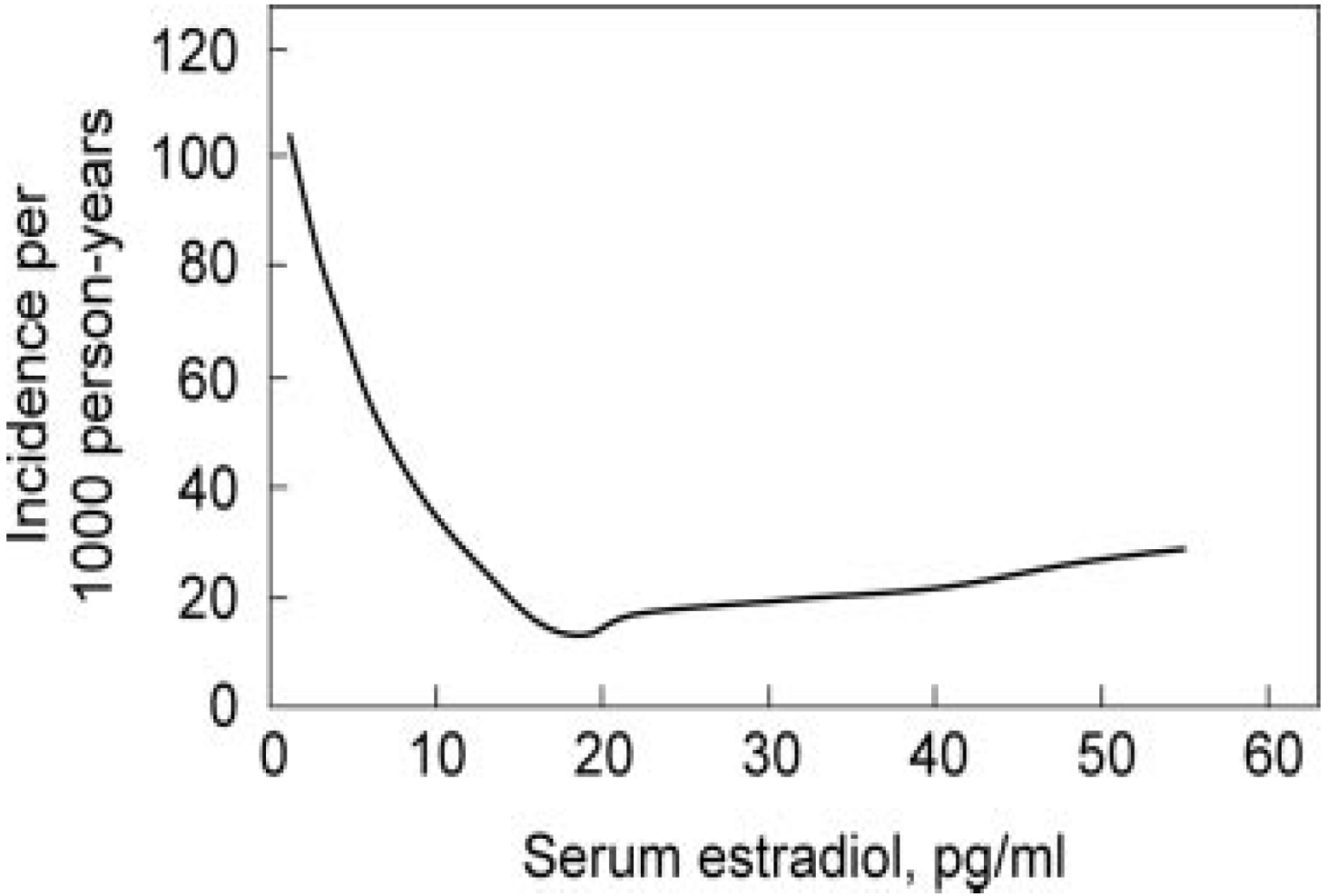
Van Pottelbergh et al
JCEM 2003







Yearly incidence of fracture as a function of serum estradiol in MrOs Sweden



Mellström et al JBMR 23:1553; 2008

CVD and MORTALITY

Endogenous T *vs* all cause & cardiovascular mortality EPIC-NORFOLK study (Khaw et al Circulation 2007)

