



Testosterone and obesity

Referent

Prof. Dr. Michael Zitzmann



Transparenzinformation arztCME

Die Bundesärztekammer und die Landesärztekammer Hessen fordern zur Schaffung von mehr Transparenz beim Sponsoring in der ärztlichen Fortbildung auf. Fortbildungsveranstalter sind gehalten, potenzielle Teilnehmer von Fortbildungen bereits im Vorfeld der Veranstaltung über Umfang und Bedingungen der Unterstützung der Arzneimittelindustrie zu informieren. Dieser Verpflichtung kommen wir nach und werden Sie hier über die Höhe des Sponsorings(*) der beteiligten Arzneimittelfirma sowie über mögliche Interessenkonflikte der Autoren informieren.

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Mögliche Interessenkonflikte – Prof. Dr. Michael Zitzmann erklärt:

Bei der Erstellung dieses Beitrags für eine durch die Landesärztekammer Hessen anzuerkennende Fortbildung bestanden keine Interessenkonflikte im Sinne der Empfehlungen des International Committee of Medical Journal Editors (www.icmje.org).

Die Produktneutralität dieser Fortbildung wurde durch ein Review mit zwei Gutachtern geprüft.

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(*) Die Sponsoringbeiträge können je nach Art und Umfang der Fortbildung unterschiedlich sein.



Testosterone and obesity

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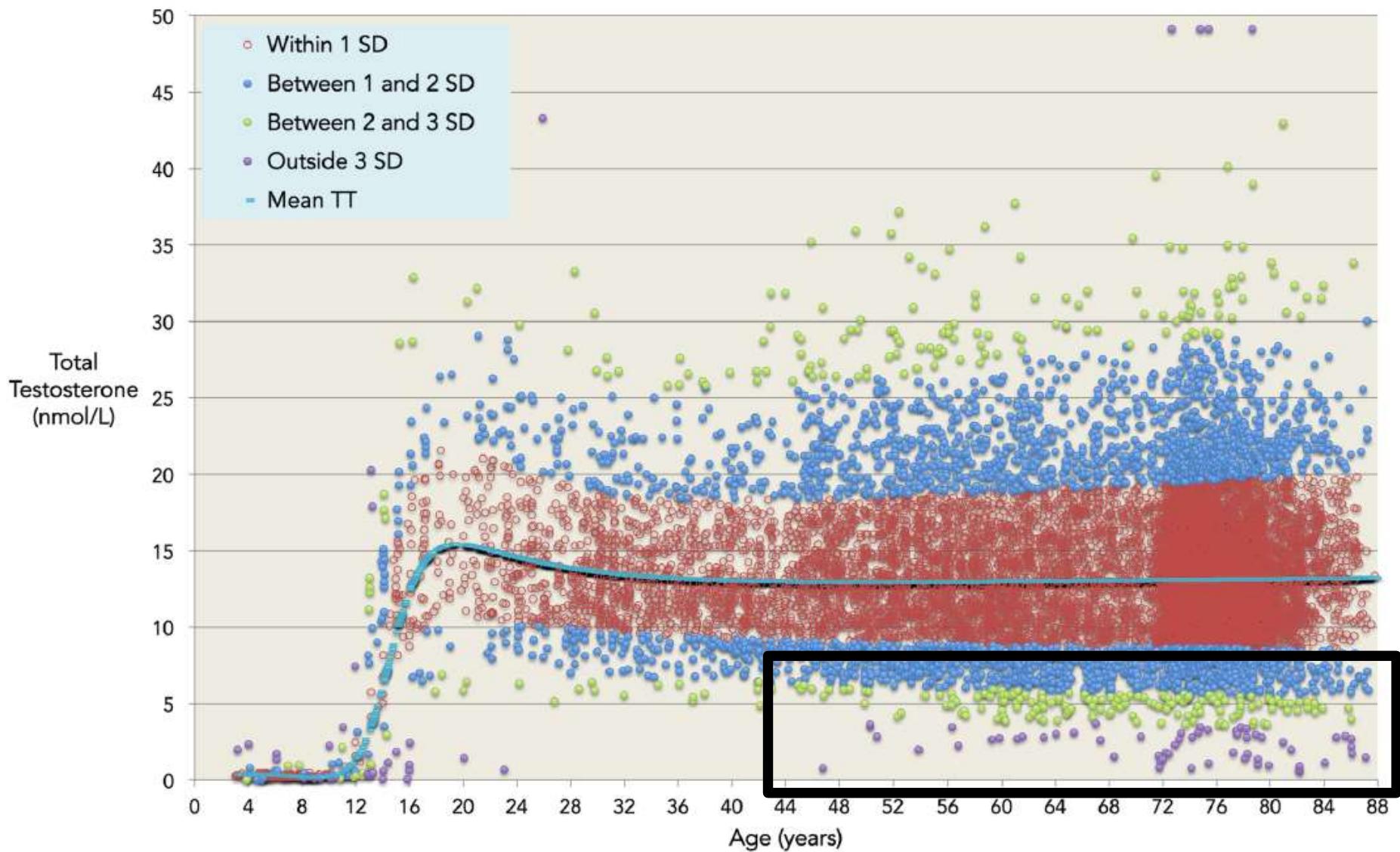


WHO Collaborating Centre for Research in Human Reproduction
Training Centre of the European Academy of Andrology



Testosterone levels in men related to age (n=10098)

Kelsey et al. PLoS one 2014



Problem: Obesity



New EAU guideline 2015

Markers

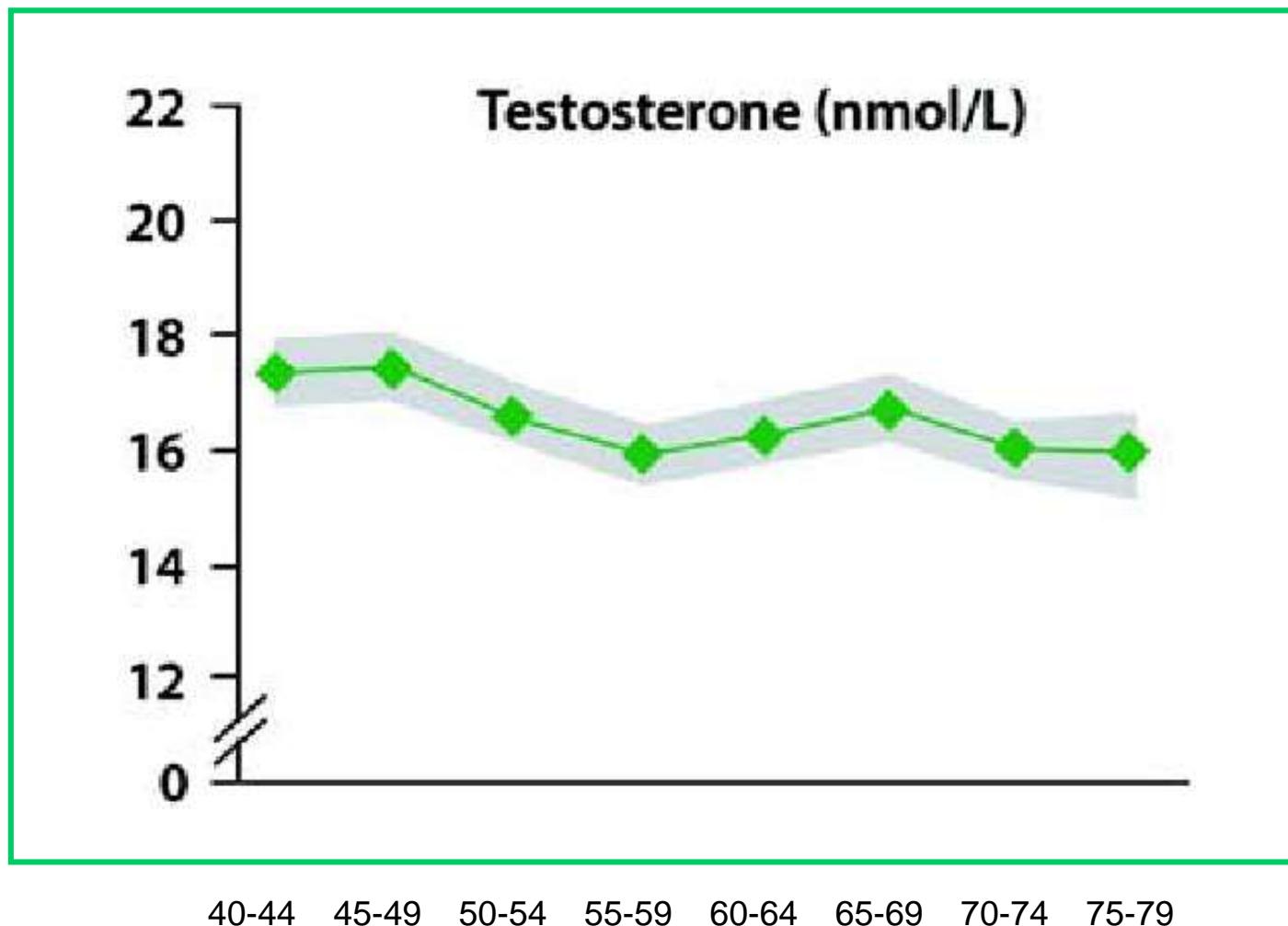
of Hypogonadism and Indications for Substitution Therapy

in case of low total T (<12.1 nmol/L) or free T (<243 pmol/L)

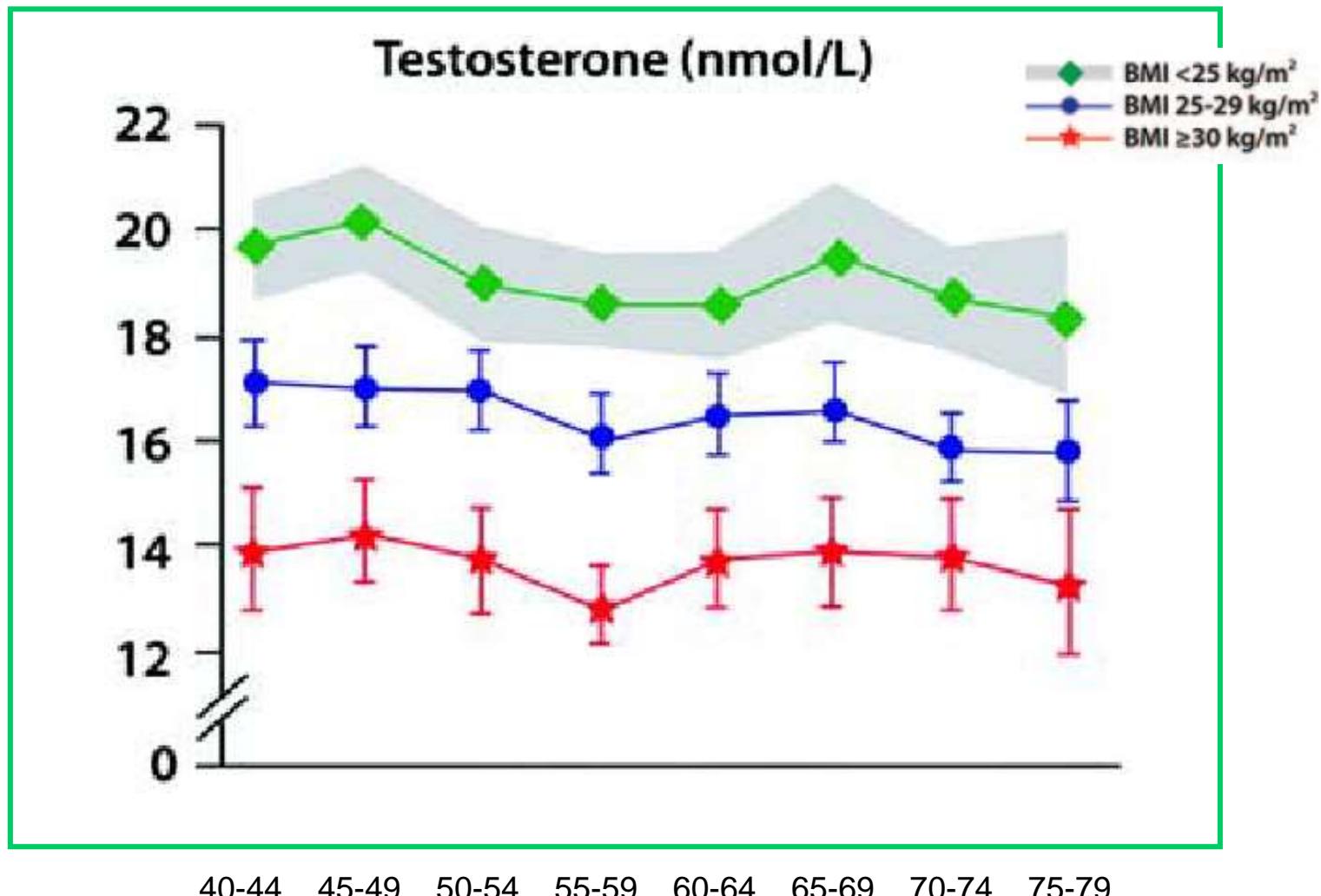
- Loss of Libido
- Depressive Mood
- Metabolic Disorders



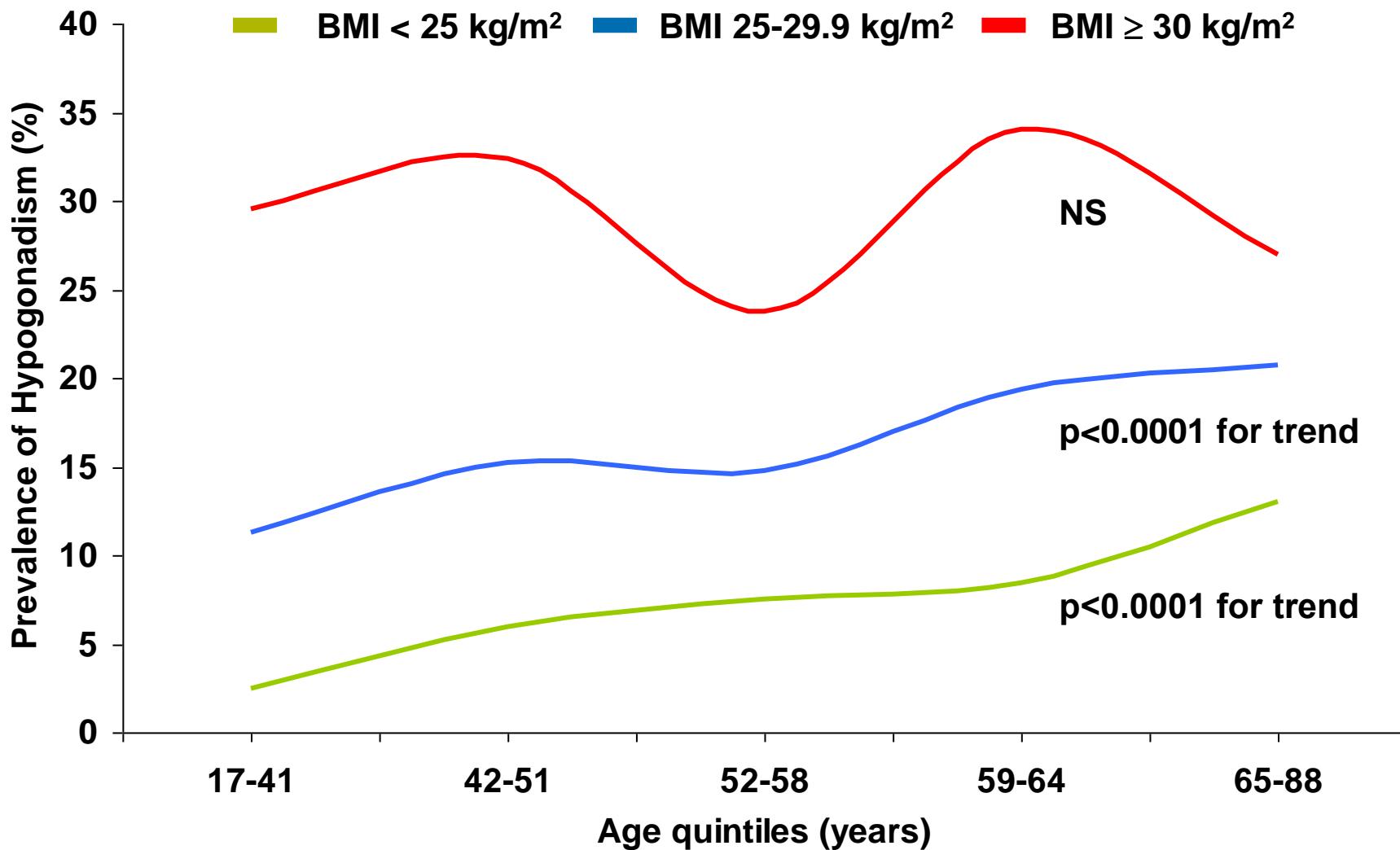
European Male Aging Study (EMAS) relation between age and testosterone (40-79)



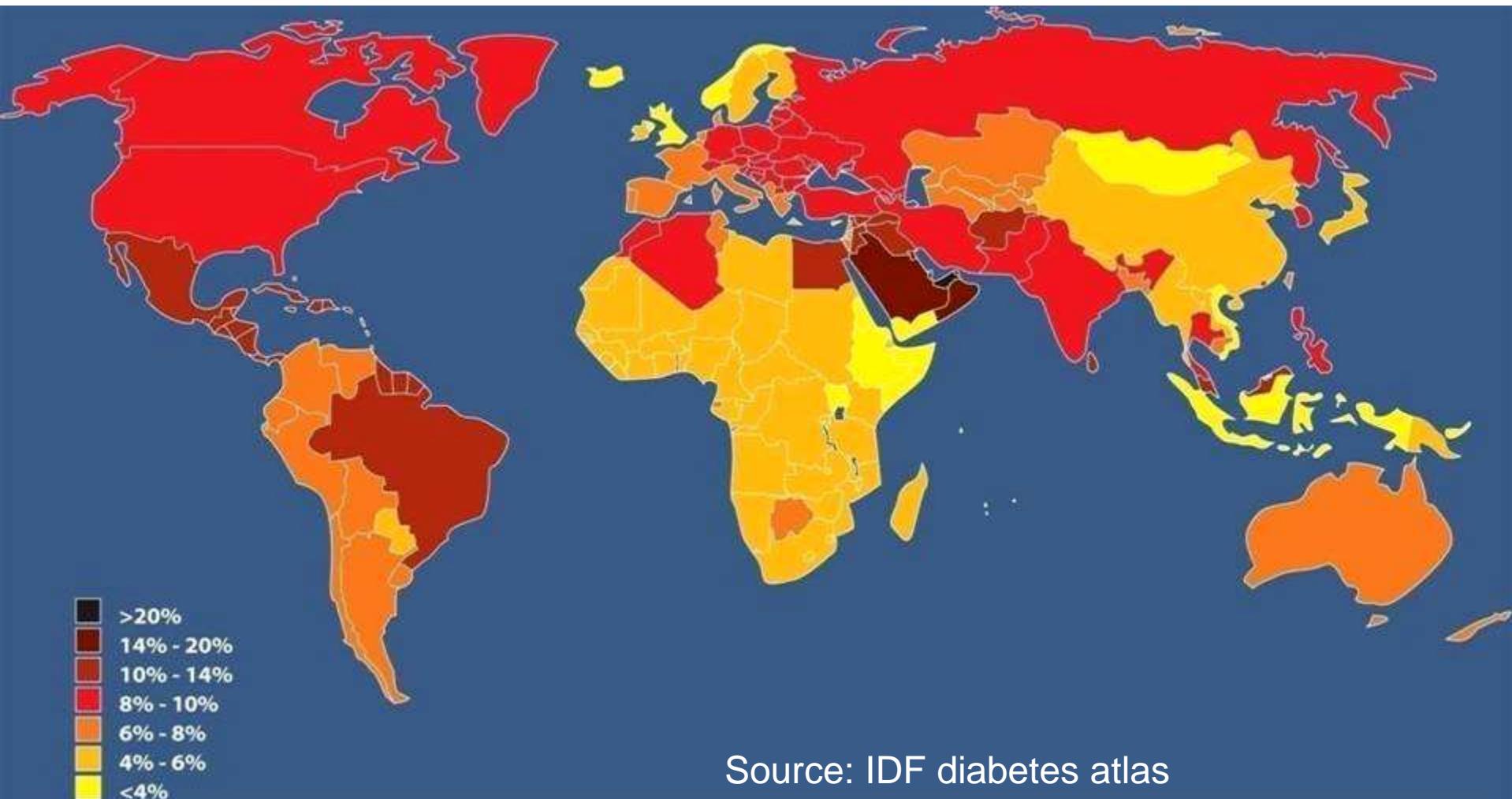
European Male Aging Study (EMAS)
relation between age and testosterone (40-79), n=3174

