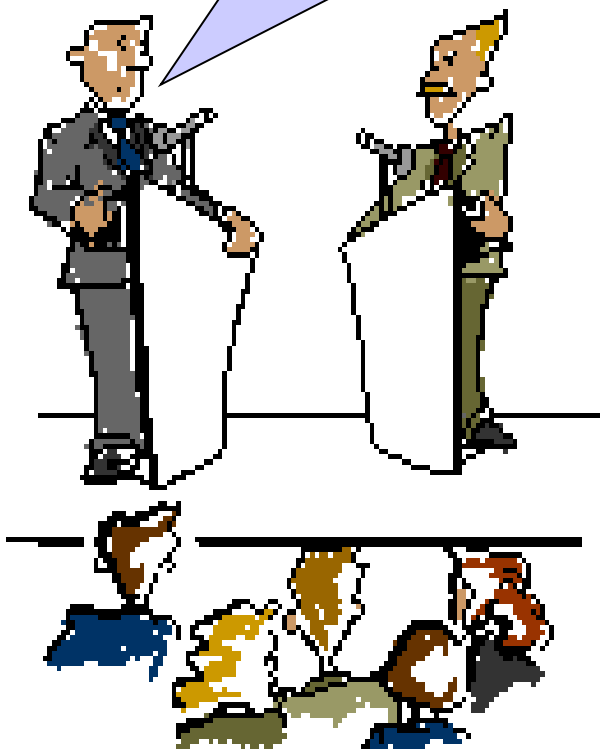
Caro Danilo…
Questa sessione mi sembra molto interessante…
Casi clinici particolari e messaggi pratici…




Mi ricordo Giovanni
che mi hai parlato di
un caso particolare
vuoi parlarcene…

CASO CLINICO

7 anni e 8 mesi, sesso maschile
Originario della Sicilia, vive a Forlì con i genitori
Sviluppo psicofisico iniziale nella norma, frequenta la seconda elementare va bene
1 sorella di 14 anni in abs
Familiarità per diabete tipo 1 (zio paterno)

Terapia in corso:
nessuna

Richiesta consulenza specialistica endocrinologica per ipostaturismo e rallentamento della velocità di crescita: porta in visione età ossea di 6 anni