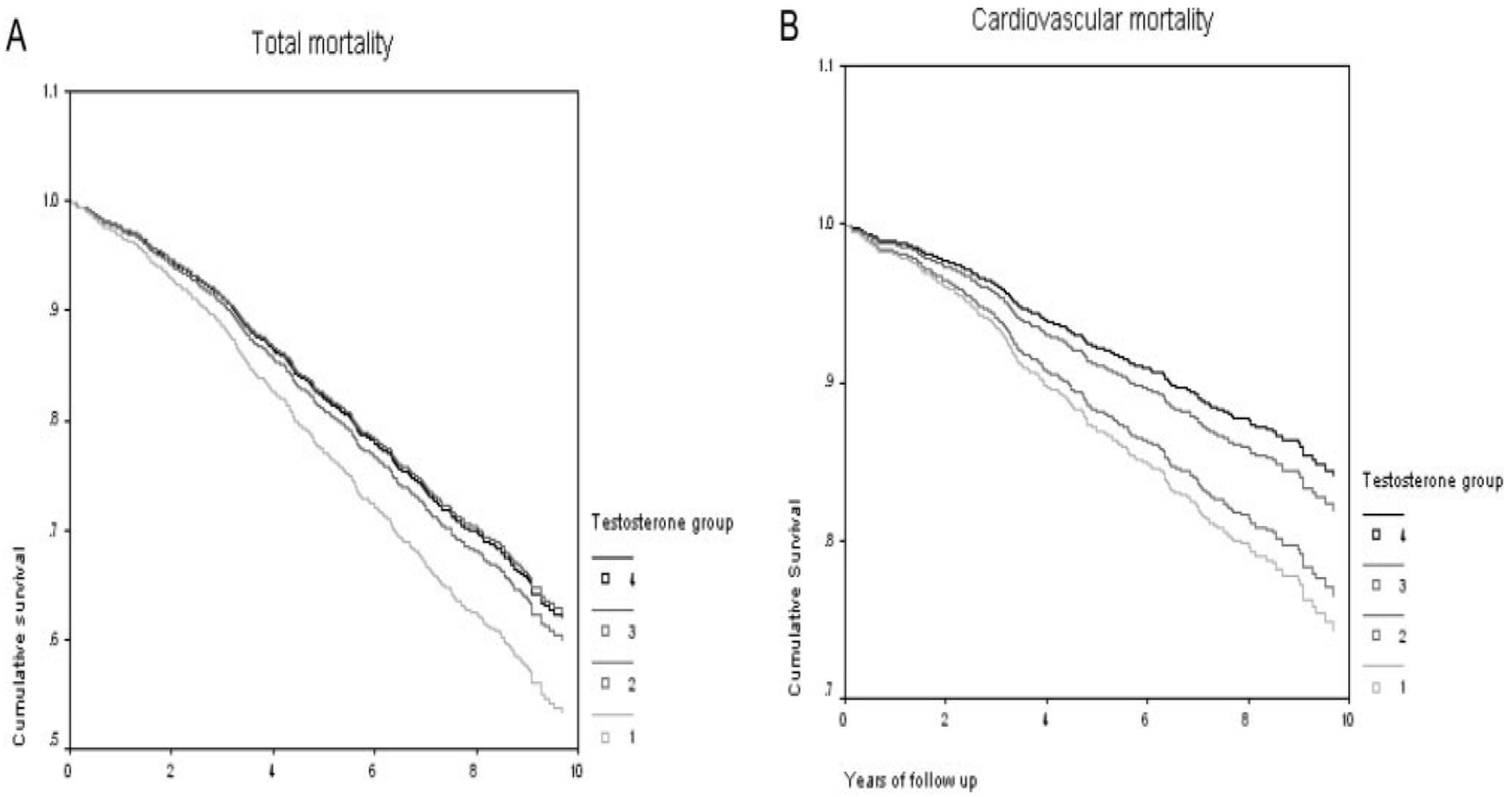
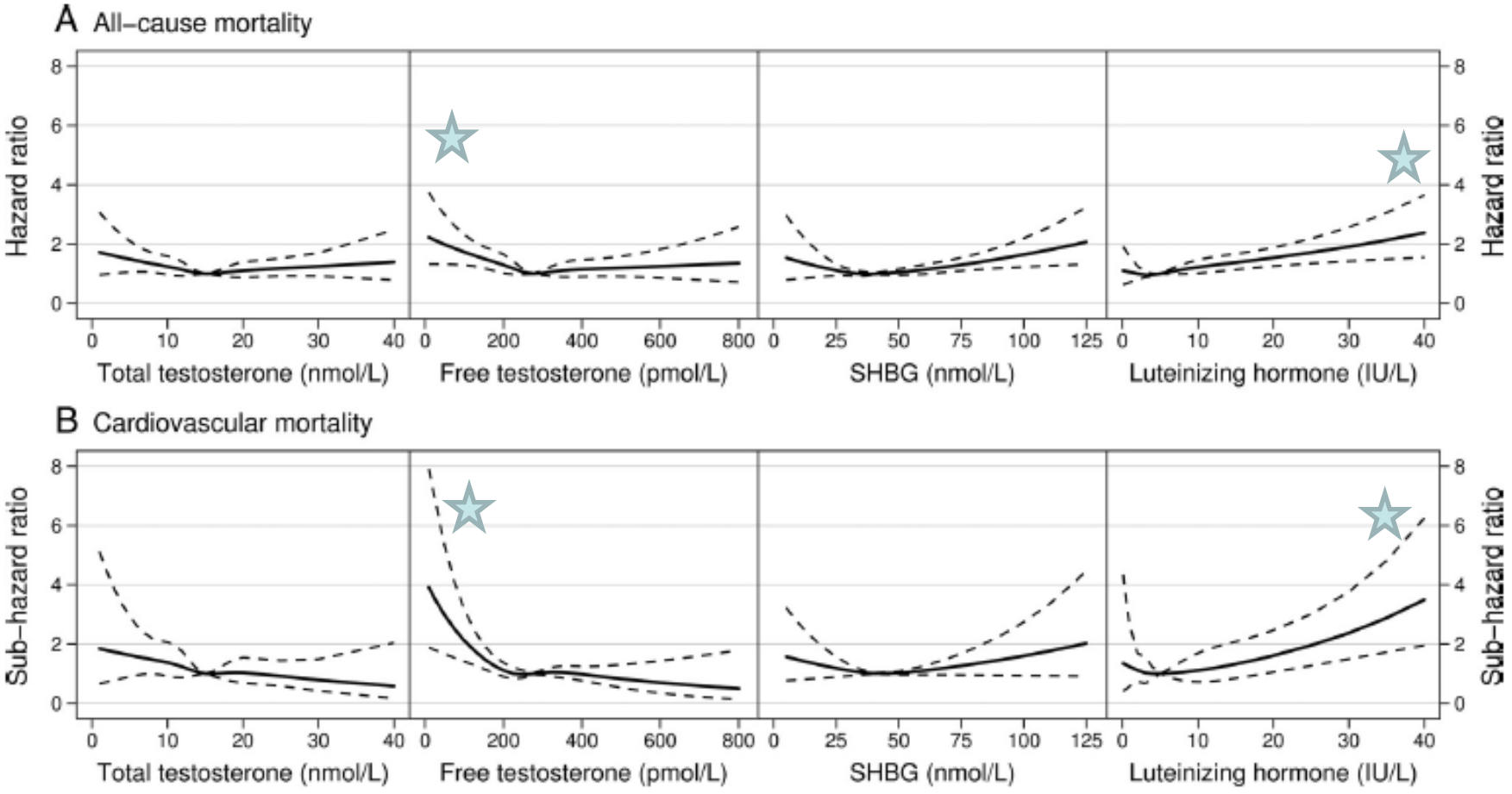


Figure. Multivariate-adjusted survival by quartile group of endogenous testosterone concentrations (1 is lowest, 4 is highest) in 2314 men 42 to 78 years old in EPIC-Norfolk 1993 to 2003.