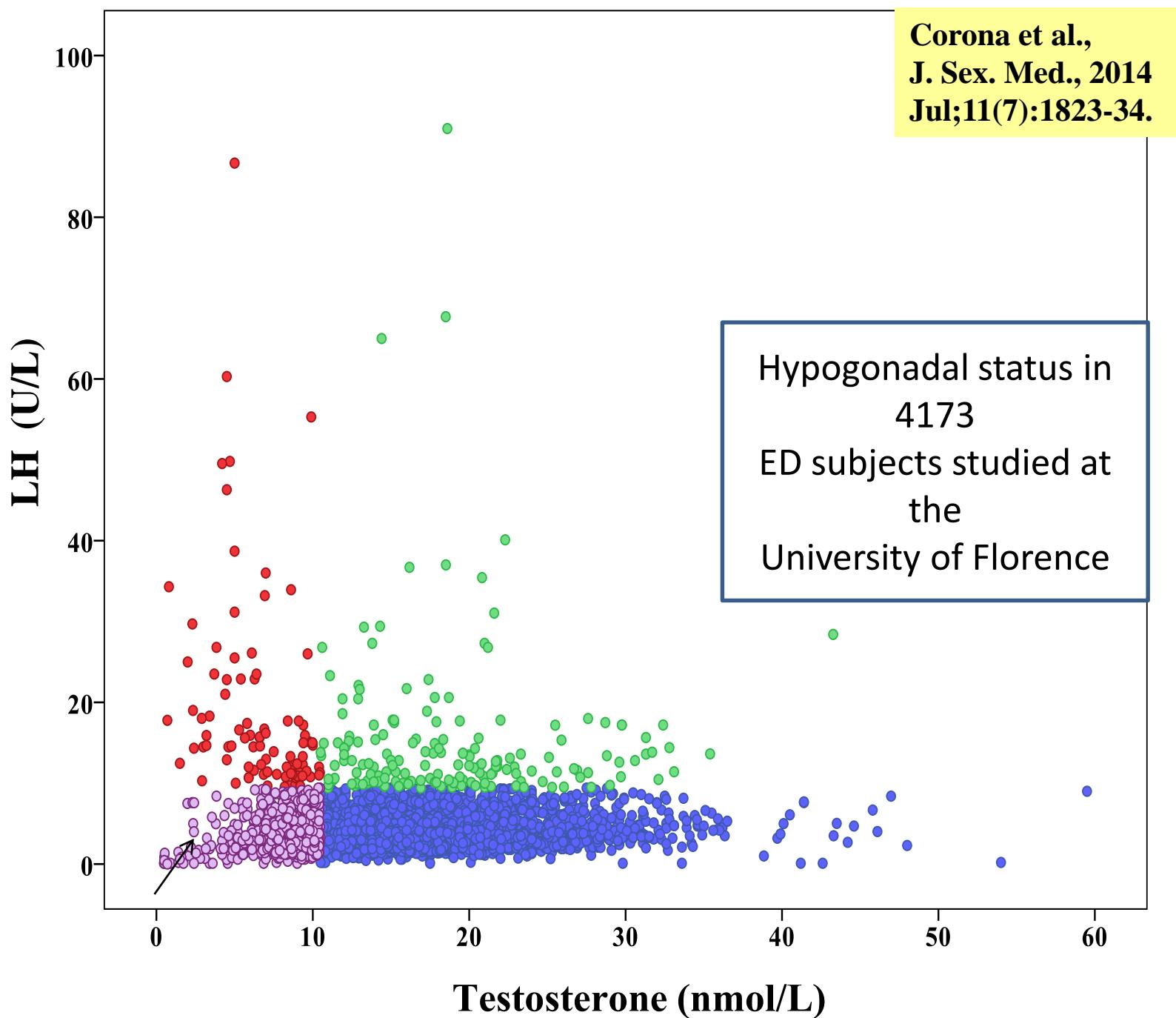


Prevalence of Hypogonadism in 1687 Men Presenting to an Outpatient Andrology Unit



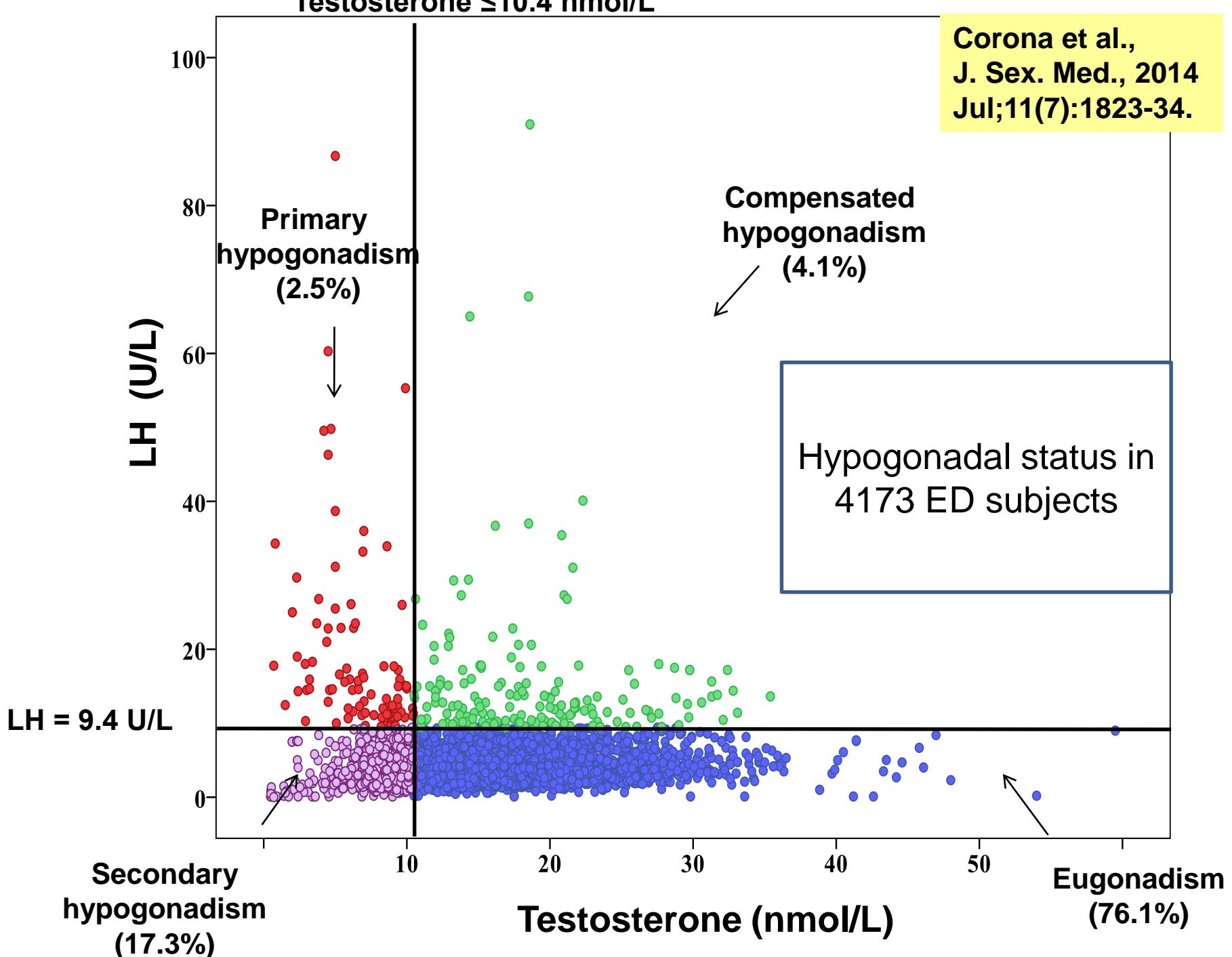
PREVALENCE OF TYPE 2 DIABETES MELLITUS, 2025



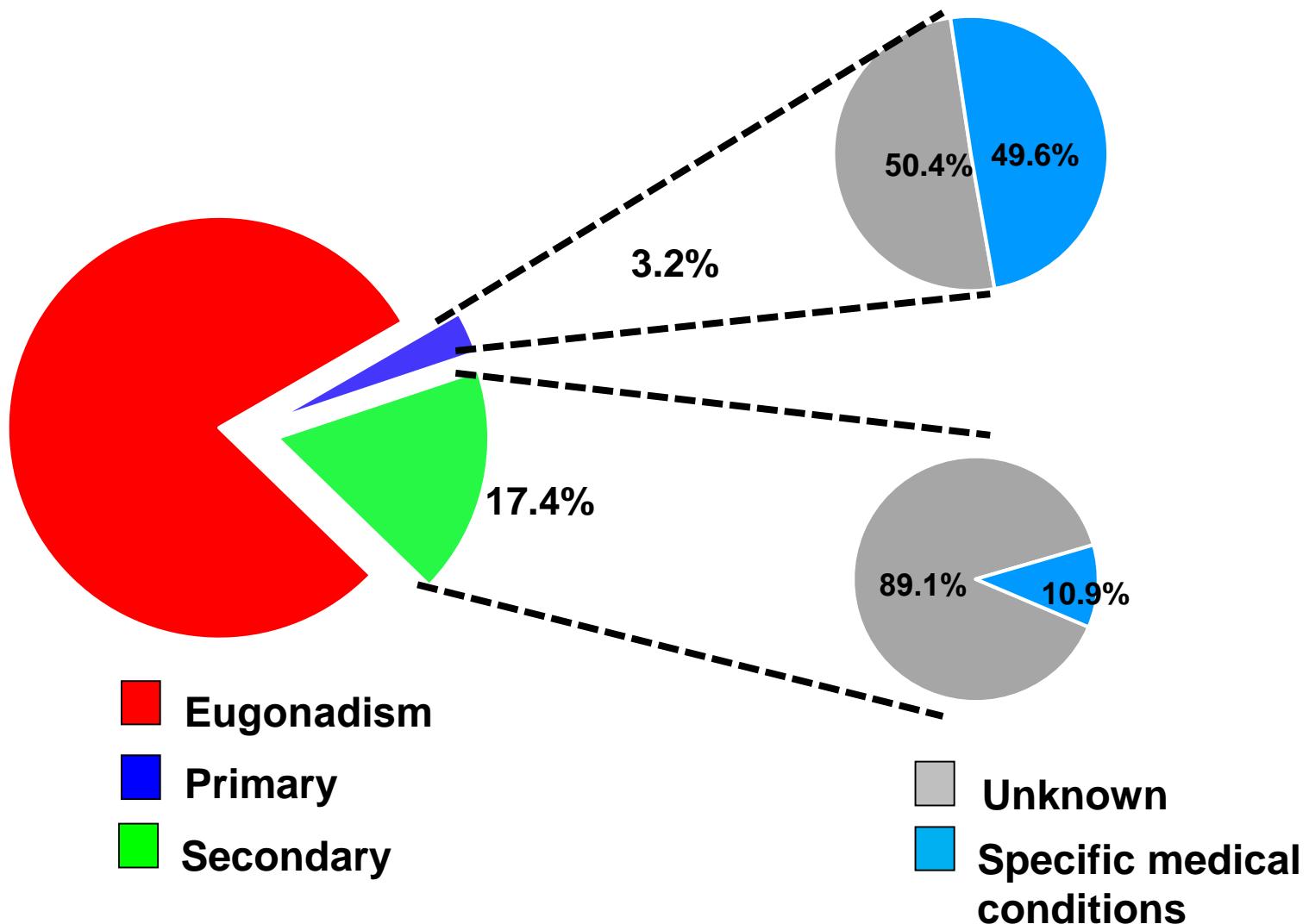


Testosterone ≤ 10.4 nmol/L

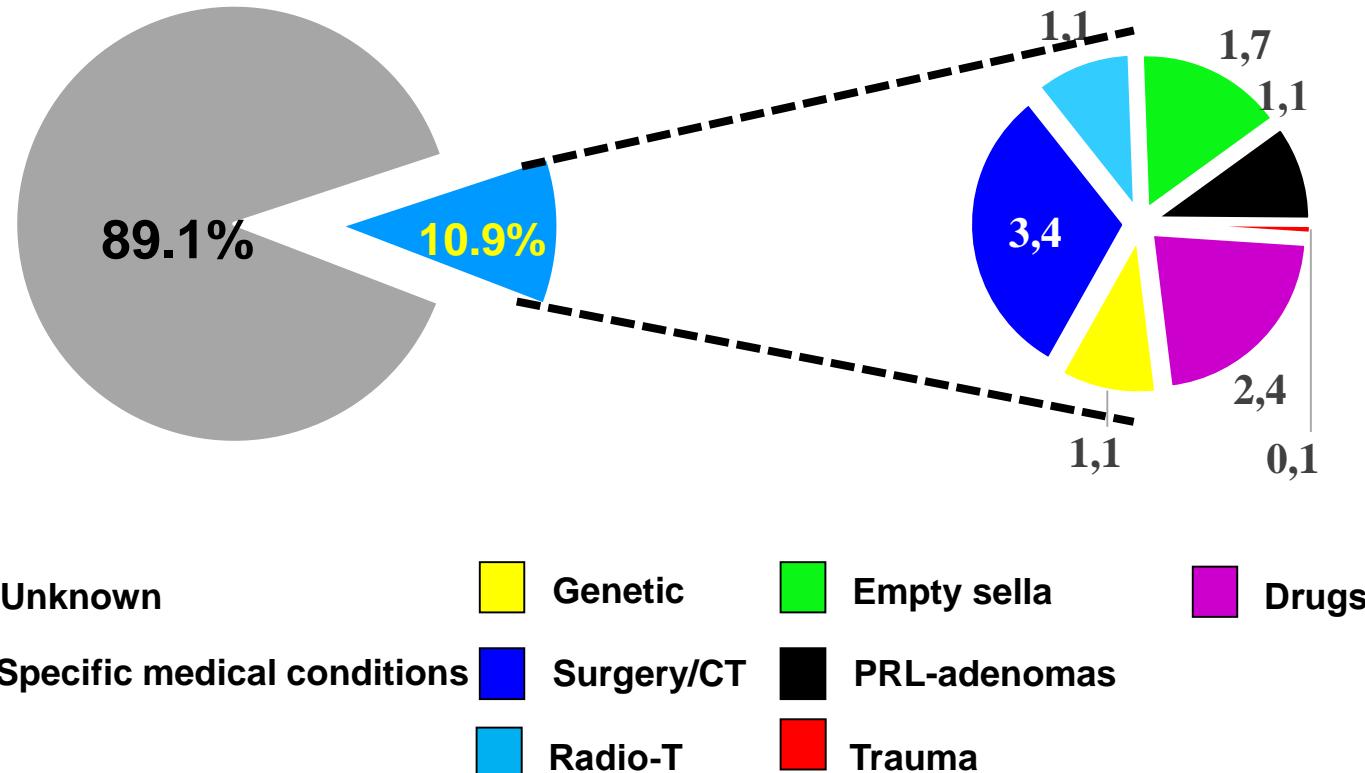
Corona et al.,
J. Sex. Med., 2014
Jul;11(7):1823-34.



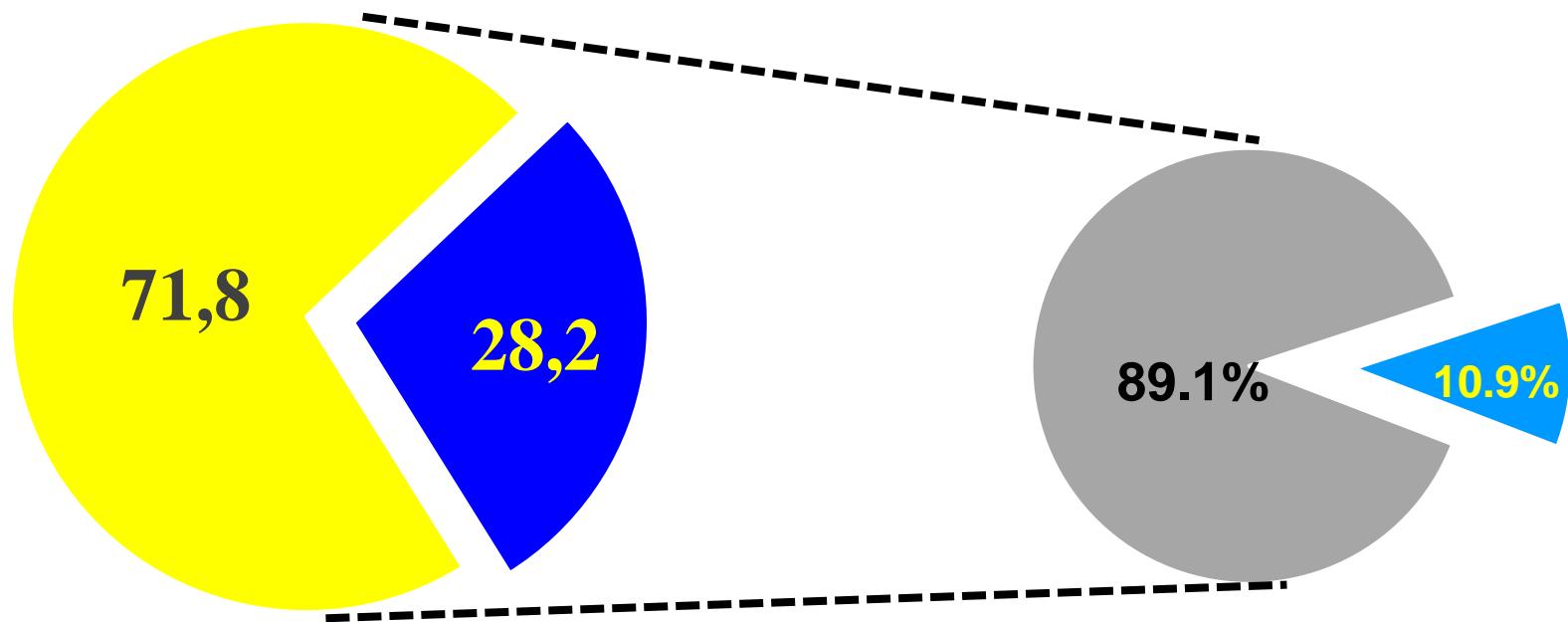
Prevalence of hypogonadism in patients seeking medical care for ED, n=4220