Low free T predicts mortality from CVD: The Health in Men Study



Hyde et al J Clin Endocrinol Metab 2012;97:179-89

Meta-analyses endogenous T *vs* mortality/CVD

Araujo et al J Clin Endocrinol Metab 2011

Conclusion: Low endogenous testosterone levels are associated with increased risk of all-cause and CVD death in community-based studies of men, but considerable between-study heterogeneity, which was related to study and subject characteristics, suggests that effects are driven by differences between cohorts (*e.g.* in underlying health status). (*J Clin Endocrinol Metab* 96: 3007–3019, 2011)

Ruige et al Heart 2011

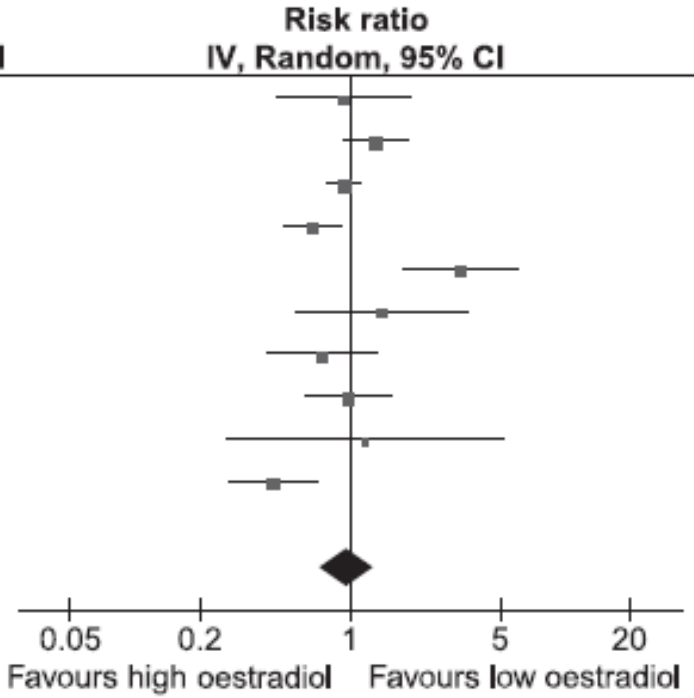
- In healthy middle aged men, testosterone does not predict cardiovascular disease (CVD).
- In elderly men, low testosterone predicts increased risk for CVD and/or mortality. It is at present unclear whether low testosterone has a direct negative effect, or whether it should be regarded as 'marker of poor health'.
- Recent studies on testosterone and CVD/mortality show more pronounced associations than earlier studies.

Endogenous E2 and CVD: meta-analysis of prospective studies

Study or Subgroup	log(risk ratio)	SE	Weight	Risk ratio IV, Random, 95% CI
Cauley *et al*[1]	−0.073	0.362	8.1%	0.93 (0.46 to 1.89)
Yarnell *et al*[2]	0.277	0.175	13.0%	1.32 (0.94 to 1.86)
Mikulec *et al*[3]	−0.061	0.089	15.1%	0.94 (0.79 to 1.12)
Arnlöv *et al*[4]	−0.4	0.157	13.5%	0.67 (0.49 to 0.91)
Abbott *et al*[5]	1.18	0.31	9.3%	3.25 (1.77 to 5.98)
Nilsson *et al*[6]	0.343	0.467	6.1%	1.41 (0.56 to 3.52)
Tivesten *et al*[7]	−0.301	0.302	9.5%	0.74 (0.41 to 1.34)
Vikan *et al*[8]	−0.02	0.237	11.3%	0.98 (0.62 to 1.56)
Akishita *et al*[9]	0.165	0.758	3.0%	1.18 (0.27 to 5.21)
Menke *et al*[10]	−0.821	0.243	11.1%	0.44 (0.27 to 0.71)
Total (95% CI)			**100.0%**	**0.98 (0.74 to 1.31)**

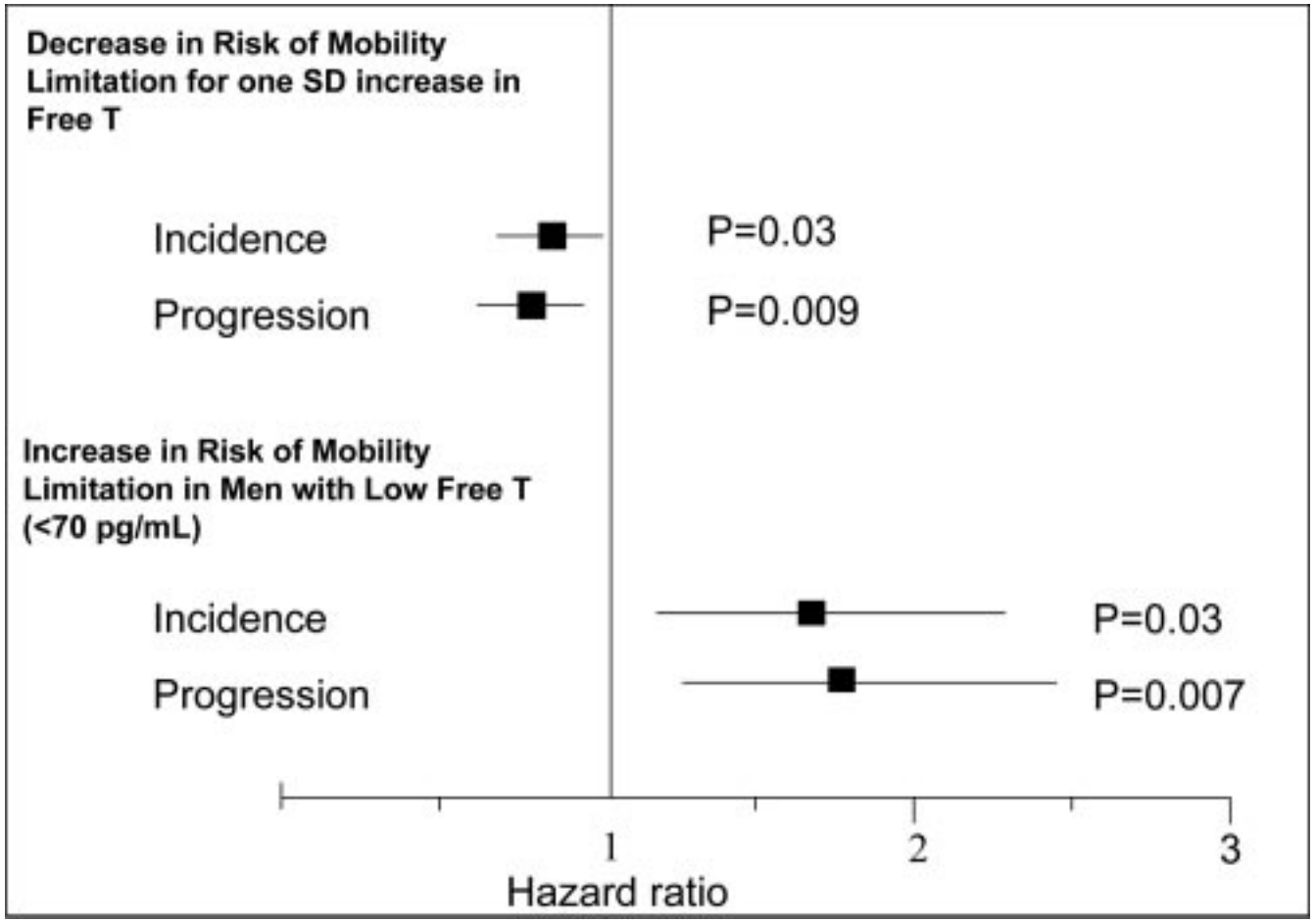
Heterogeneity: Tau² = 0.14; χ^2 = 35.68, df = 9 (p<0.0001); I² = 75%