Specific medical conditions associated with secondary hypogonadism



Specific medical conditions associated with secondary hypogonadism



■ Concomitant metabolic disease

Obesity, T2DM or MetS

■ Unknown

■ Unknown

■ Specific medical conditions

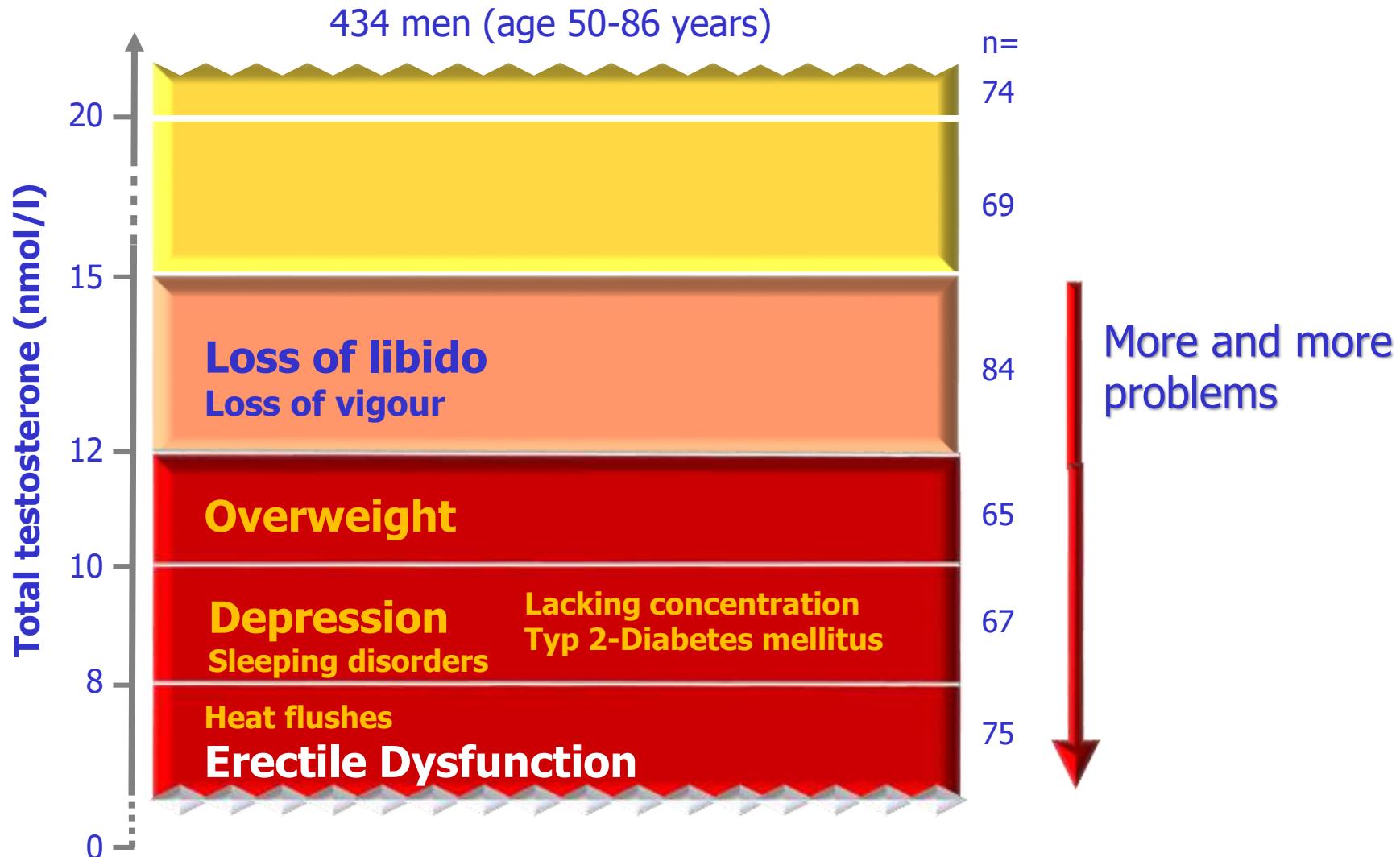
Men with TDS as patients in general practice

Complaints related to testosterone levels

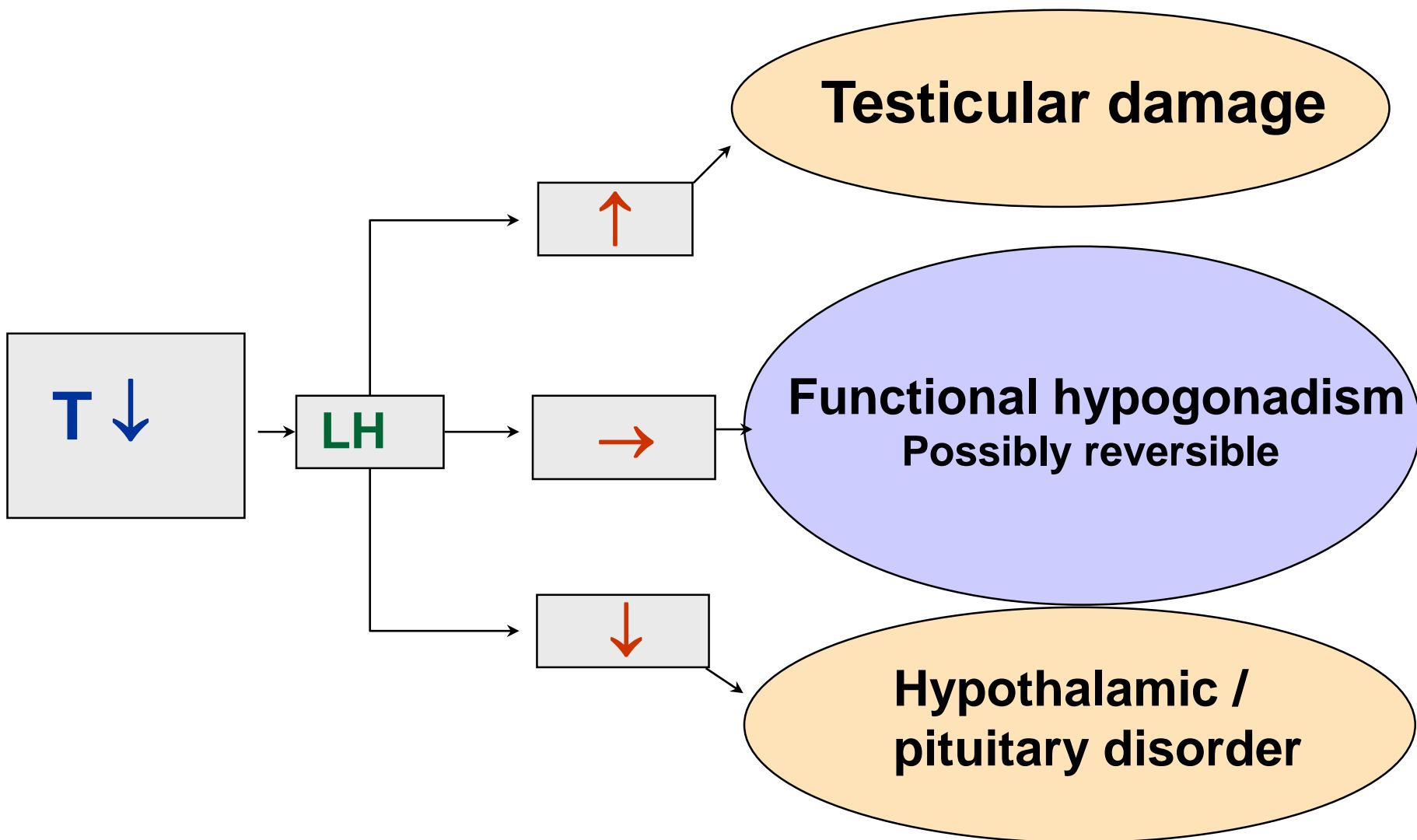
Risk factor	Hypogonadism prevalence rate (95% CI)	Odds ratio (95% CI)
Obesity	52.4 (47.9–56.9)	2.38 (1.93–2.93)
Diabetes mellitus	50.0 (45.5–54.5)	2.09 (1.70–2.58)
Hypertension	42.4 (39.6–45.2)	1.84 (1.53–2.22)
Hyperlipidemia	40.4 (37.6–43.3)	1.47 (1.23–1.76)

CI, confidence interval

Testosterone levels and symptoms



Hormone constellations in male hypogonadism



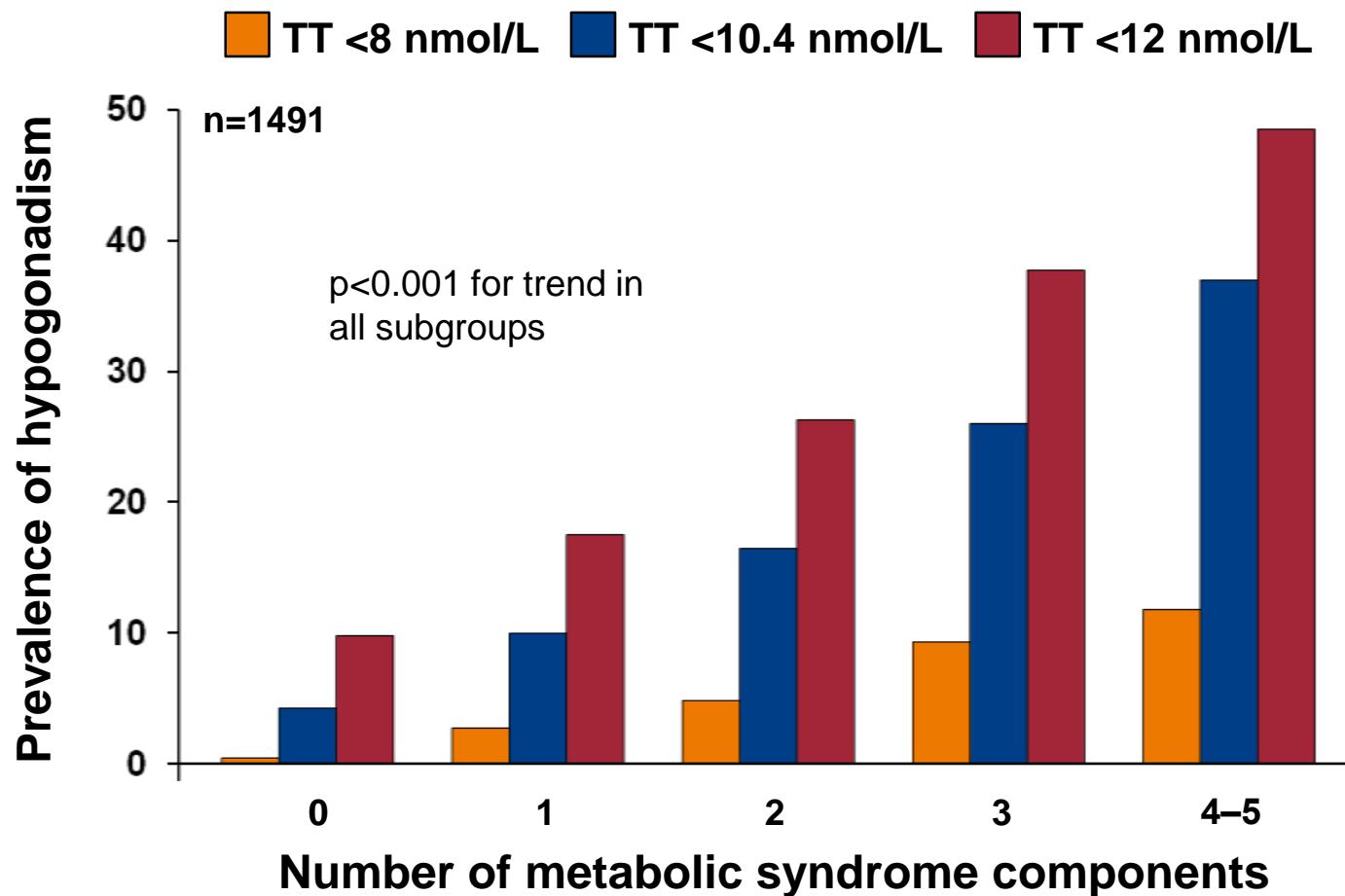
New Criteria for the Definition of the Metabolic Syndrome



1. **Waist Circumference >94-102 cm**
2. **Triglycerides** > 150 mg/dl
or treatment
3. **HDL-Cholesterol** < 40 mg/dl
or treatment
4. **Arterial Blood Pressure** > 130 mmHg systolic
and/or > 85 mmHg diastolic
or treatment
5. **Fasting glucose** > 100 mg/dl
or known Type 2 Diabetes mellitus

3 of 5 Criteria have to be met (Consensus IDF & NCEP ATP III)