Test for overall effect: Z = 0.13 (p=0.90)



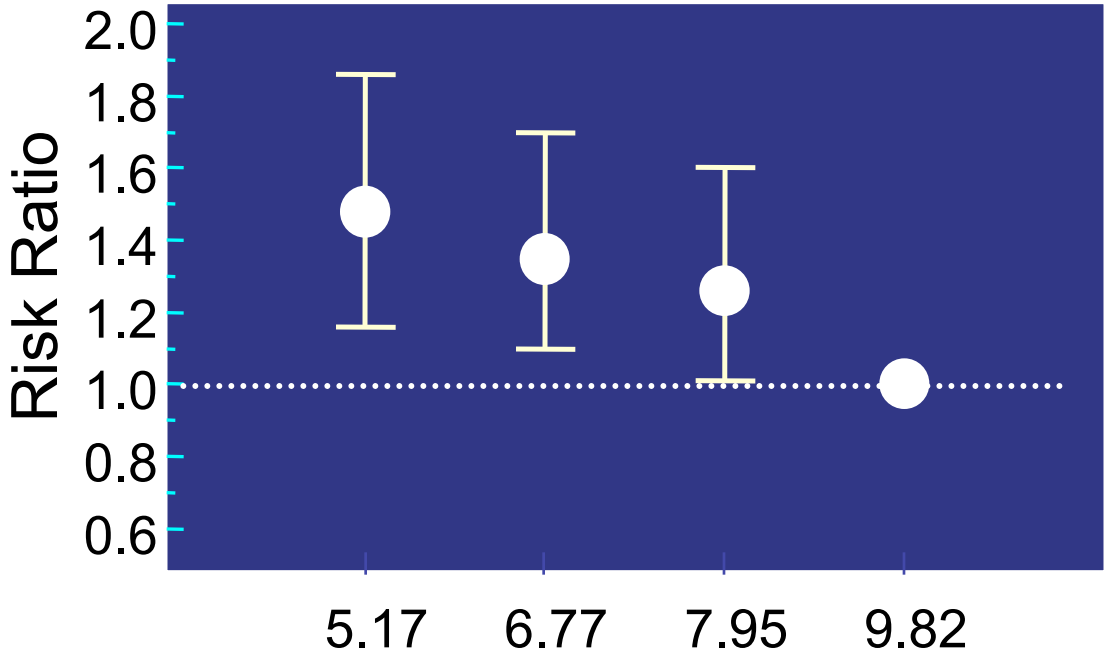
Vandenplas et al Heart 2012;98:148-82

Prevalence and incidence of mobility limitations in the Framinham Offspring Study



Krasnoff et al JCEM 95:2790; 2010

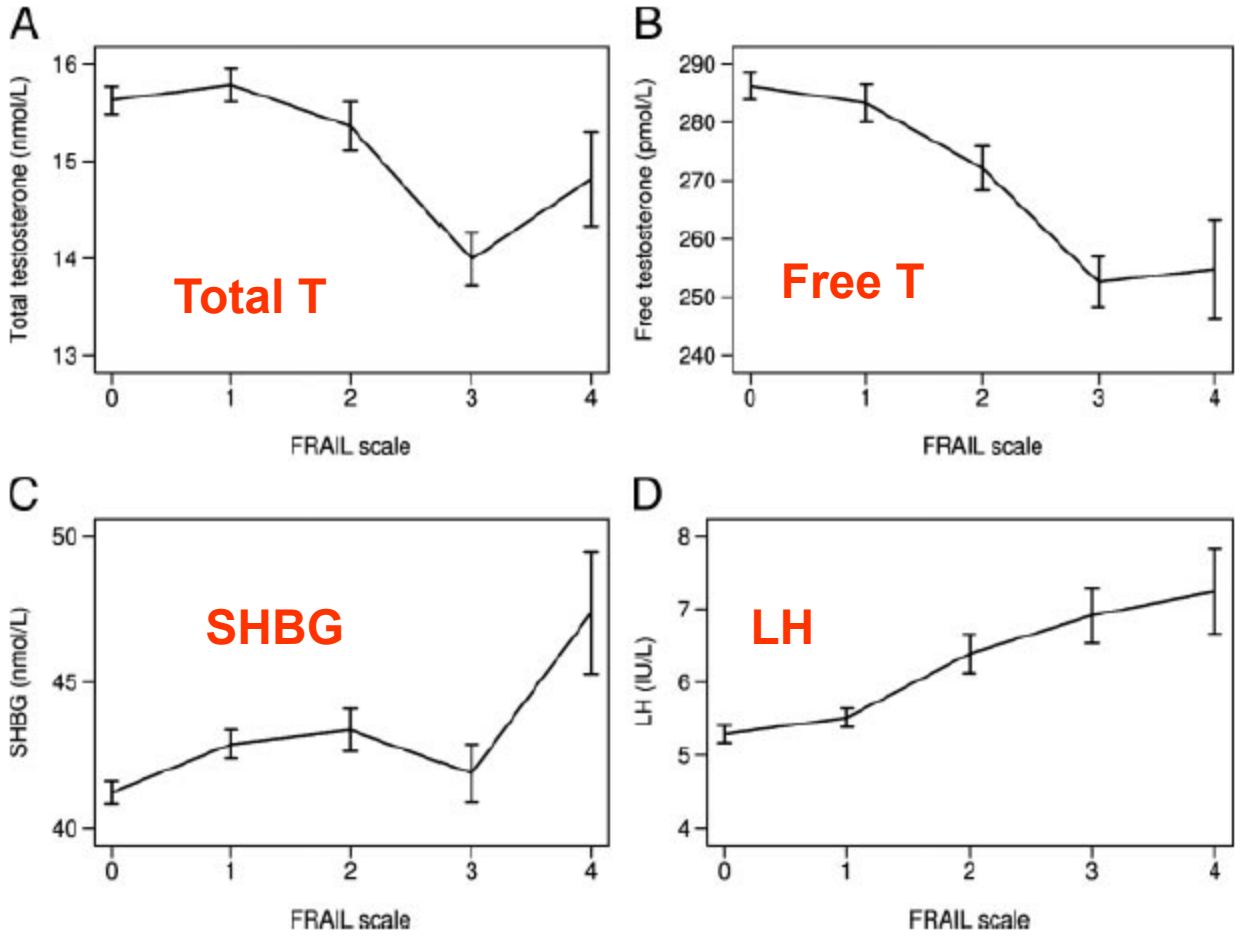
Increased risk of incident falls in men with lower freeT amongst 2587 community-dwelling men 65-99y



- No association with FT > 80y!

Orwoll et al.Arch Intern Med 2006;166:2124

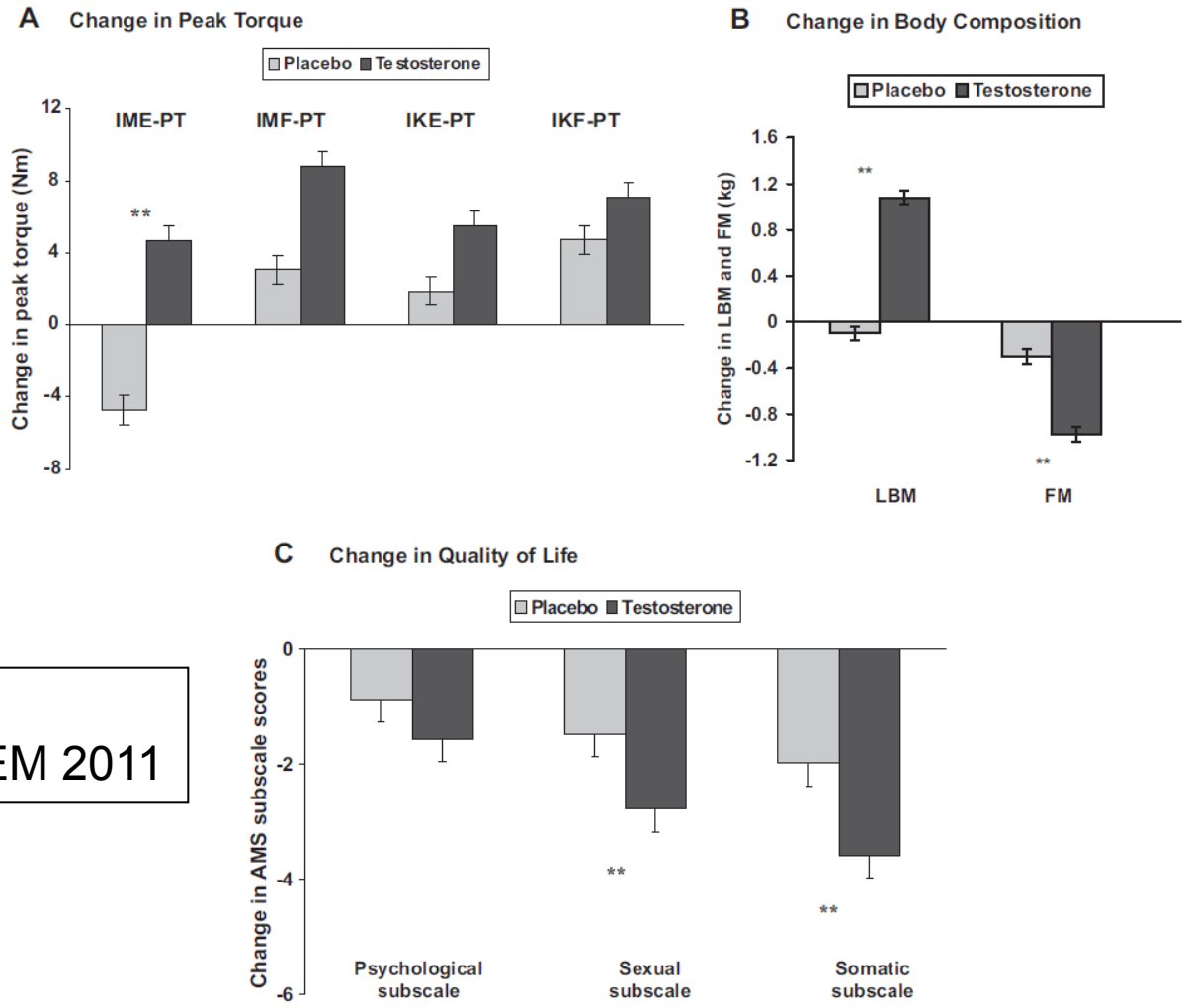
Low freeT predicts frailty in older men



Frail scale

Hyde et al J Clin endocrinol Metab 2010;95:3165-72

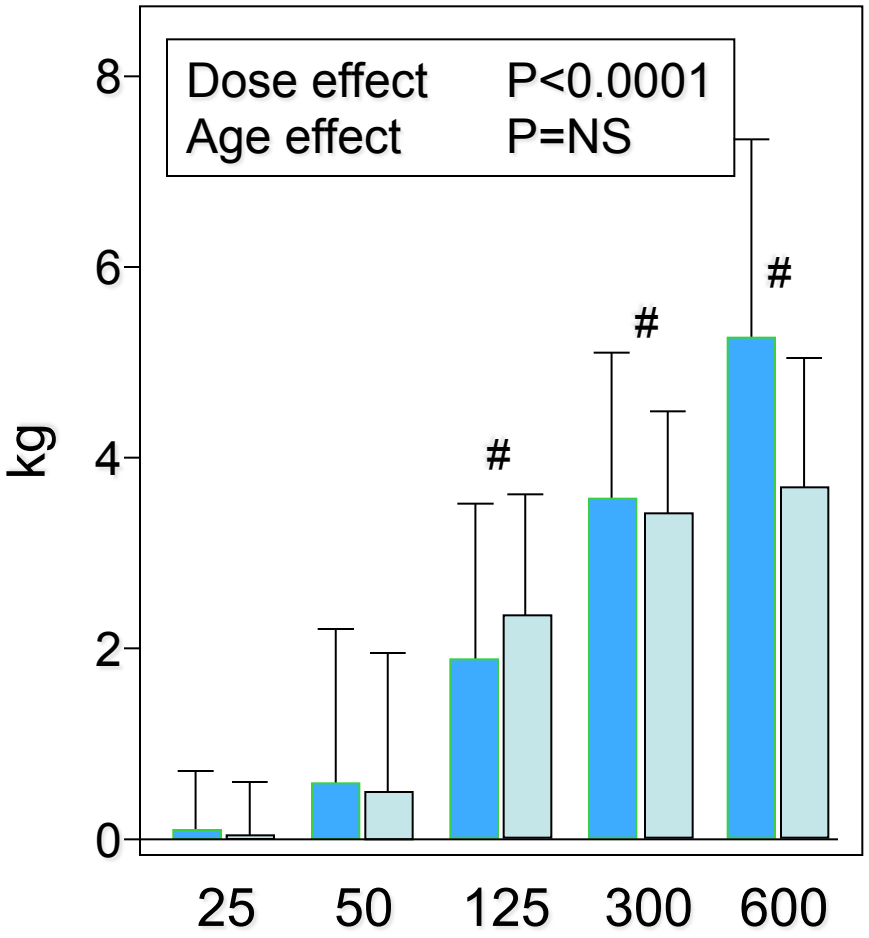
Transdermal T (50mg/day) in intermediary-frail and frail elderly (T< 12nmol/l or FT <250pmol/l)