Total T levels decrease with increasing number of metabolic syndrome components



BMI and BMI are not the same... the role of visceral fat tissue

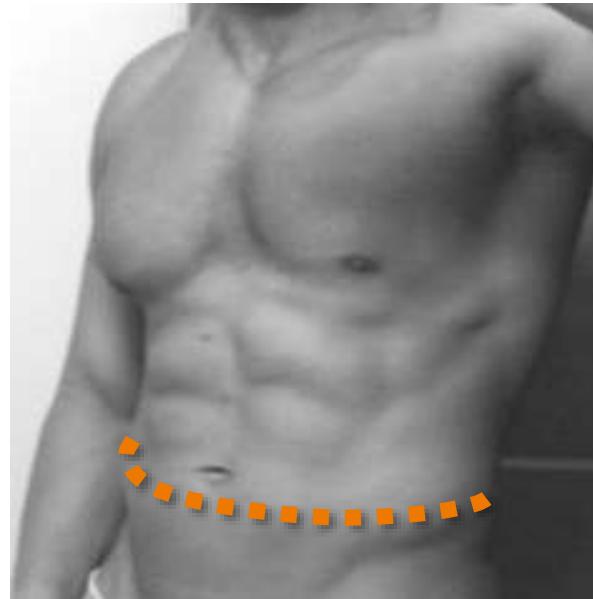
189 cm, 93 kg = BMI 26



Waist circumference

Testosterone

190 cm, 94 kg = BMI 26

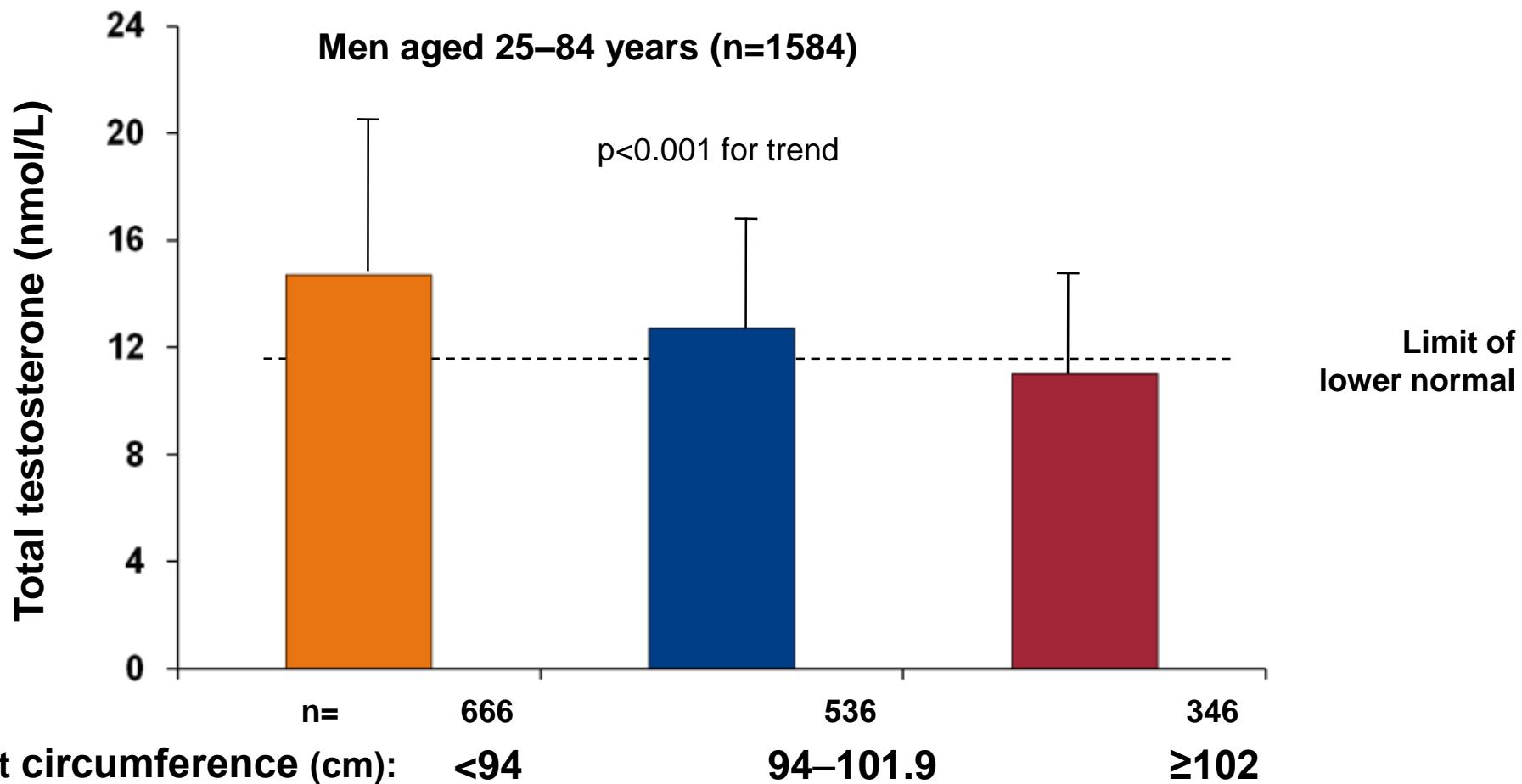


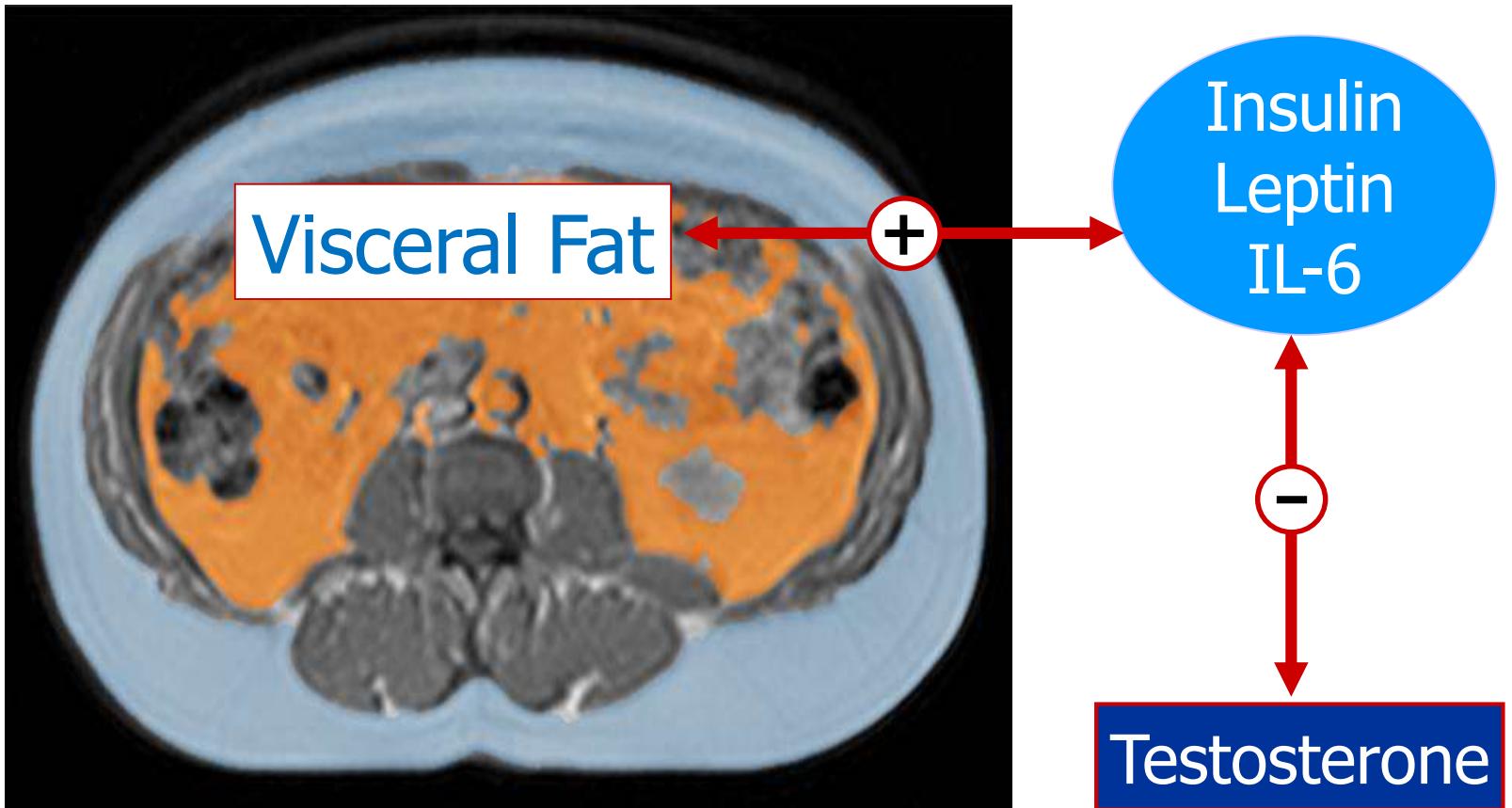
Waist circumference



Testosterone

Testosterone levels decrease with increasing waist circumference

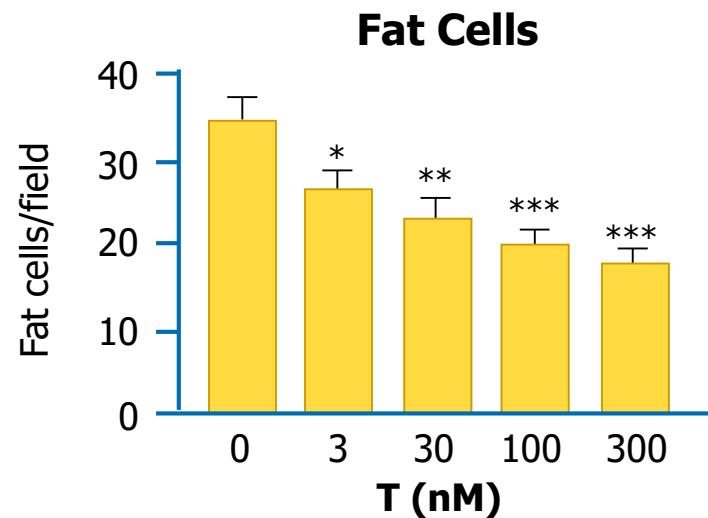
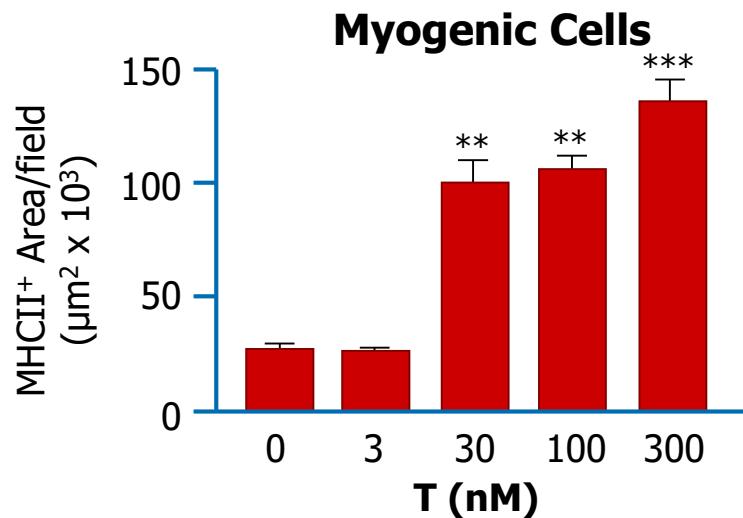




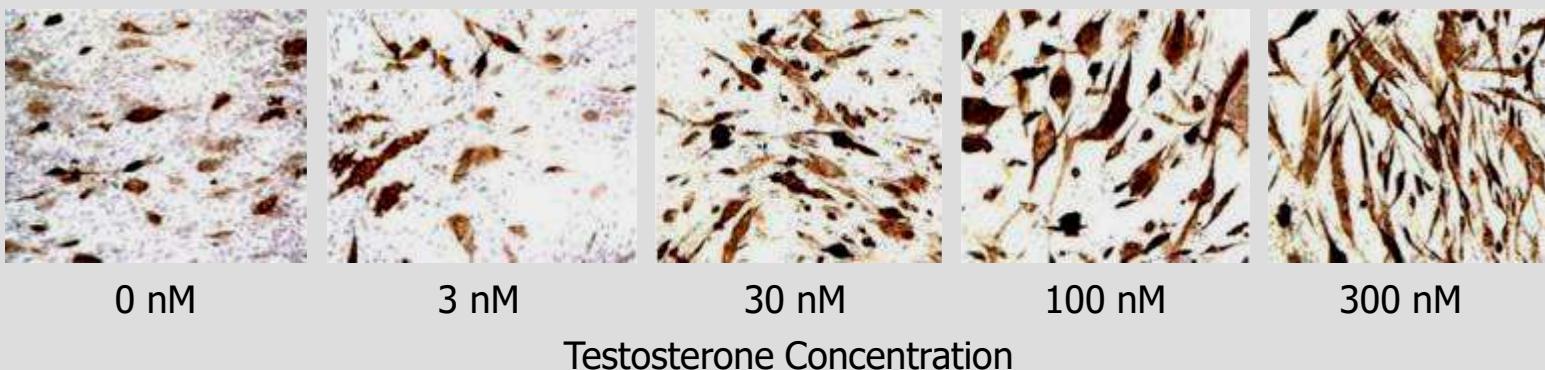
With agreement of Rob McLachlan und Carolyn Allan, Monash University, Melbourne, Australia

Zitzmann et al. 2003 + 2005, Walsh et al. 2005, Mulligan et al. 2006

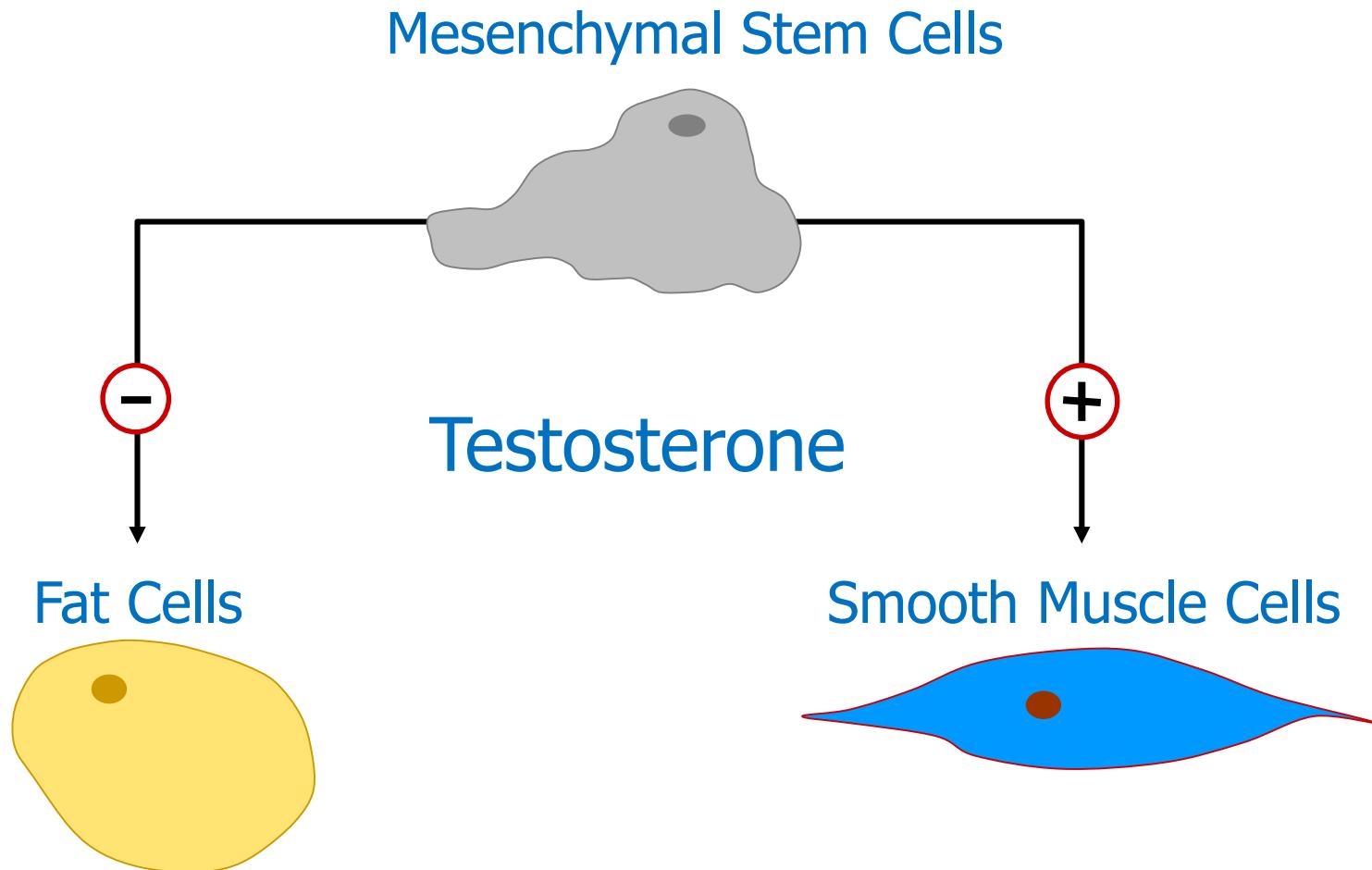
Testosterone induces Myogenesis in pluripotent Stem Cells



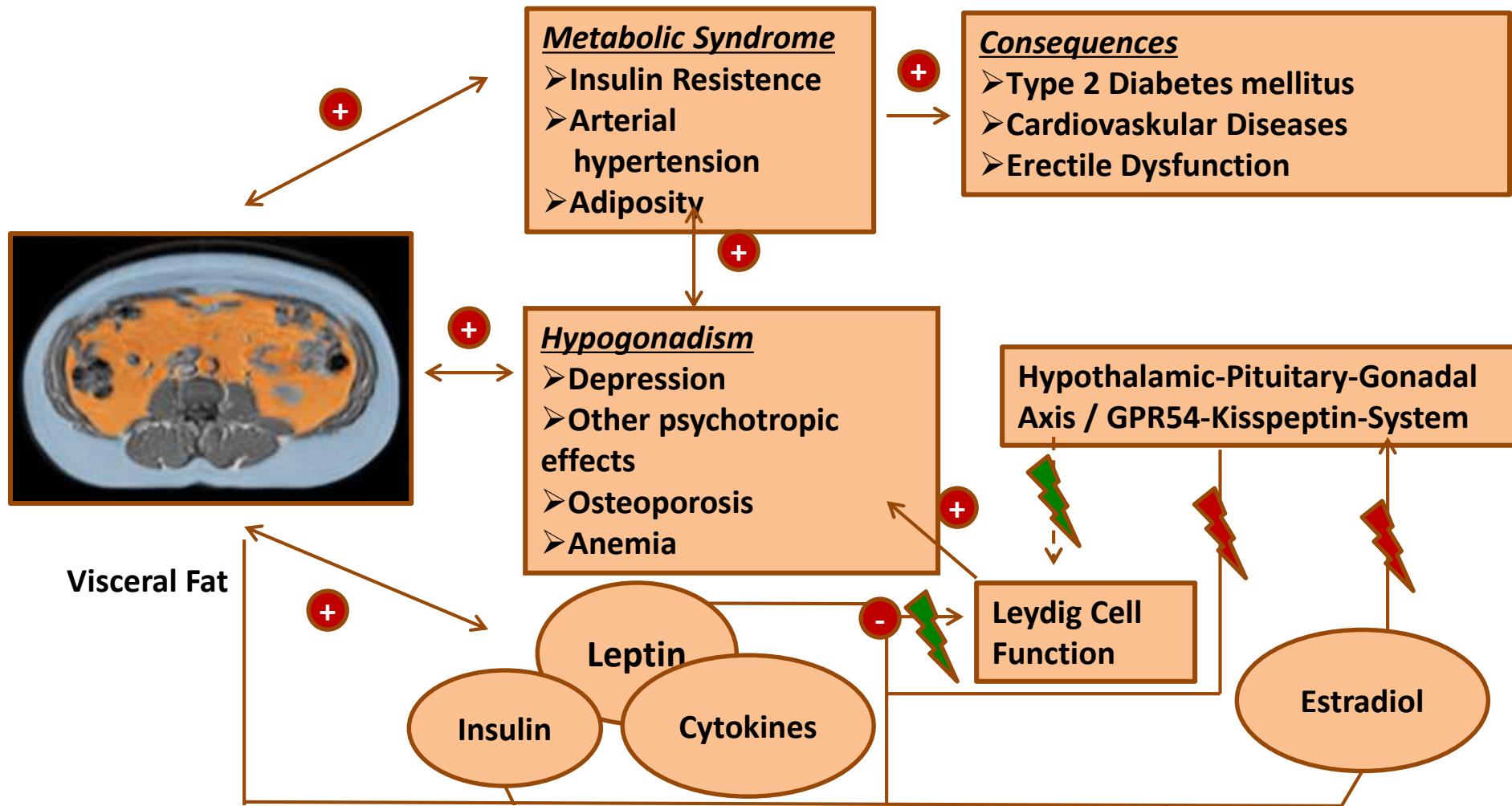
MHC⁺ Myogene Zellen



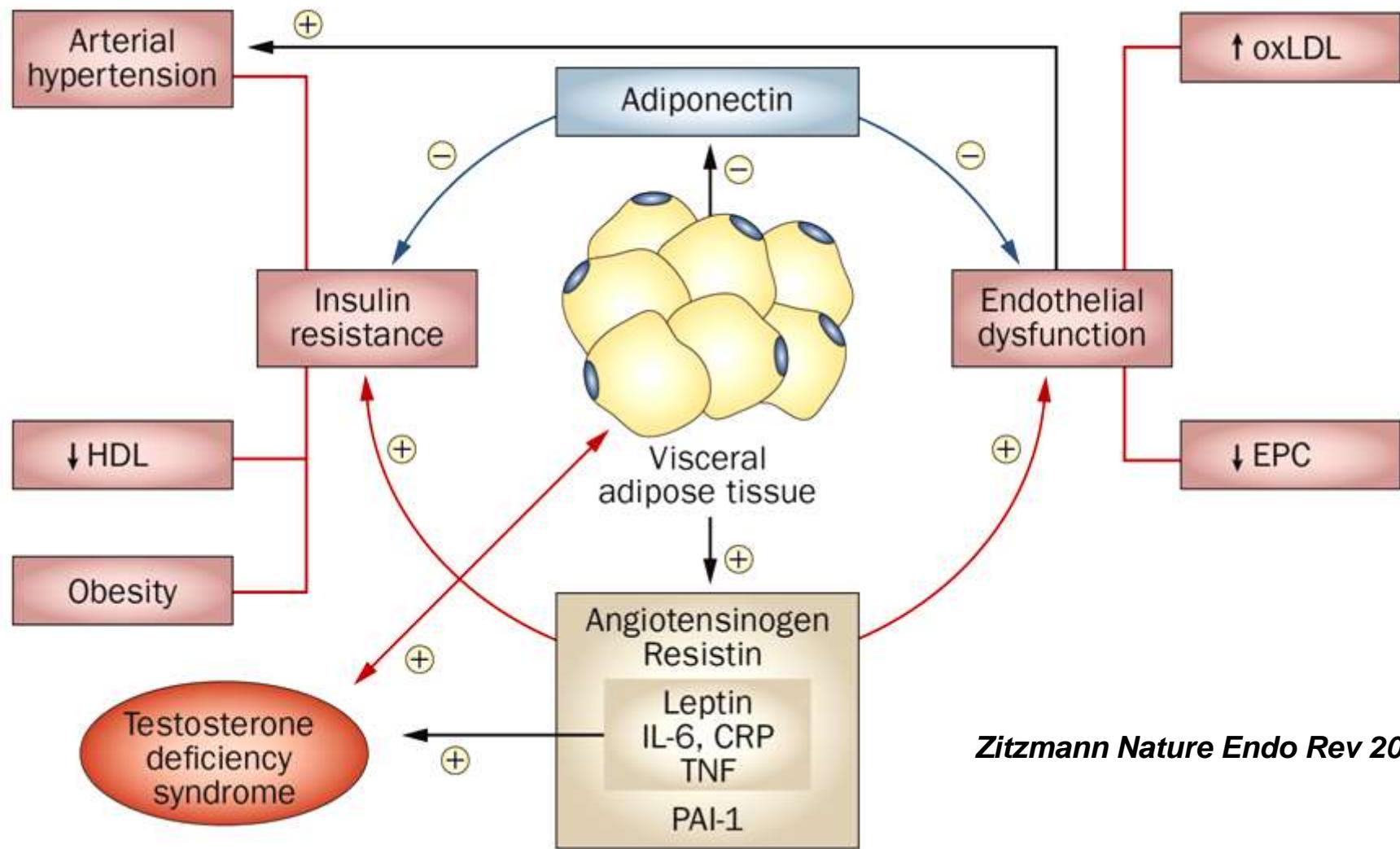
Testosterone changes pathways for stem cells



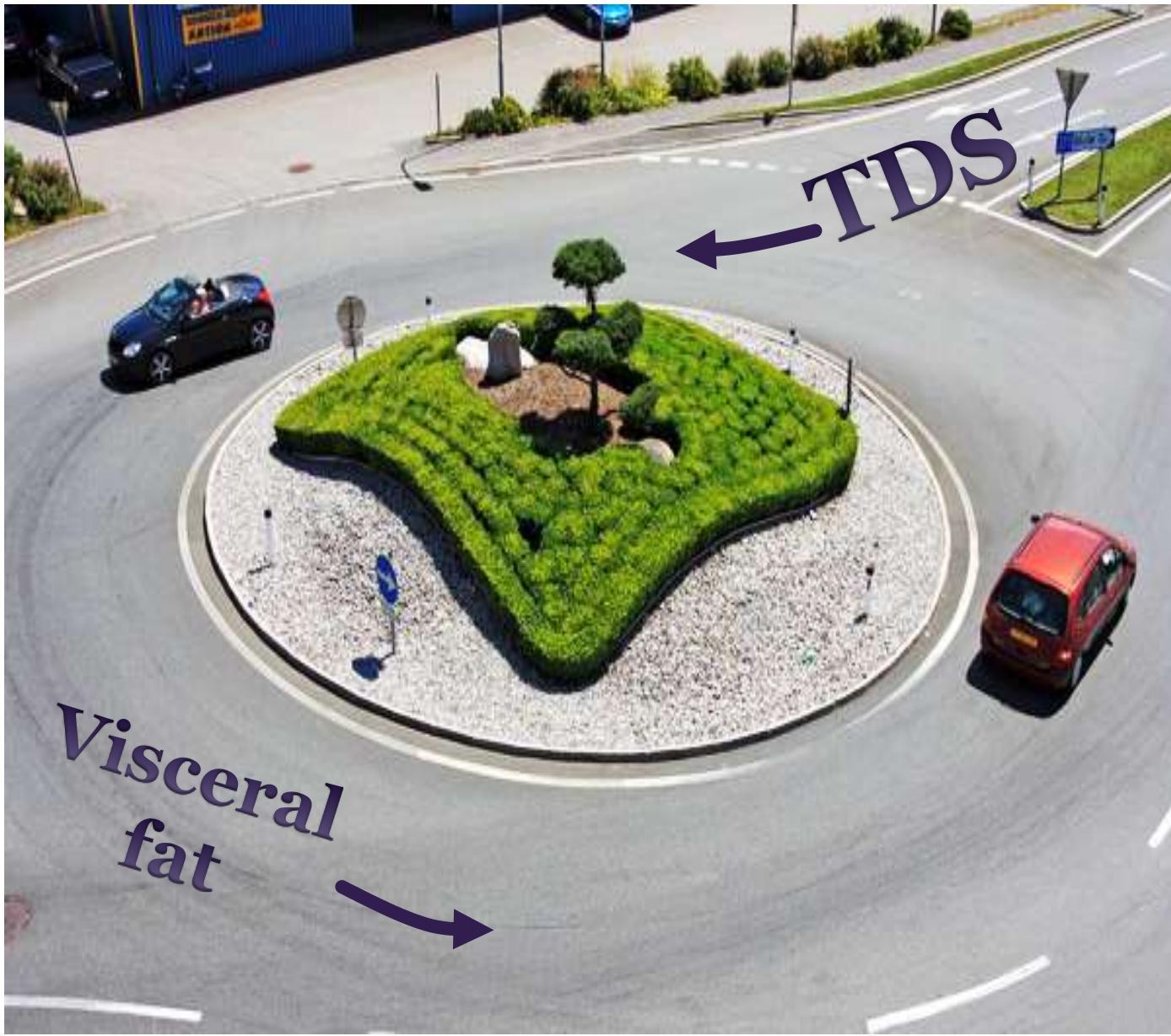
Visceral fat tissue



The interplay of fat tissue, insulin resistance, testosterone deficiency and VASCULAR INTEGRITY