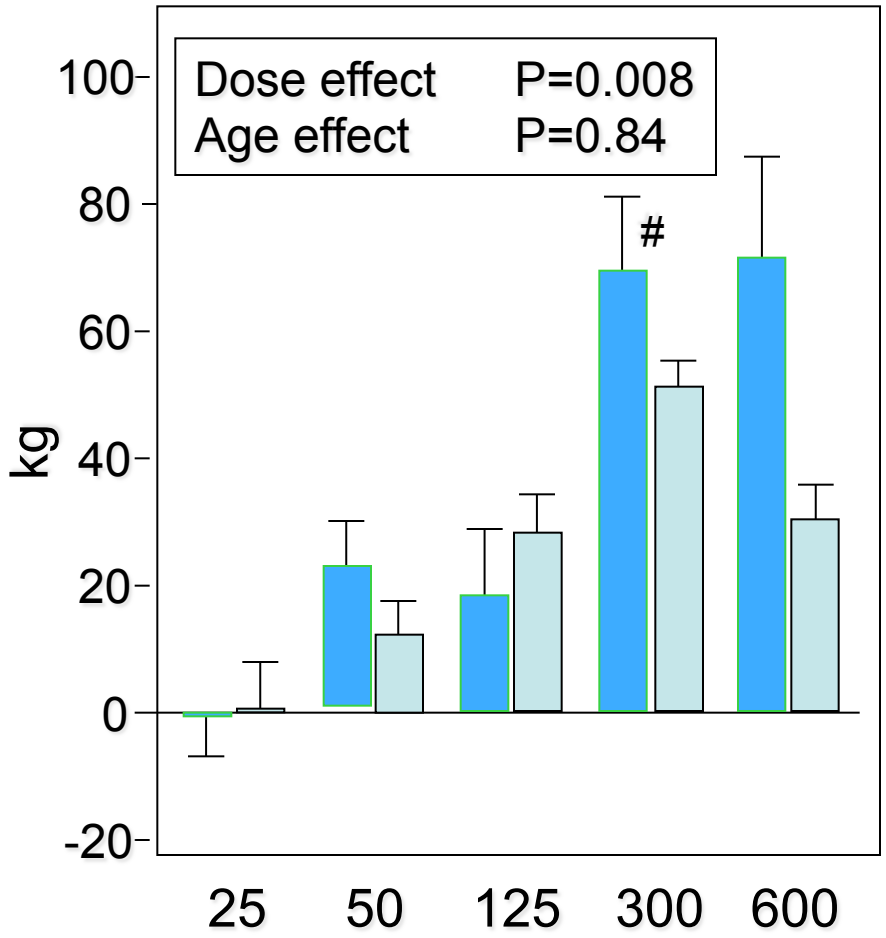
Remark:
O'Connel et al JCEM 2011

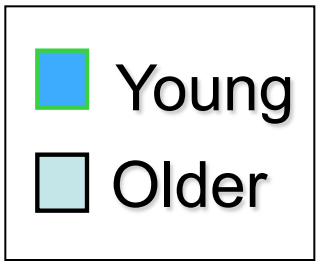
Srinivas-Shankar et al JCEM 95:639; 2010