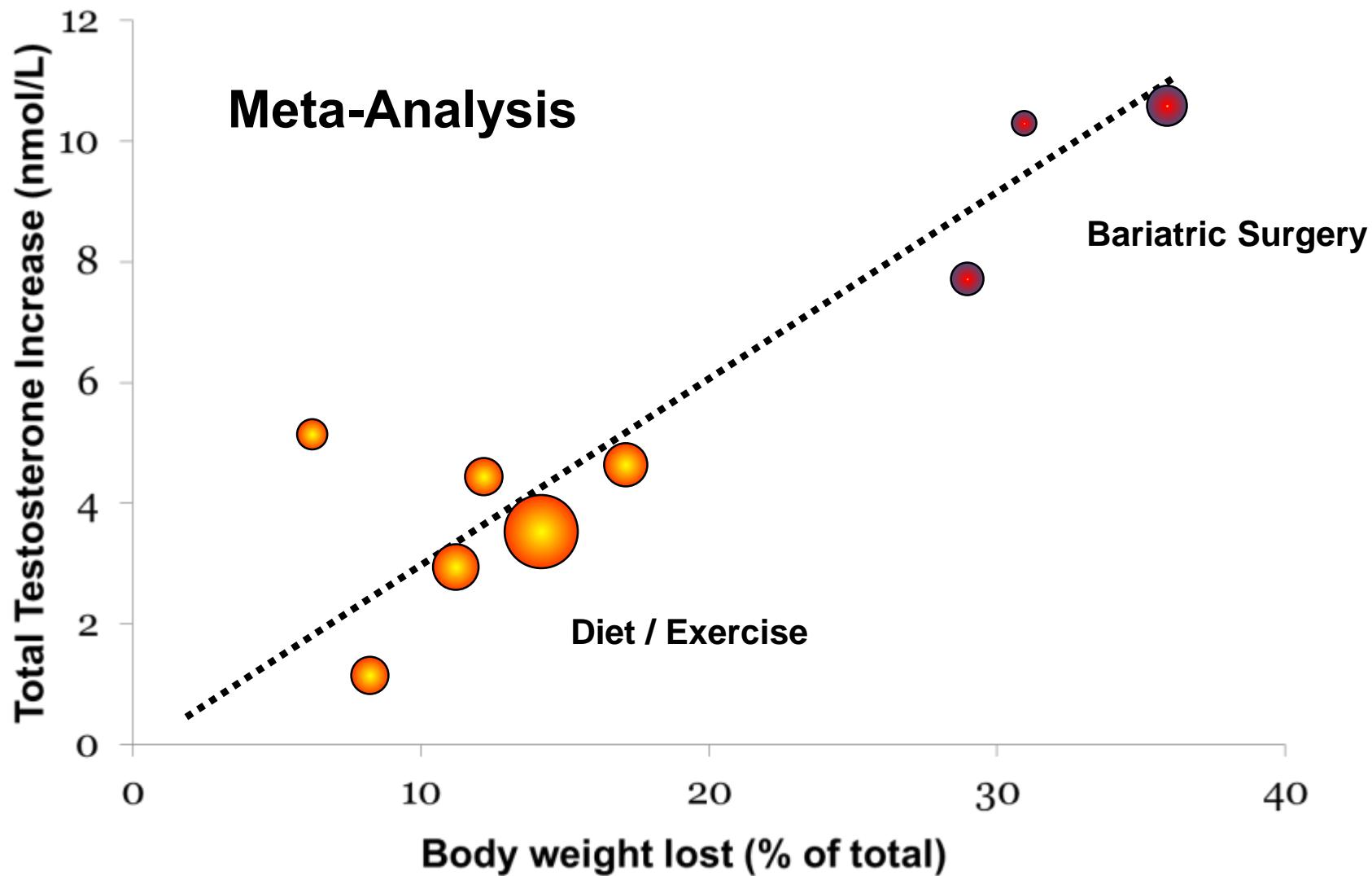


Zitzmann Nature Endo Rev 2009

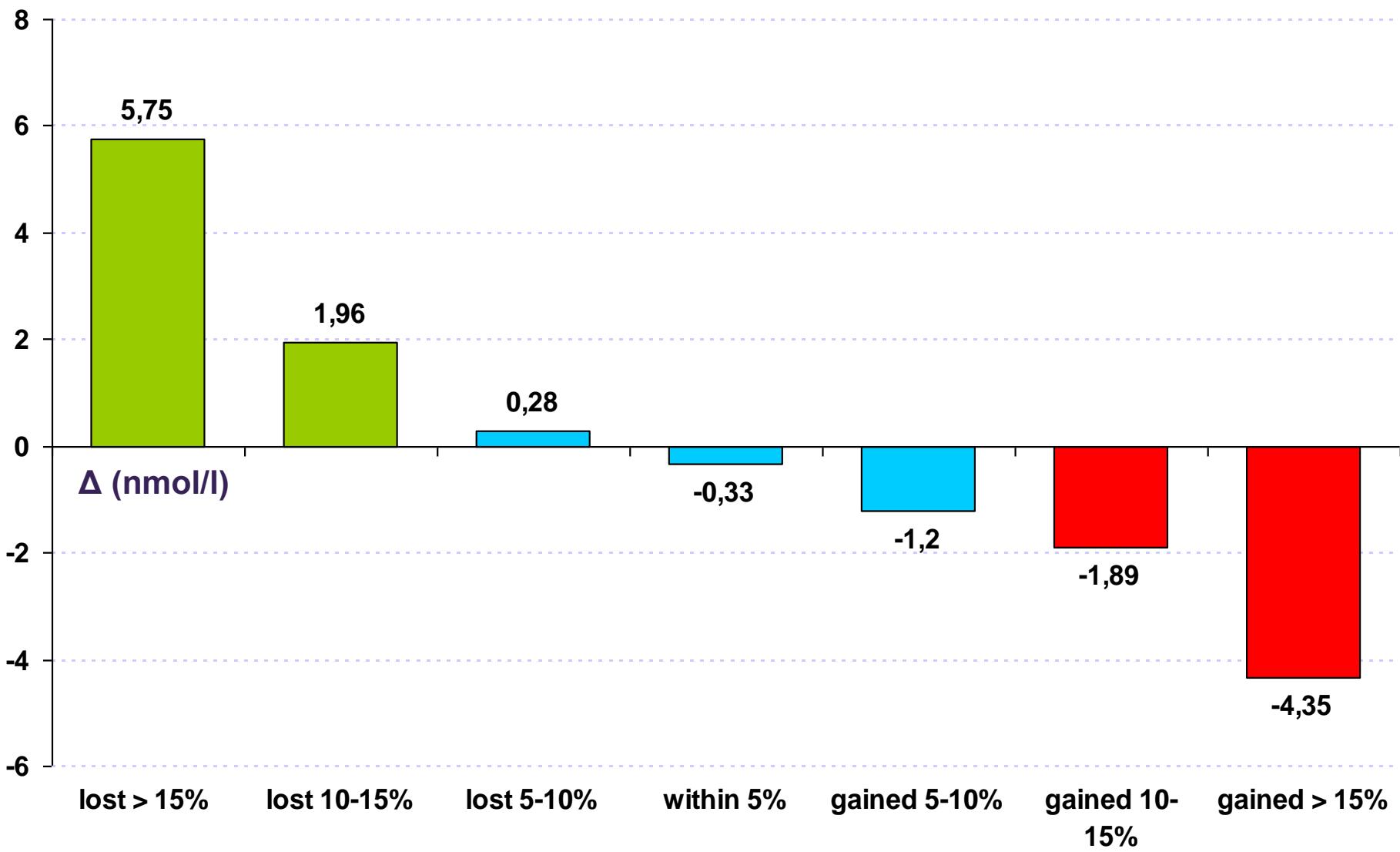




Effects of Weight Loss on Testosterone Levels



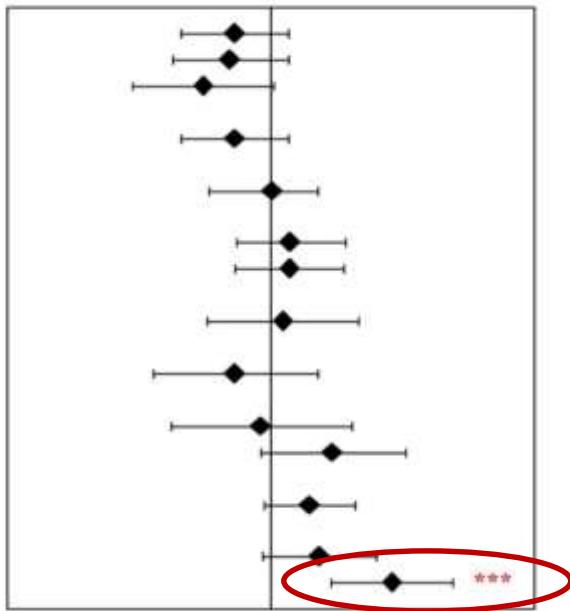
Changes Testosterone related to weight change – longitudinal results European Male Ageing Study (n=2395)



Camacho EM et al. Eur J Endocrinol 168: 445-455 (2013)

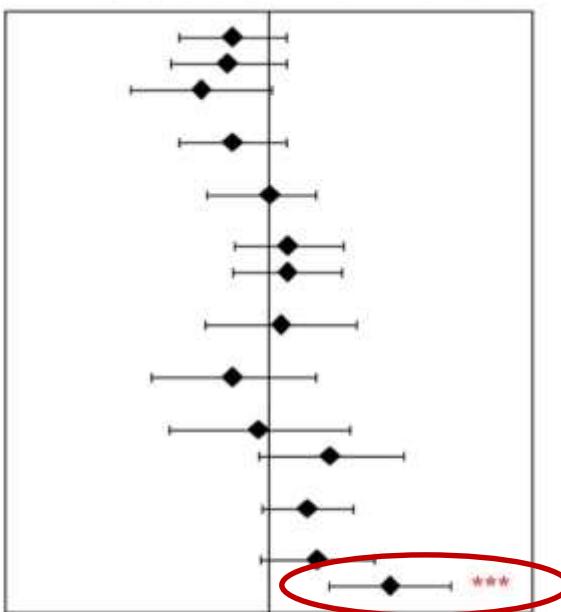
Predictors of incident sHG

A

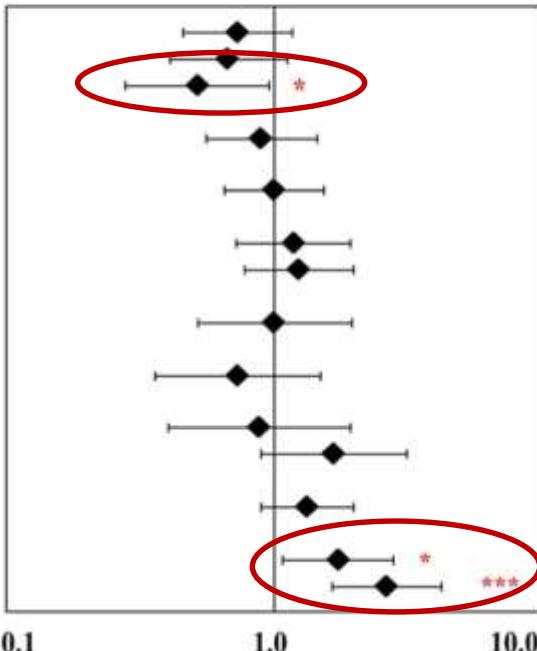


Predictors of incident sHG

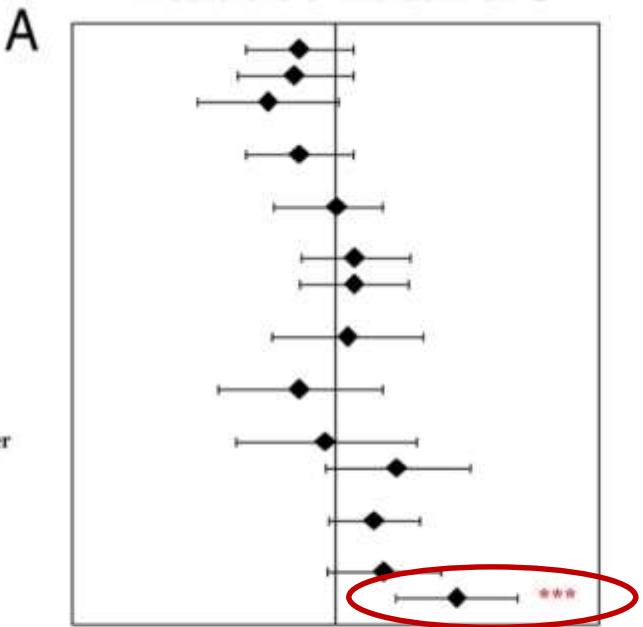
A



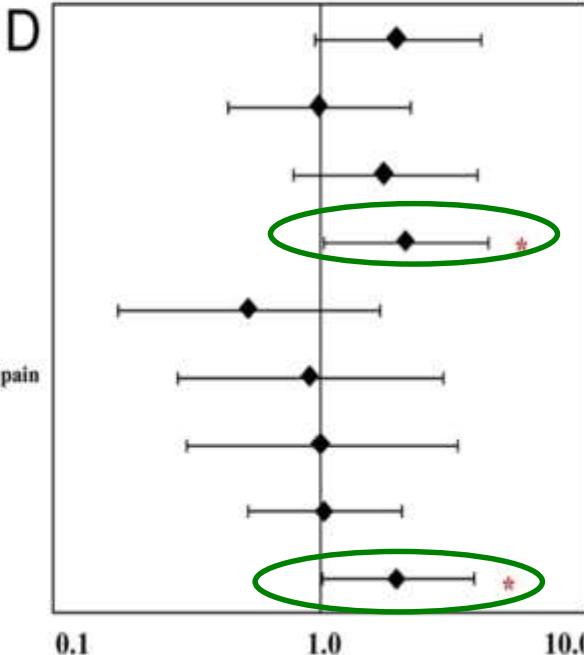
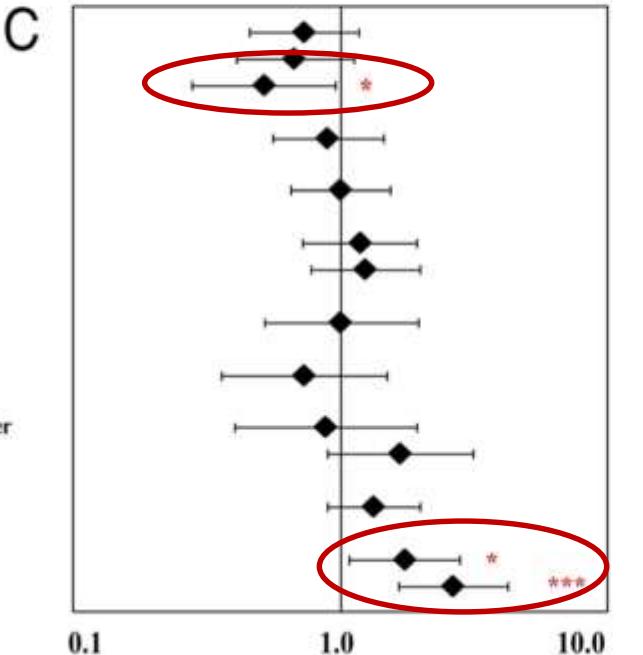
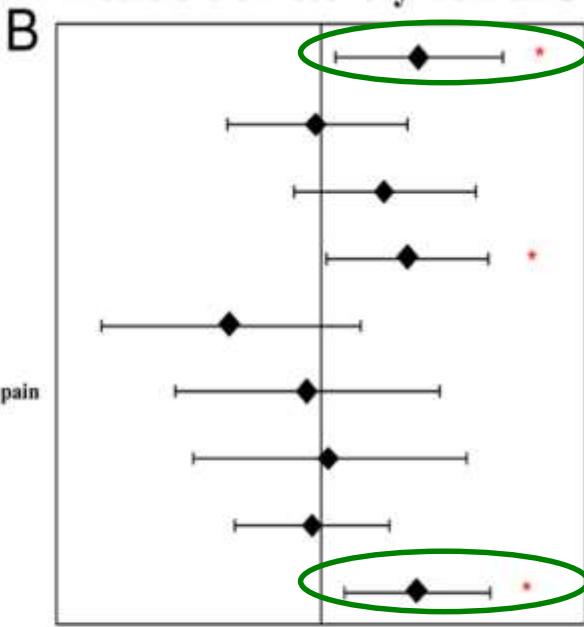
C



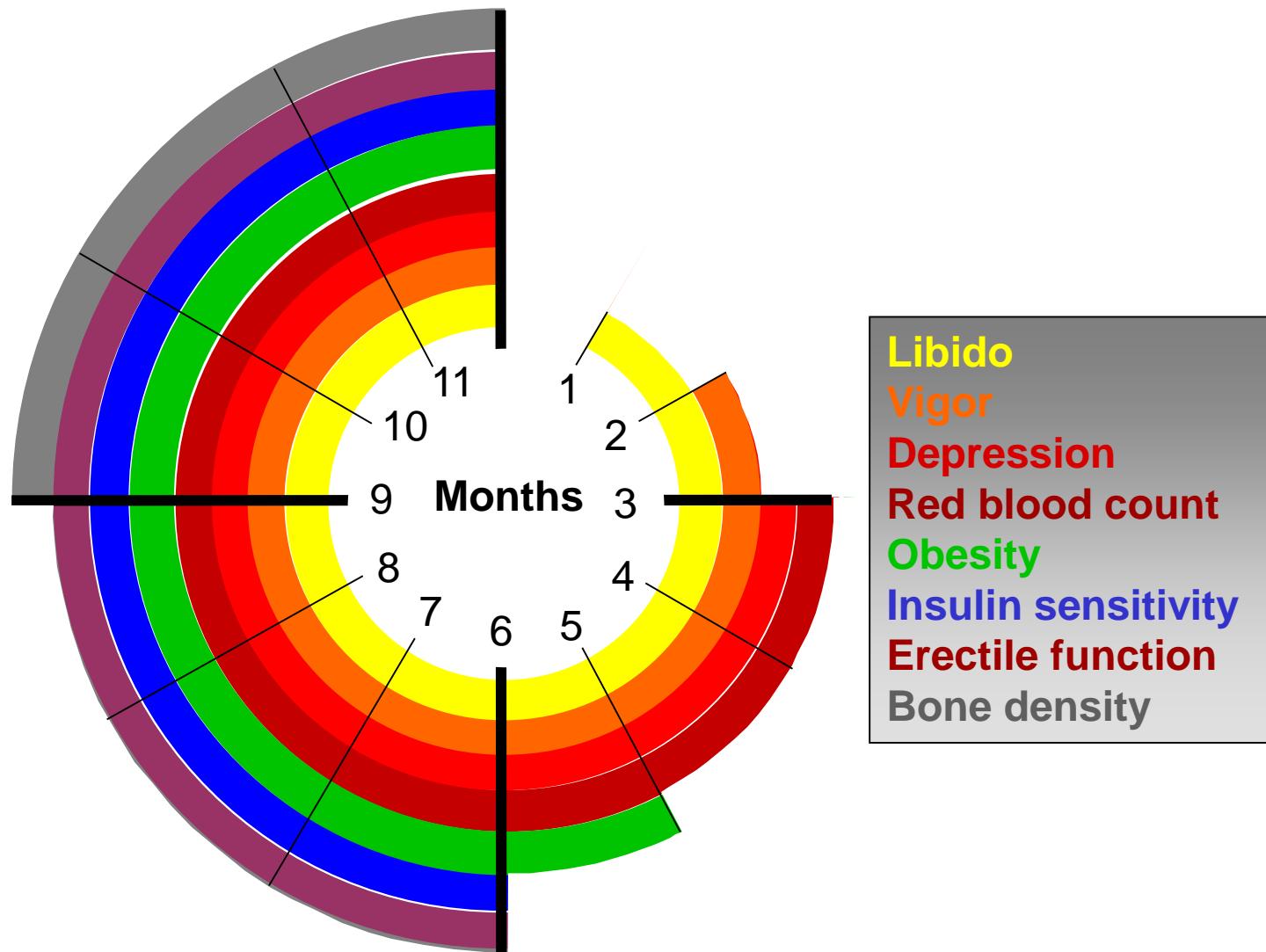
Predictors of incident sHG



Predictors of recovery from sHG



Time-dependent and symptom-specific onset of effects of testosterone substitution



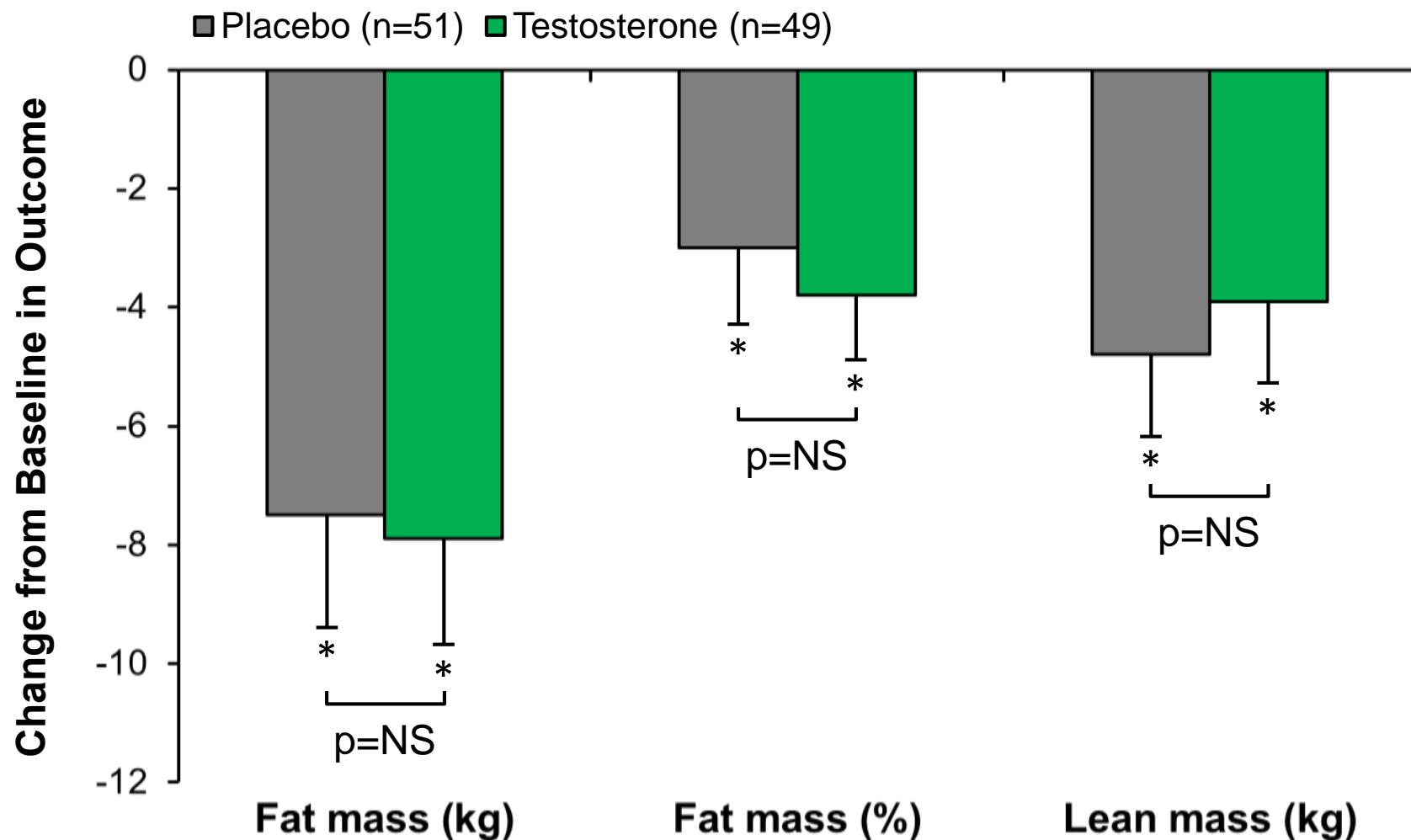
Saad, Zitzmann et al. EJE 2011

Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial

Fui MNT et al. BMC Med 14:153 (2016)

- **Design:** 56-week, randomised, double-blind, parallel, placebo-controlled study conducted at a tertiary referral centre
- **Subjects:** 100 obese adult men ($\text{BMI} \geq 30 \text{ kg/m}^2$) with a repeated total testosterone level $<12 \text{ nmol/L}$ and median age 53 years receiving 10 weeks of a VLED followed by 46 weeks of weight maintenance
- **Treatment:** randomisation to 56 weeks of 1000 mg intramuscular testosterone undecanoate ($n=49$) or matching placebo ($n=51$)
- **Key outcome measures (pre-specified):** differences in fat and lean mass by DXA scan, and visceral fat area by CT scan

Change from Baseline in Body Composition After **10 Weeks** of a VLED and Treatment with Intramuscular Testosterone Undecanoate or Placebo

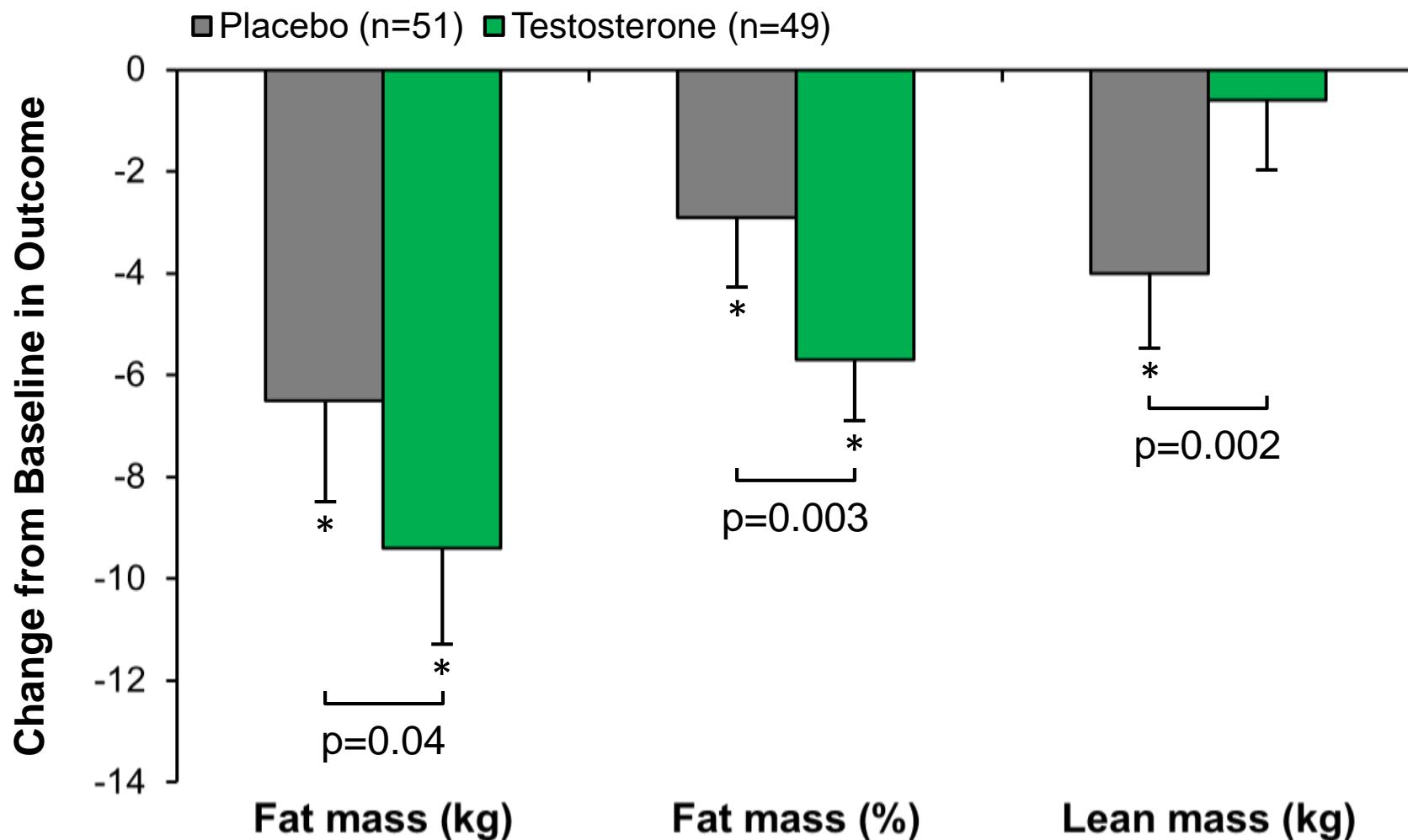


*p<0.05 versus baseline within group; data are mean + 95% confidence interval

NS, not significant; VLED, very low energy diet

Fui MNT et al. BMC Med 14(1):153 (2016)

Change from Baseline in Body Composition After **56 Weeks** of Treatment with Intramuscular Testosterone Undecanoate or Placebo

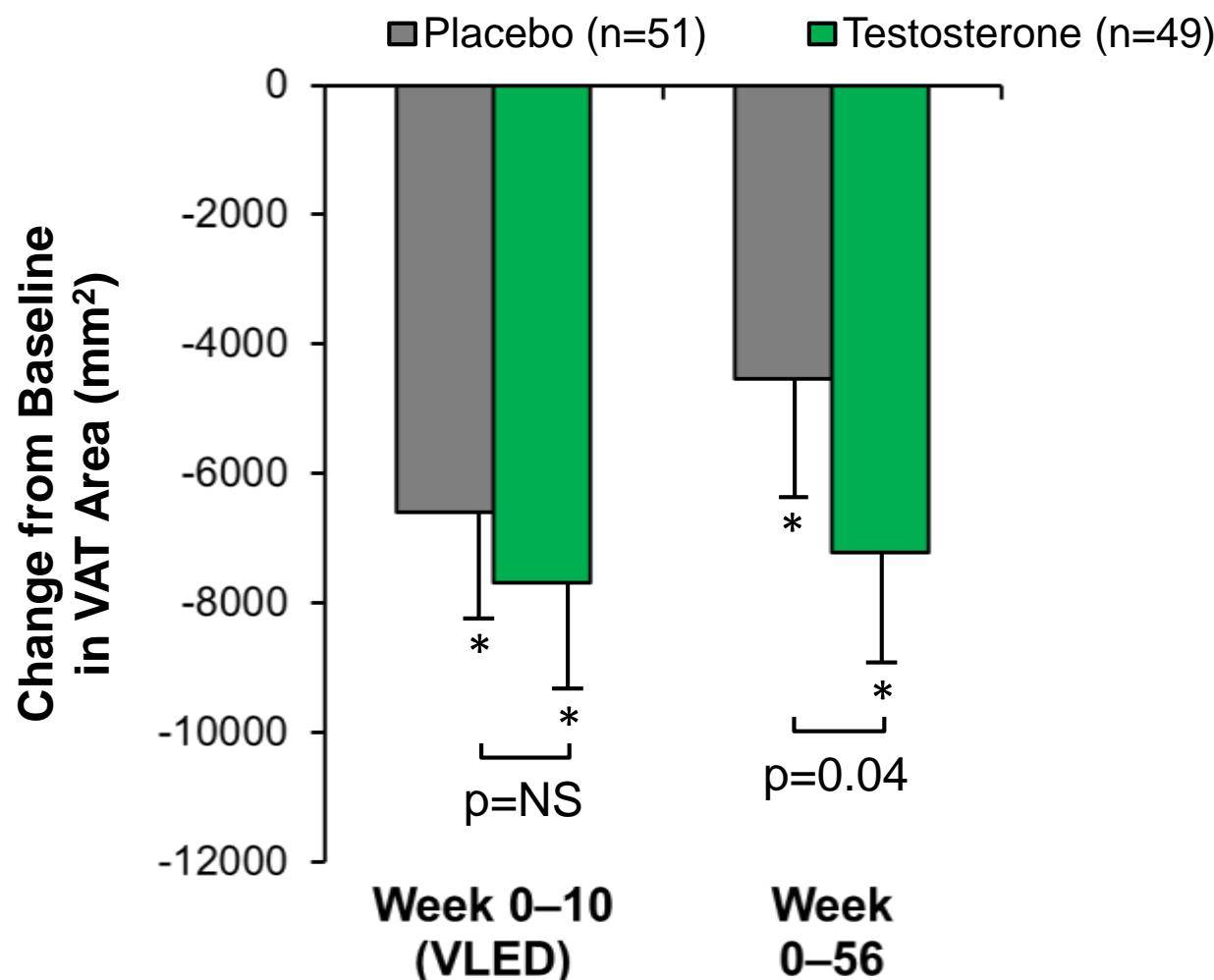


*p<0.05 versus baseline within group; data are mean + 95% confidence interval

NS, not significant

Fui MNT et al. BMC Med 14(1):153 (2016)

Change from Baseline in Body Composition After 10 and 56 Weeks of Treatment with Intramuscular Testosterone Undecanoate or Placebo

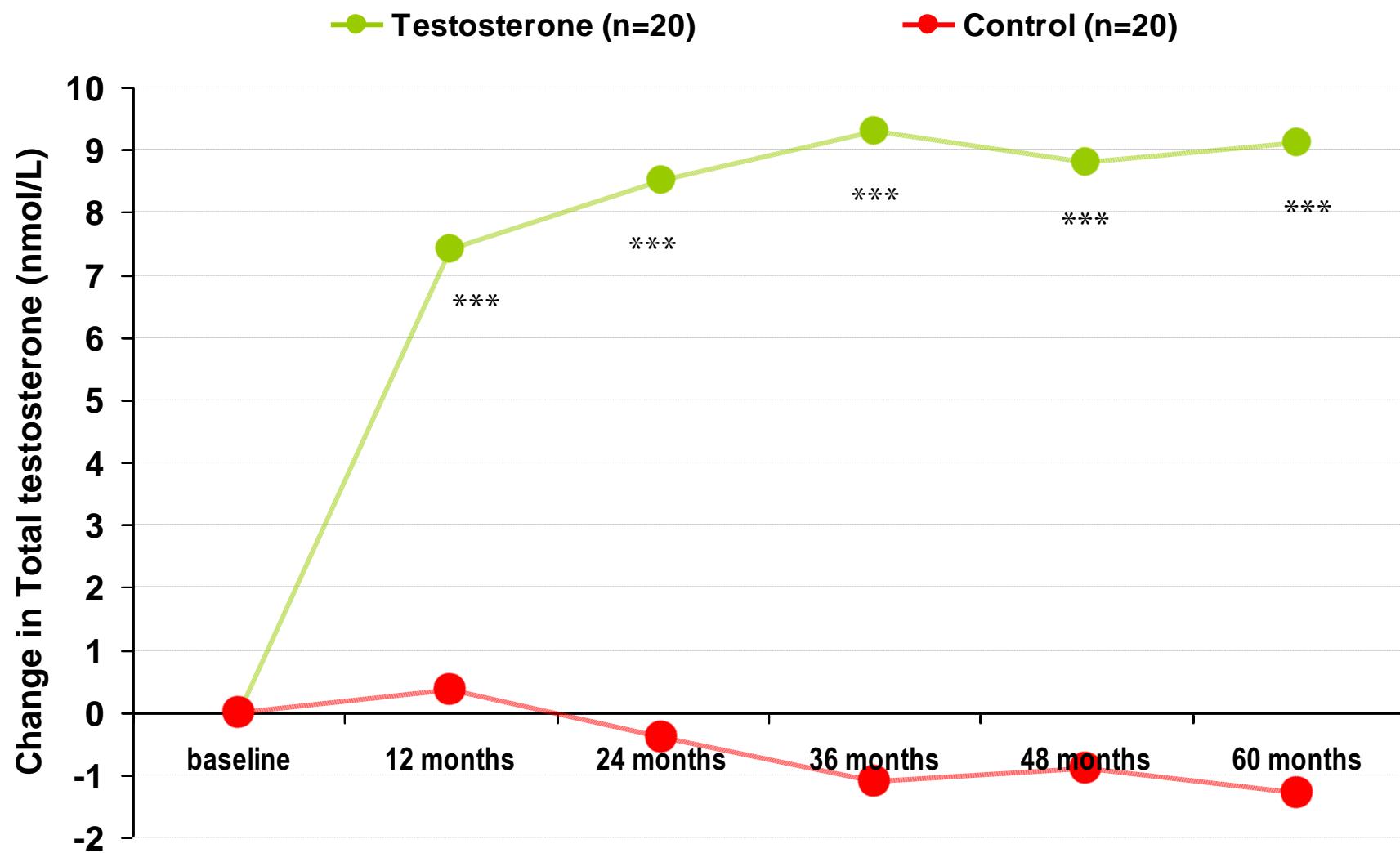


*p<0.05 versus baseline within group; data are mean + 95% confidence interval

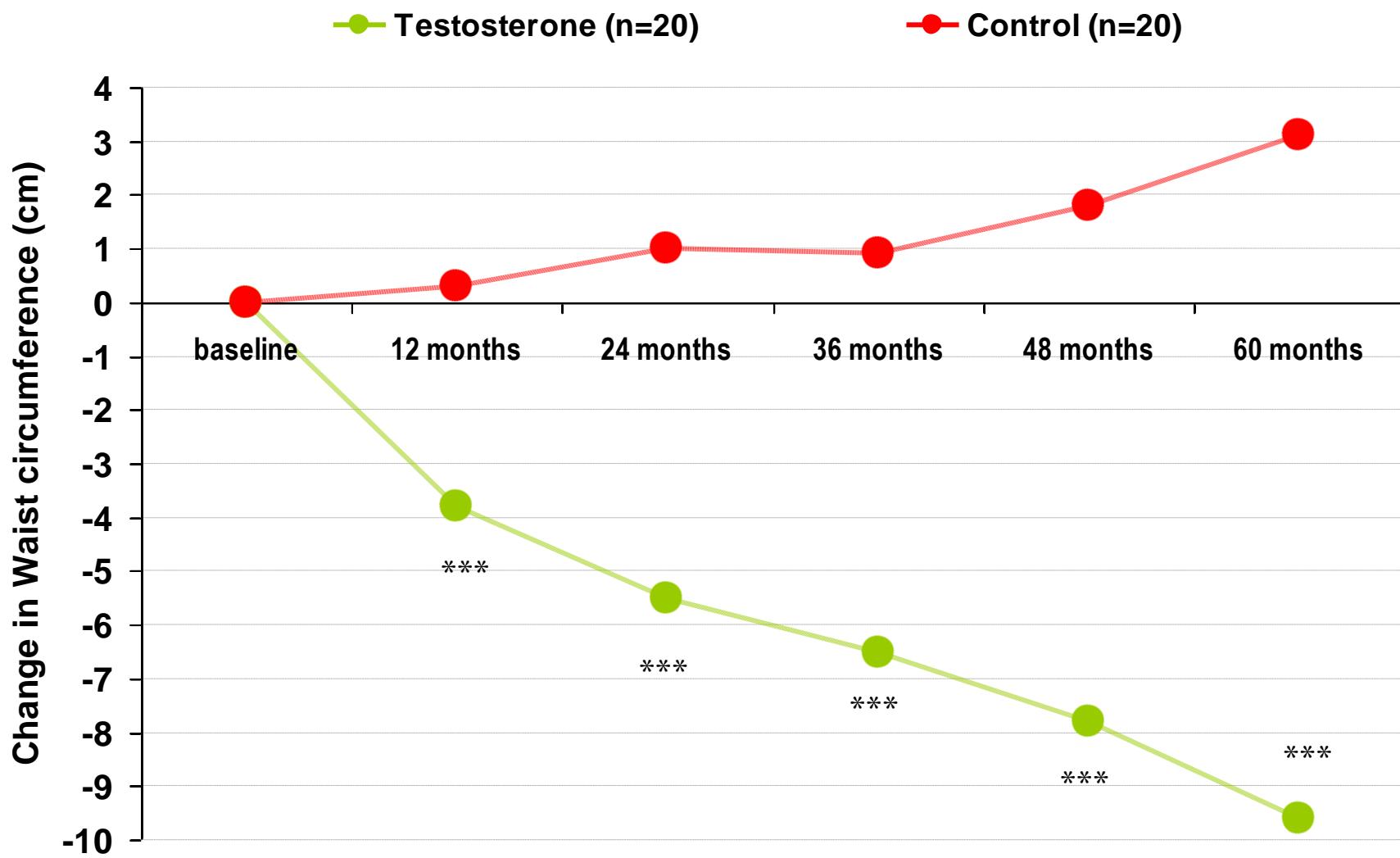
NS, not significant; VAT, visceral abdominal tissue; VLED, very low energy diet