Change Skeletal Muscle Mass

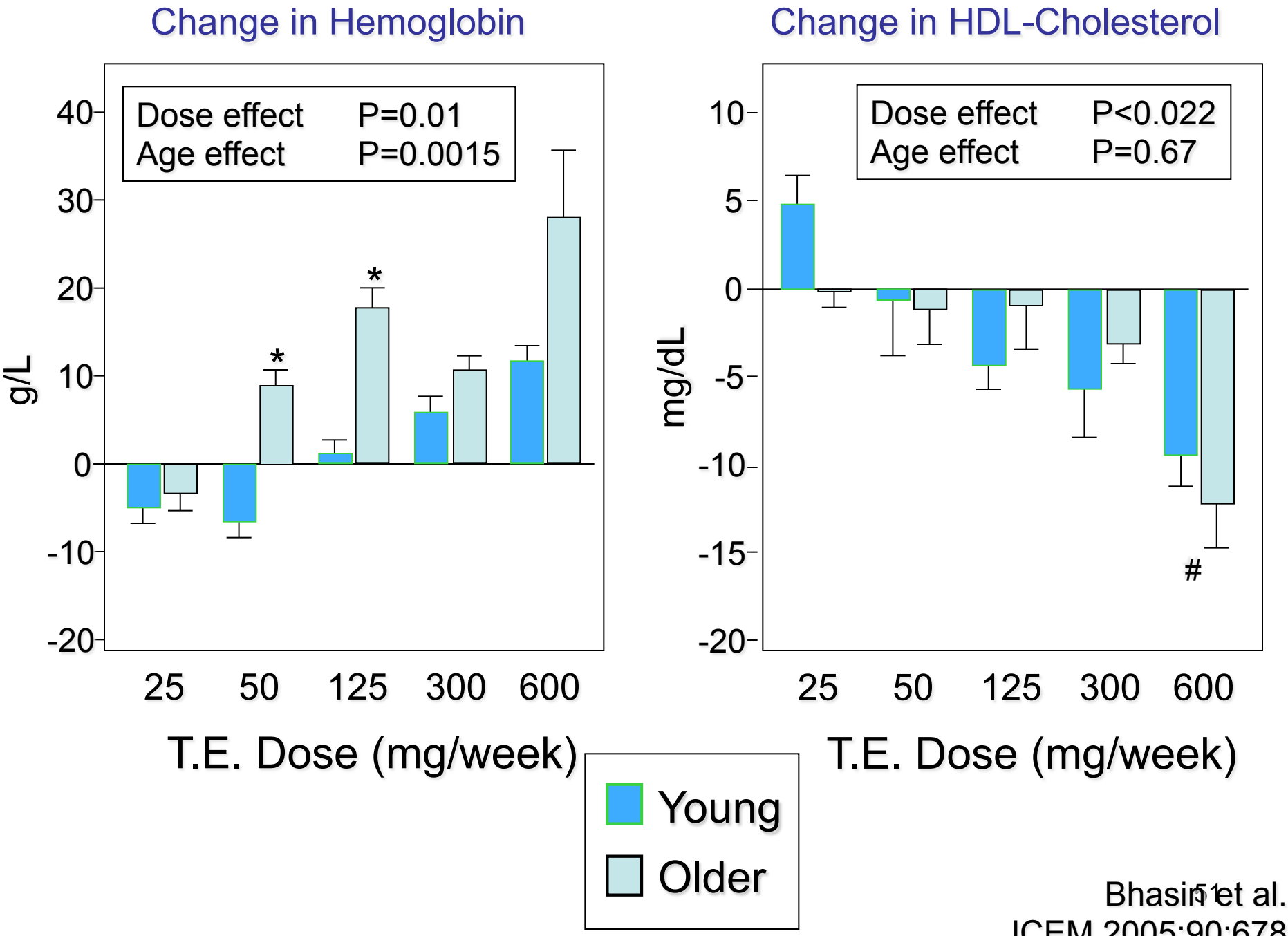


Change Leg Press Strength 1 RM





Bhasin et al.
JCEM 2005;90:678

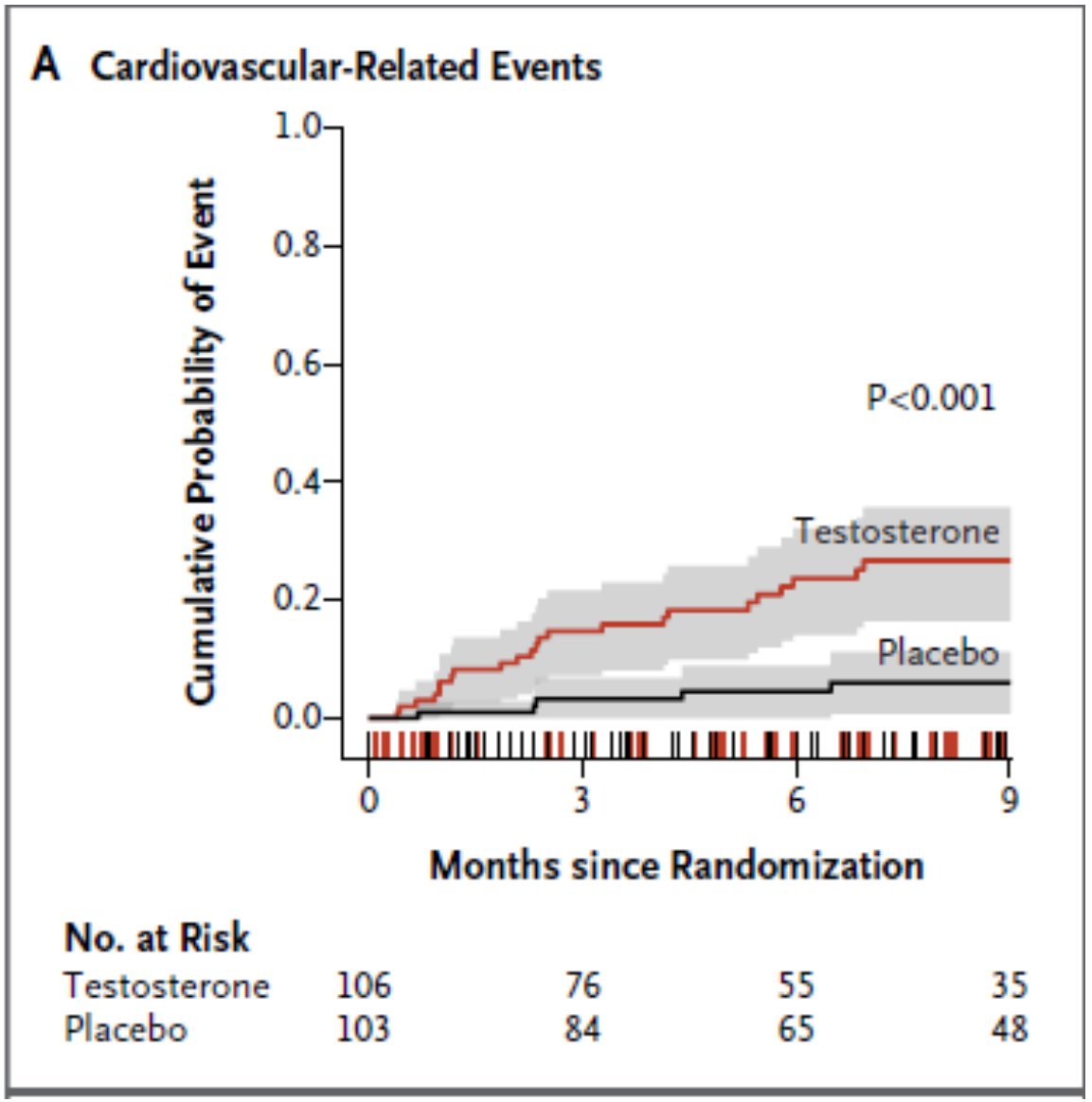


Bhasin et al.
JCEM 2005;90:678

The NEW ENGLAND JOURNAL of MEDICINE

Adverse Events Associated with Testosterone Administration

Shehzad Basaria, M.D., Andrea D. Coviello, M.D., Thomas G. Travison, Ph.D., Thomas W. Storer, Ph.D., Wildon R. Farwell, M.D., M.P.H., Alan M. Jette, Ph.D., Richard Eder, B.A., Sharon Tennstedt, Ph.D., Jagadish Ulloor, Ph.D., Anqi Zhang, Ph.D., Karen Choong, M.D., Kishore M. Lakshman, M.D., Norman A. Mazer, M.D., Ph.D., Renee Miciek, M.S., Joanne Krasnoff, Ph.D., Ayan Elmi, B.A., Philip E. Knapp, M.D., Brad Brooks, B.S., Erica Appleman, M.A., Sheetal Aggarwal, B.S., C.C.R.P., Geeta Bhasin, B.A., Leif Hede-Brierley, Ashmeet Bhatia, M.B., B.S., Lauren Collins, R.N.P., Nathan LeBrasseur, Ph.D., Louis D. Fiore, M.D., and Shalender Bhasin, M.D.