Fui MNT et al. BMC Med 14(1):153 (2016)

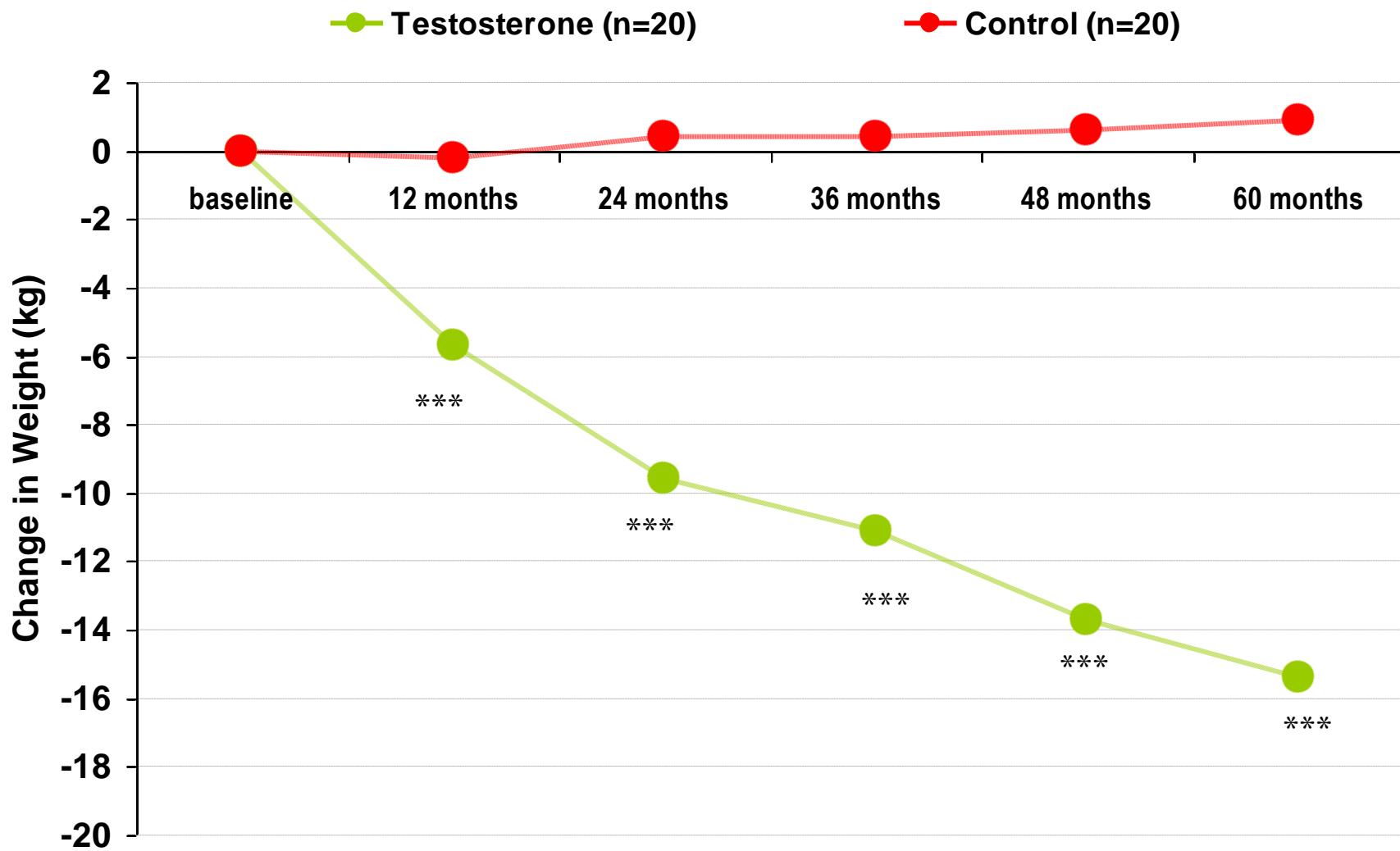
Effects of 5 years Treatment with Testosterone on Δ Total Testosterone (nmol/L) in 40 Hypogonadal Men ($T < 11$ nmol/L) with Metabolic Syndrome (IDF criteria)



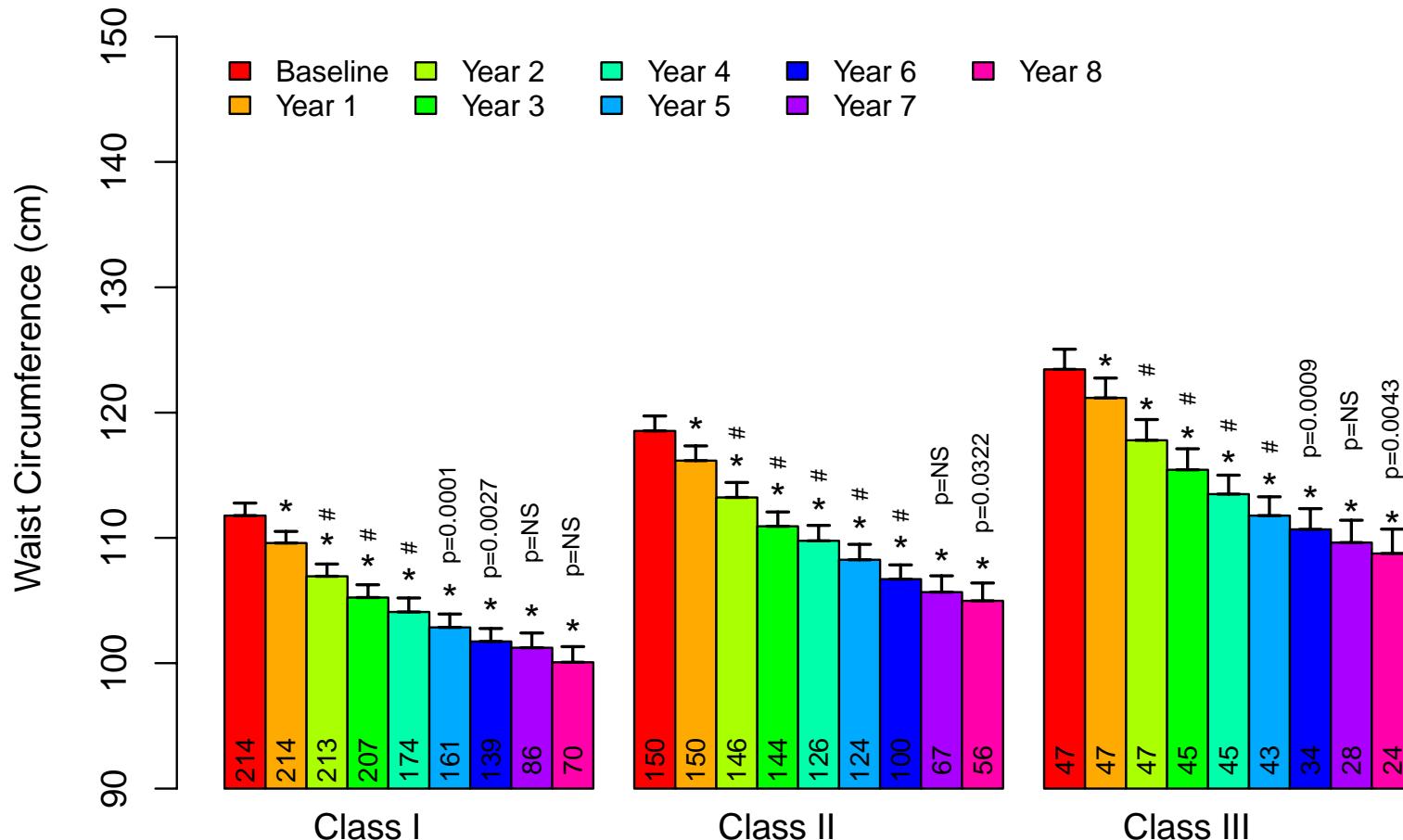
Effects of 5 years Treatment with Testosterone on Δ Waist Circumference (cm) in 40 Hypogonadal Men ($T<11$ nmol/L) with Metabolic Syndrome (IDF)



Effects of 5 years Treatment with Testosterone on Δ Body Weight (kg) in 40 Hypogonadal Men ($T<11$ nmol/L) with Metabolic Syndrome (IDF)

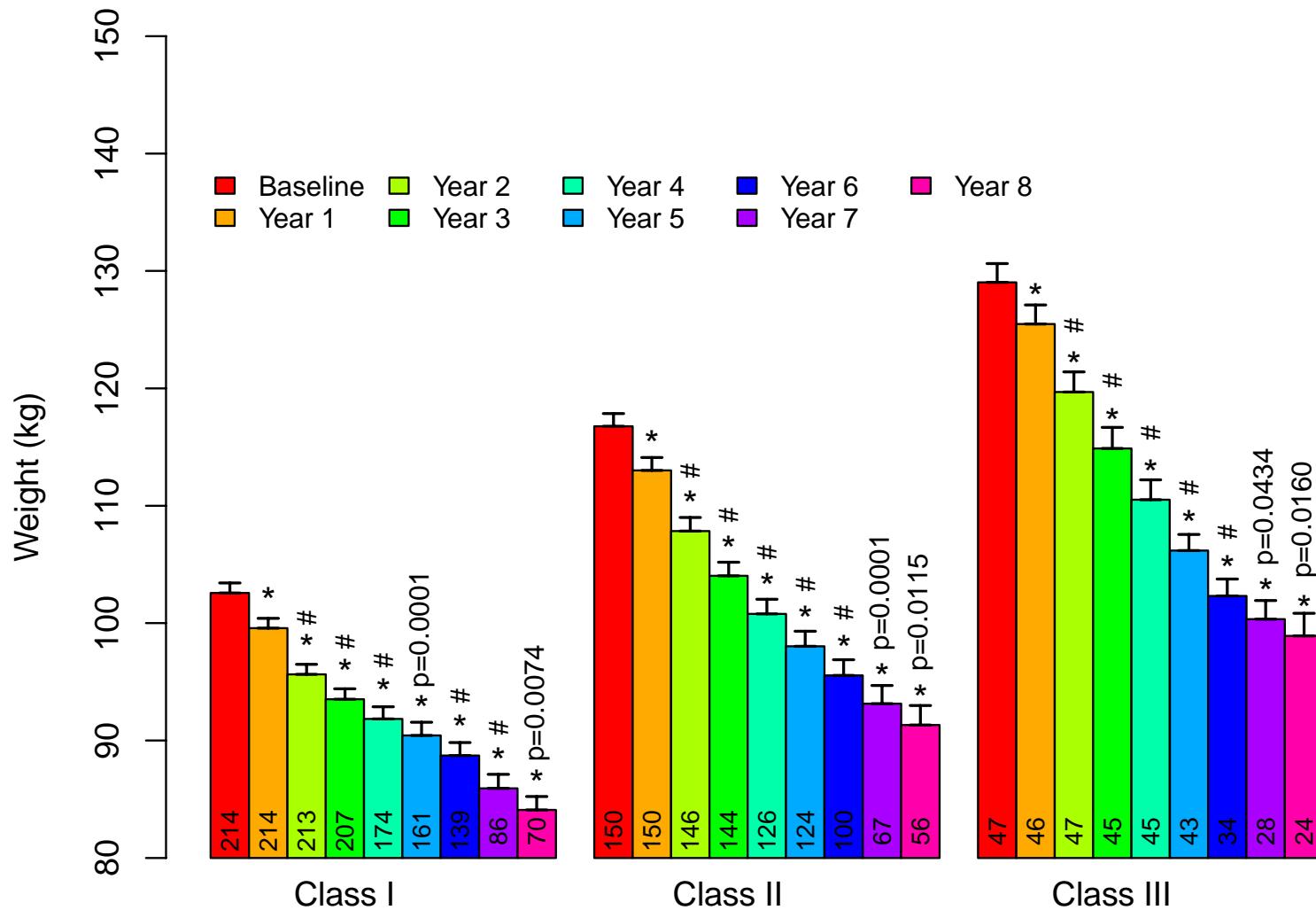


Reduction of Waist Circumference (mean \pm S.E.s) in 411 Hypogonadal Men in Obesity Classes I, II, and III Receiving Long-Term Testosterone Treatment



* p<0.0001 vs. baseline; # p<0.0001 vs. previous year; all other p values indicate comparison to previous yr.

Reduction of Body Weight (mean \pm S.E.s) in 411 Hypogonadal Men in Obesity Classes I, II, and III Receiving Long-Term Testosterone Treatment



* p<0.0001 vs. baseline; # p<0.0001 vs. previous year; all other p values indicate comparison to previous yr.

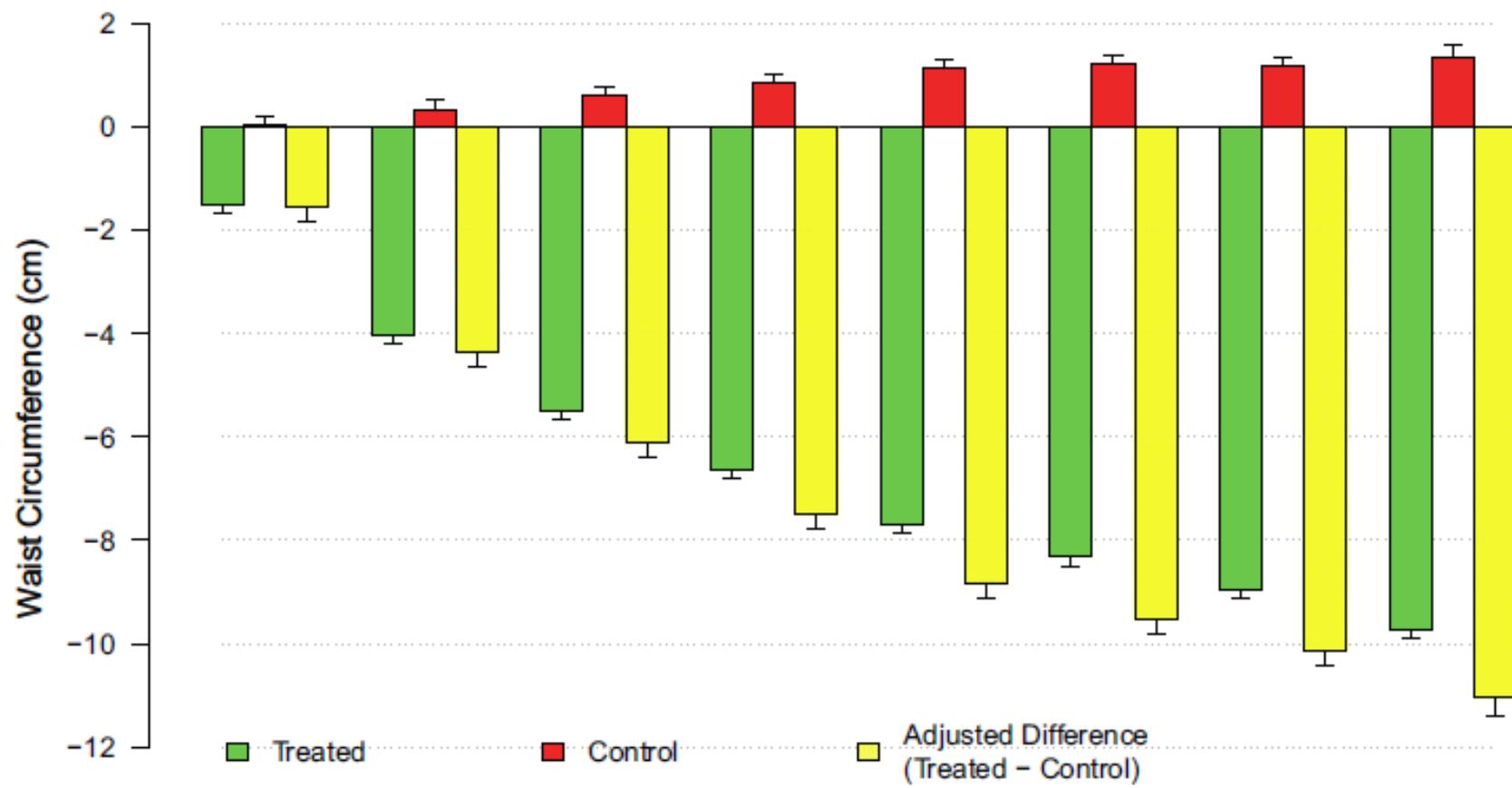
Long-Term Testosterone Therapy Improves Cardiometabolic Function and Reduces Risk of Cardiovascular Disease in Men with Hypogonadism: A Real-Life Observational Registry Study Setting Comparing Treated and Untreated (Control) Groups

Baseline Characteristics, Comorbidities and Concomitant Medication in Total and Propensity-Matched Groups

	Total Group Treated (n = 360)	Total Untreated Group (Control; n = 296)	P Value Between Groups
Mean age, years	57.4 (7.3)	64.8 (4.3)	<.0001
Mean follow-up, years	6.5 (2.4)	6.5 (1.2)	-
Median follow-up, years	7	7	
	Matched Group Treated (n = 82)	Matched Group Control (n = 82)	P Value Between Groups
	61.7 (5.1)	61.6 (2.9)	NS
	7.0 (2.6)	6.4 (1.3)	
	7	8	

Changes in Waist Circumference in Total Testosterone-Treated and Untreated Groups

Yellow bars show the estimated mean difference between groups, adjusted for baseline age, weight, waist circumference, fasting glucose, lipids, blood pressure, and quality of life (measured by AMS)



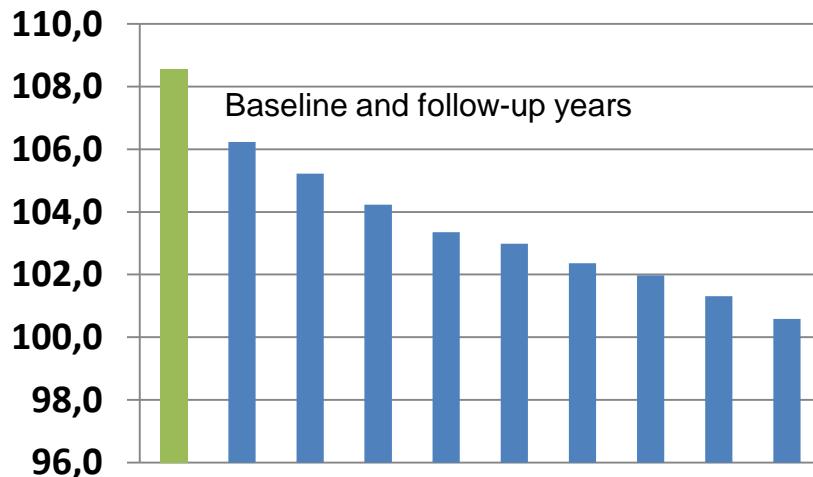
Longterm treatment of hypogonadal men: results from a 9-year-registry