A Cardiovascular-Related Events
Cumulative Probability of Event
1.0
0.8
0.6
0.4
0.2
0.0
P<0.001
Testosterone
Placebo
0
3
6
9
Months since Randomization
No. at Risk
Testosterone 106 76 55 35
Placebo 103 84 65 48

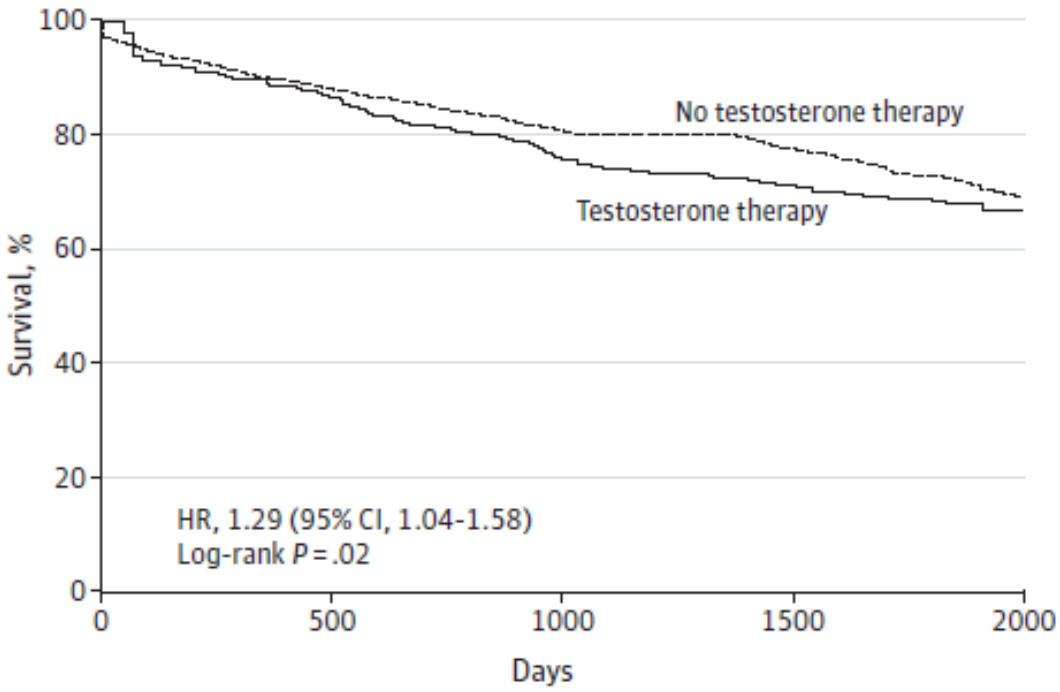
Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

JAMA. 2013;310(17):1829-1836. doi:10.1001/jama.2013.280386

CONCLUSIONS AND RELEVANCE Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.

Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate



No. at risk					
Testosterone therapy					
No	8709	5337	2897	918	206
Yes	0	439	500	233	61

Vigen et al JAMA 2013; 310:1829-36

T treatment and mortality in men with low T (observational data)

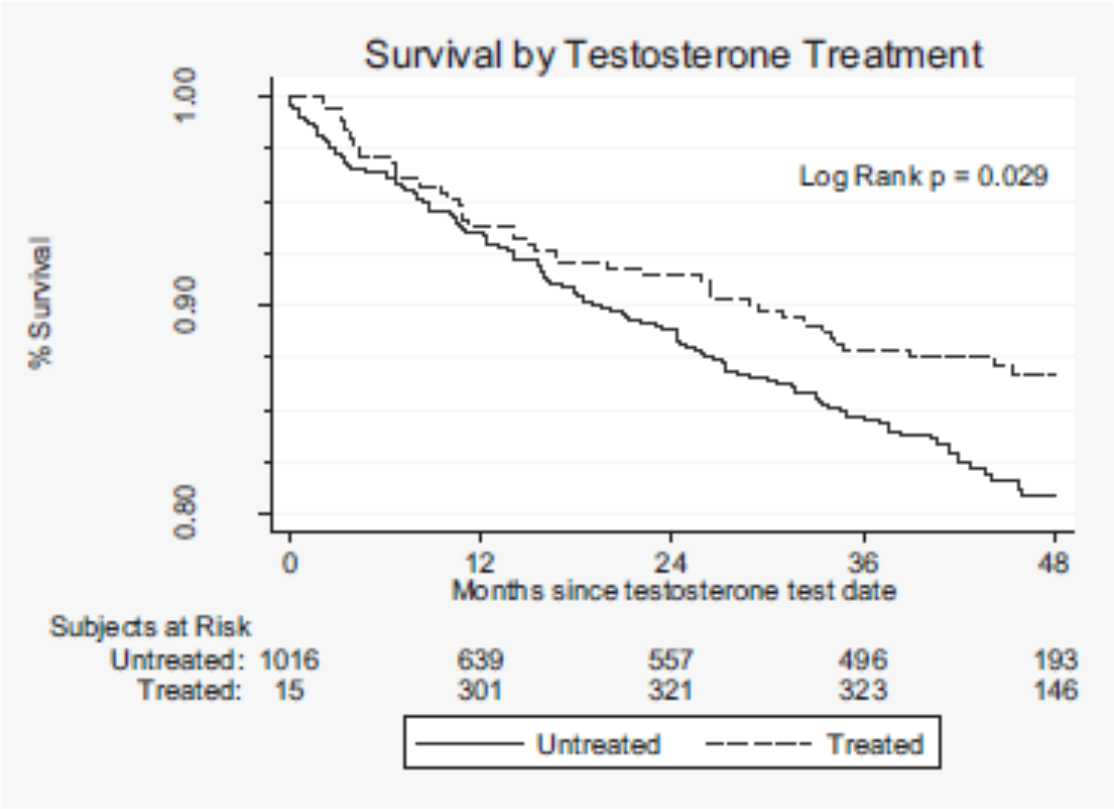


Fig. 1. Unadjusted Kaplan-Meier survival curves illustrate that testosterone-treated men had a longer survival time than untreated men ($P = 0.029$).

Shores et al J Clin Endocrinol Metab 2012;97: 2050-58

Who should we consider for treatment ?

- Established hypogonadism in young men will usually be treated unless conra-indications even though there is understandably little data from controlled trials in young men
- Positive findings in the elderly largely limited to elderly with initially low serum testosterone

- Unknown longer term risk/benefit

Who should we consider for treatment ?

- Free testosterone frankly below normal for the young
- Unequivocal signs and symptoms of hypogonadism (preferably spontaneous reporting)
- No reversible cause
- No contra-indications
- Consider also the alternatives
  alternatives first if only low total testosterone!
- Remarks: dosage; monitoring; treatment interrupted

Thank You