Zitzmann et al AUA 2017

- 650 patients with hypogonadism
- 266 with primary forms (age 34 ± 12 y) including 149 Klinefelter patients
- 196 with secondary origin (age 32 ± 12 y)
- 188 with non-classical (“functional”) hypogonadism (age 42 ± 11 y)
- receiving intramuscular of T undecanoate (1000 mg) for max 9 y

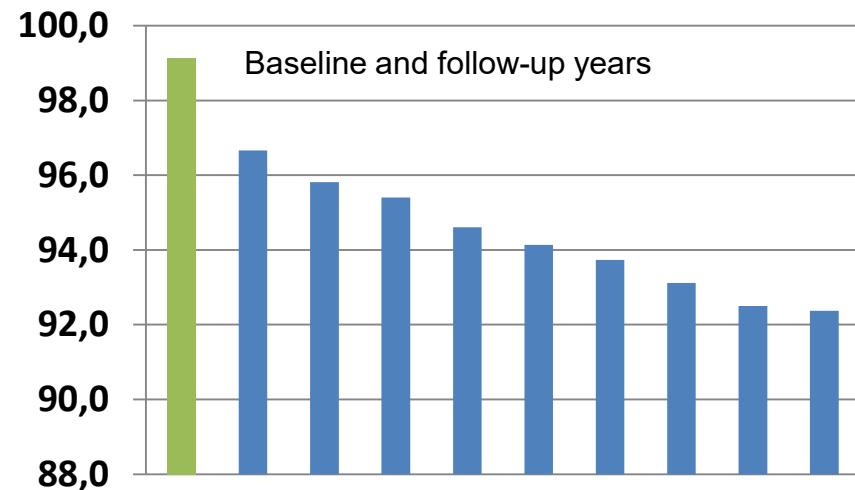
Waist Circumference (cm)

ANOVA p<0.0001



Body weight (kg)

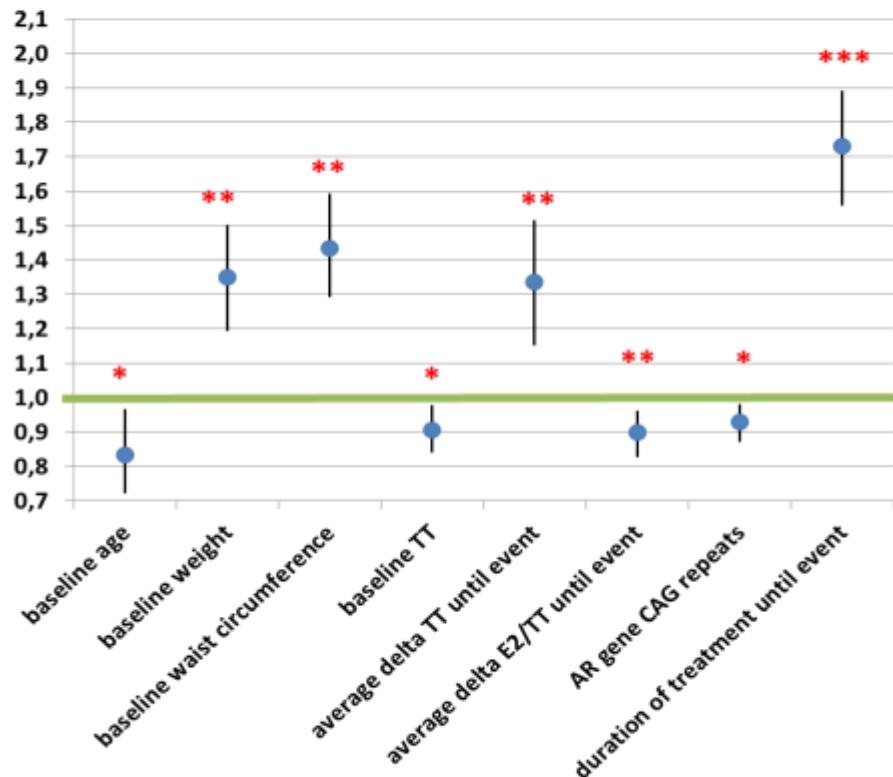
ANOVA p<0.0001



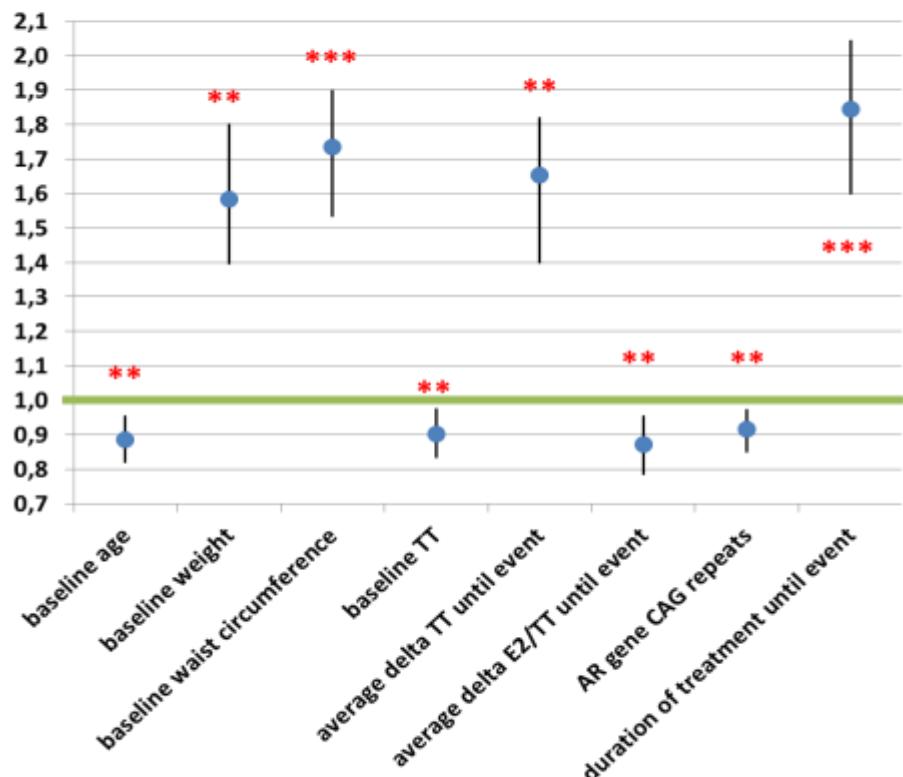
Longterm treatment of hypogonadal men: results from a 9-year-registry

Univariate analysis of continuous parameters (reaching a threshold, Cox regression)
Hazard ratios and 95 % Confidence Intervals

Loosing > 10 % of Body Weight



Loosing > 5 % of Waist Circumference



TT = Total Testosterone

E2 = Estradiol

*=p<0.05, **=p<0.01, ***=p<0.001

Zitzmann et al AUA 2017

Longterm treatment of hypogonadal men: results from a 9-year-registry

Univariate analysis of categorial parameters (reaching a threshold, Kaplan-Meier-Method)
Hazard ratios and 95 % Confidence Intervals

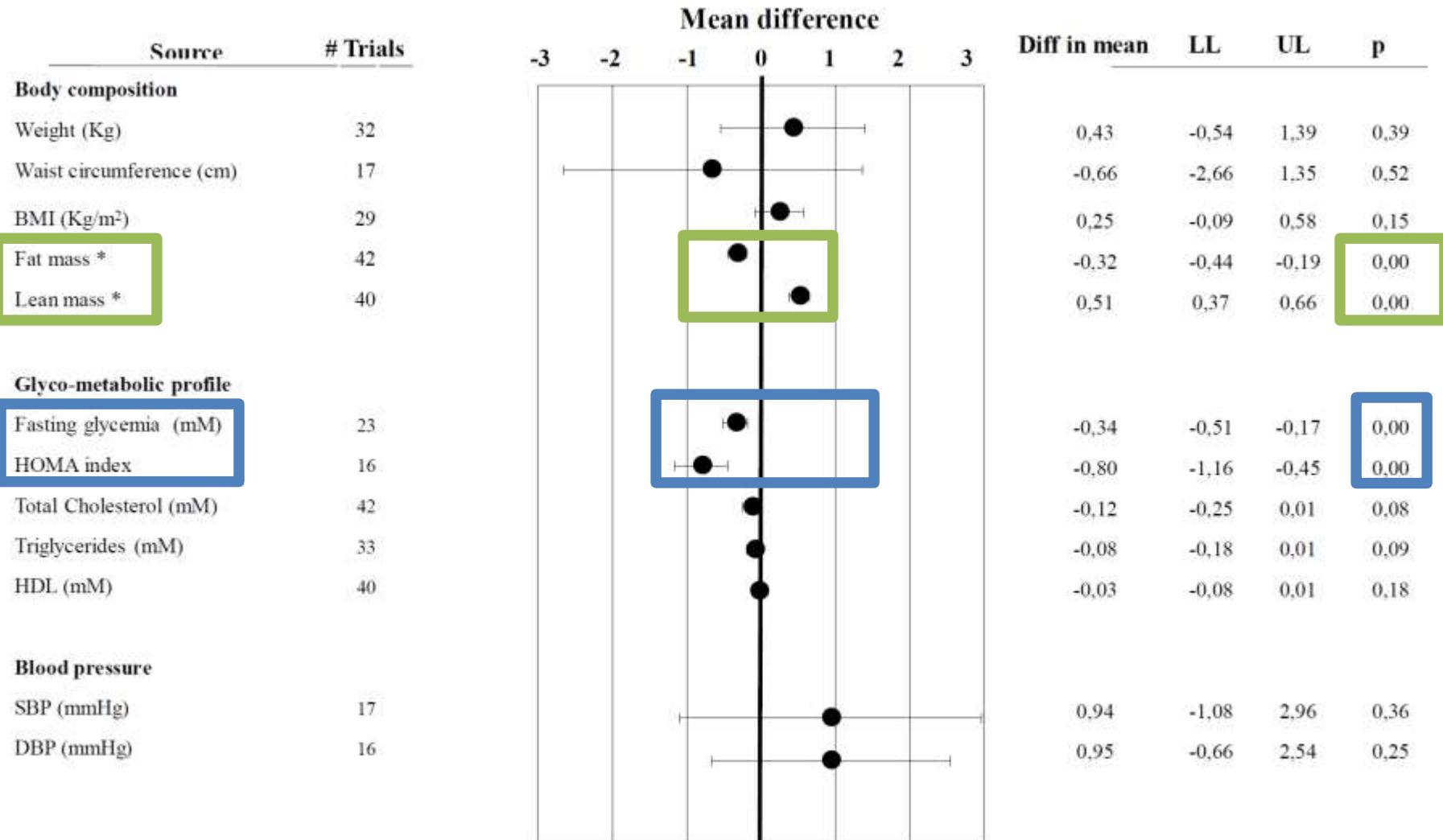
	hazard ratio	95% CI LL	95% CI UL	p
Classical hypogonadism (ref) vs functional hypogonadism				
Loosing > 10 % of Body Weight	1,266	1,117	1,445	0,008
Loosing > 5 % of Waist Circumference	1,384	1,259	1,497	0,001
Reaching Hematocrit > 50%	1,225	0,963	1,442	ns
Reaching PSA > 2 µg/L	1,338	1,102	1,596	0,003

Primary hypogonadism [non-Klinefelter] (ref) vs Klinefelter

Loosing > 10 % of Body Weight	0,904	0,831	0,983	0,012
Loosing > 5 % of Waist Circumference	0,892	0,826	0,967	0,003
Reaching Hematocrit > 50%	0,972	0,818	1,203	ns
Reaching PSA > 2 µg/L	0,864	0,776	0,965	0,008

Meta-Analysis of 59 randomized controlled trials of T substitution in hypogonadism

3029 men (treated) vs 2049 (controls)

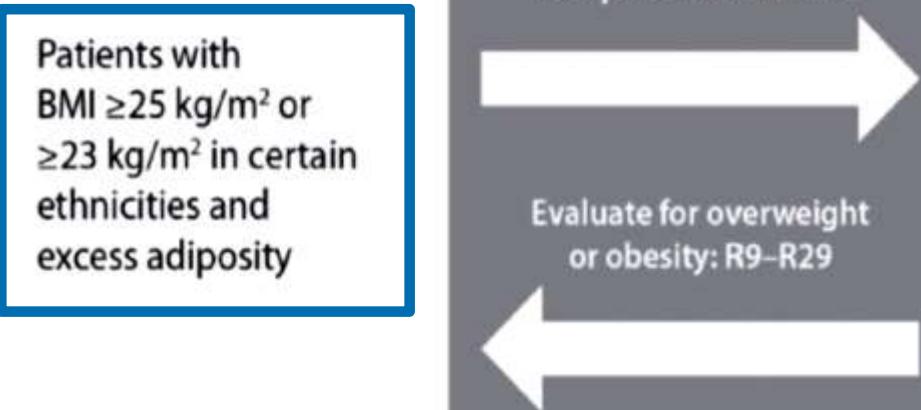


Corona, Maggi, Zitzmann et al
EJE 2016; 174(3):R99-R116

Testosterone vs. placebo

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN COLLEGE OF ENDOCRINOLOGY
COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR
MEDICAL CARE OF PATIENTS WITH OBESITY**

*W. Timothy Garvey, MD, FACE¹; Jeffrey I. Mechanick, MD, FACP, FACE, FACN, ECNU²;
Elise M. Brett, MD, FACE, CNSC, ECNU³; Alan J. Garber, MD, PhD, FACE⁴;
Daniel L. Hurley, MD, FACE⁵; Ania M. Jastreboff, MD, PhD⁶; Karl Nadolsky, DO⁷;
Rachel Pessah-Pollack, MD⁸; Raymond Plodkowski, MD⁹; and
Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines**

Patients Present With Overweight or Obesity	Candidates for Weight-Loss Therapy	Patients Present With Weight-Related Disease or Complications
<p>Patients with $\text{BMI} \geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ in certain ethnicities and excess adiposity</p> 	<p>Evaluate for weight-related complications: R9–R29</p> <p>Evaluate for overweight or obesity: R9–R29</p>	<p>R9, R10 Prediabetes</p> <p>R9, R10 Metabolic syndrome</p> <p>R11 Type 2 diabetes</p> <p>R12 Dyslipidemia</p> <p>R13 Hypertension</p> <p>R14, R15 Cardiovascular disease</p> <p>R16 Nonalcoholic fatty liver disease</p> <p>R17 Polycystic ovary syndrome</p> <p>R18 Female infertility</p> <p>R19, R20 Male hypogonadism</p> <p>R21 Obstructive sleep apnea</p> <p>R22 Asthma/reactive airway disease</p> <p>R23 Osteoarthritis</p> <p>R24 Urinary stress incontinence</p> <p>R25, R26 Gastroesophageal reflux disease</p> <p>R28 Depression</p>

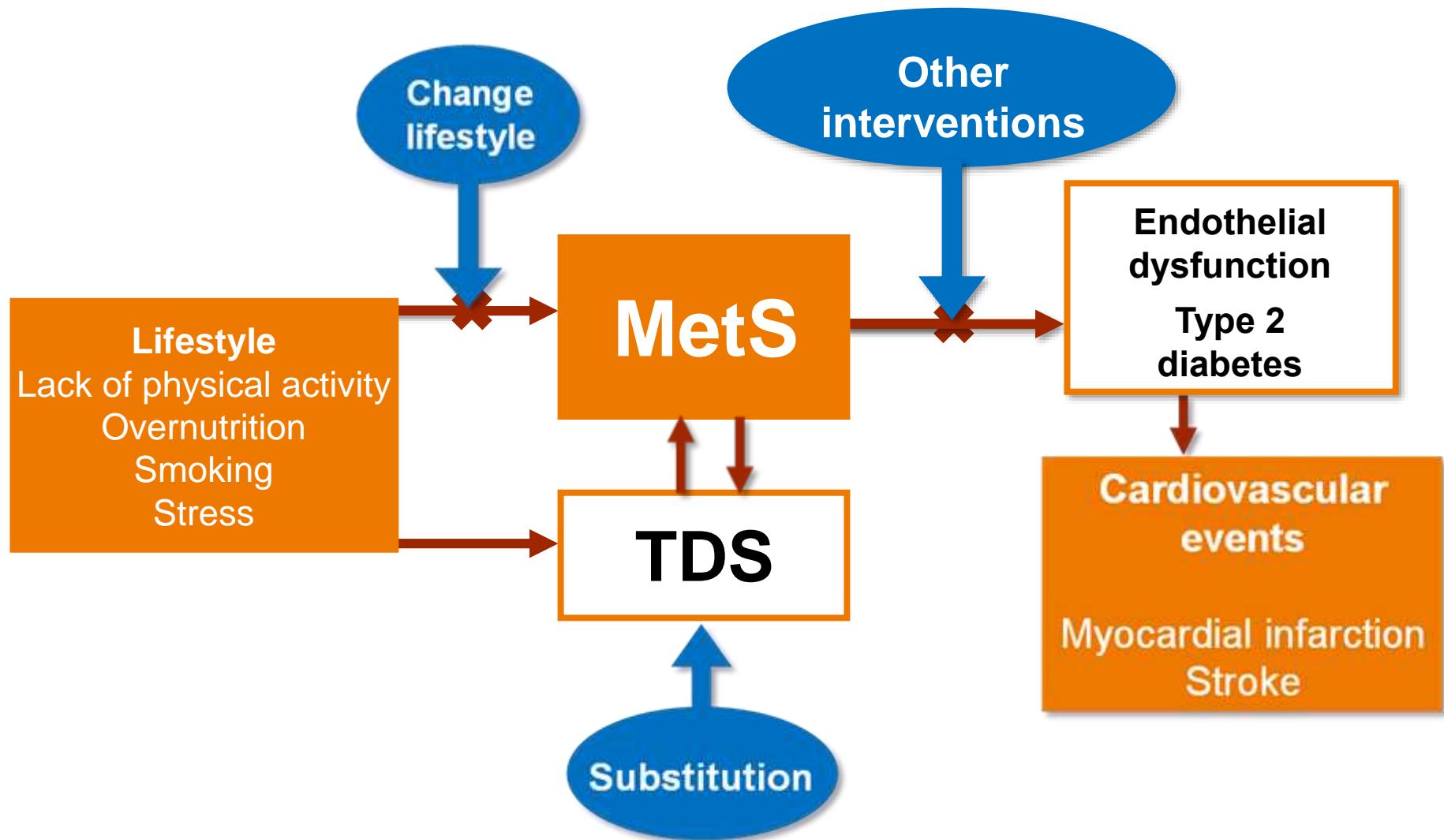
- *Q.3.9. Male hypogonadism*

- **R19.** All men who have an increased waist circumference or who have obesity should be assessed for hypogonadism by history and physical examination and be tested for testosterone deficiency if indicated; all male patients with hypogonadism should be evaluated for the presence of overweight or obesity (**Grade B; BEL 2**).

- **R20.** All male patients with T2DM should be evaluated to exclude testosterone deficiency (**Grade B; BEL 2**).

- **R54.** Men with true hypogonadism and obesity who are not seeking fertility should be considered for testosterone therapy in addition to lifestyle intervention because testosterone in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters (glucose, A1C, lipids, and blood pressure) (**Grade A; BEL 1**).

A pathway to endothelial dysfunction and vascular morbidity



Modified after Makhsida et al. J Urol 2005; 174: 827-834