Esame obiettivo

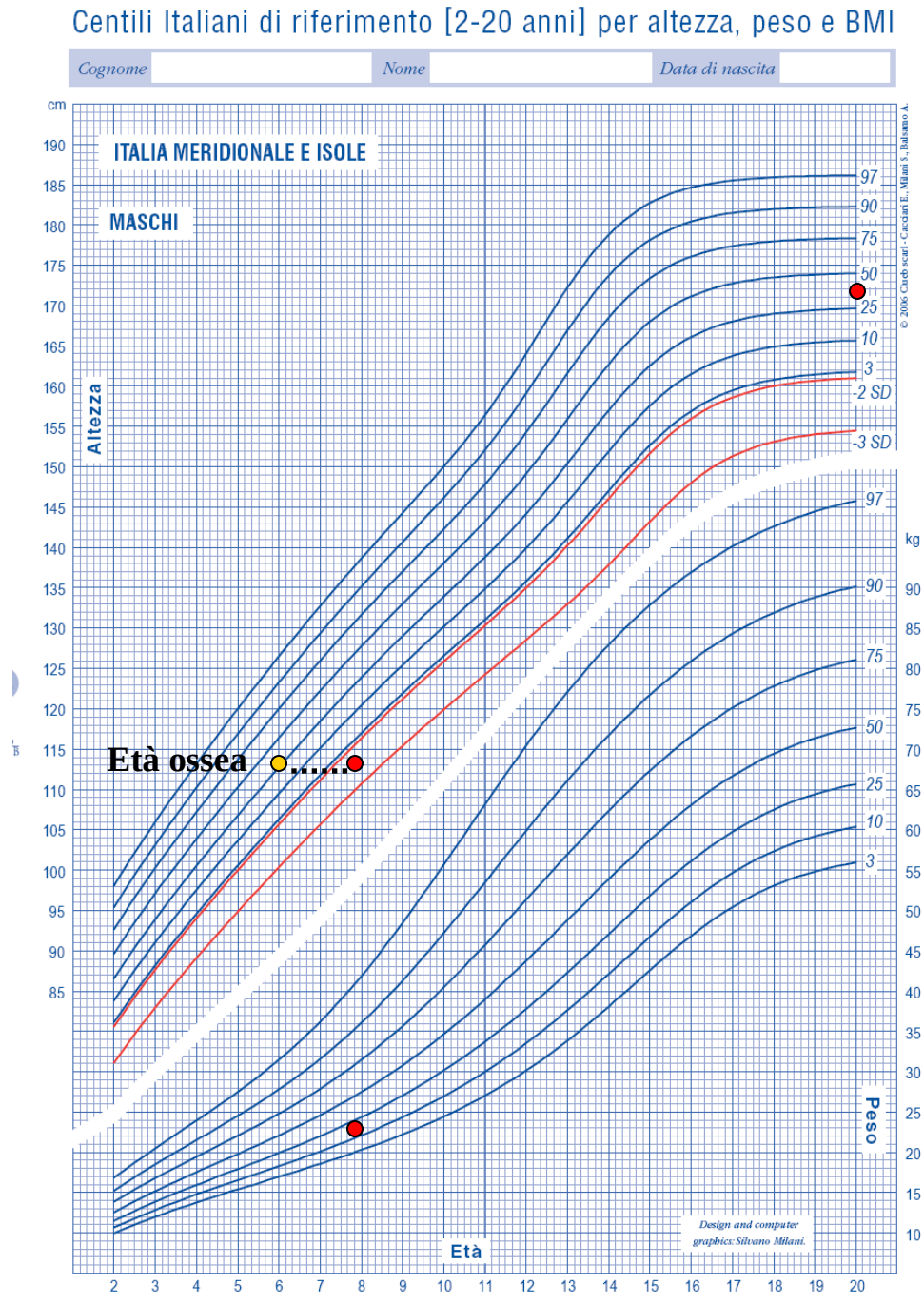
Paziente vigile, orientato
obiettività riferita negativa

Pa 100/65 mmHg; Fc 72 bpm R;

peso 24.3 Kg, altezza 113.4 cm,

Genitali esterni nella norma testicoli in sede 1 cc bilateralmente Tanner 1

7 anni e 8 mesi



Altezza bersaglio 173

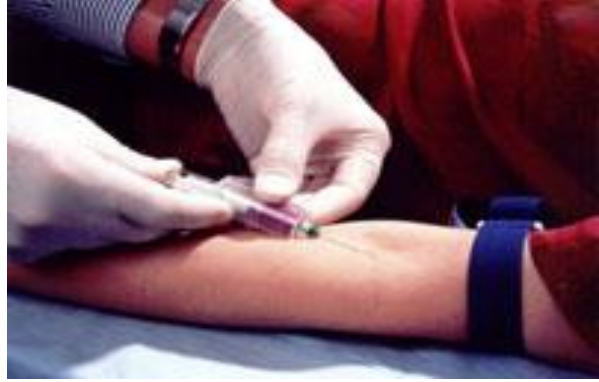
Quali accertamenti diagnostici consiglierereste?

1. **Nulla, rassicuriamo e lo rivalutiamo a 3 mesi**
2. **RMN ipofisi**
3. **Esami generali e ormonali basali±dinamici**
4. **RX sella turcica**
5. **Non saprei**

Dati bioumorali generali

Na^{+} mEq/L	137	(135-146)
Ca^{++} mEq/L	9.6	(8-11.5)
K^{+} mg/dl	3.8	(3.5-5.3)
Glicemia mg/dl	85	(60-110)
Creatinina mg/dl	0.53	(0.5-1.2)
Globuli bianchi	$6.55x10^{3}$	(4.2-9)
Globuli rossi	4.7^{6}	(4.2-5.5)
Piastrine	$288x10^{3}$	(130-400)
Emoglobina	13.2	(13-16.5)
VCM fL	85.6	(80-96)
MCH	40.2	(27-31)
Formula leucocitaria Neutrofili Linfociti Monociti **Eosinofili** Basofili	 40.0 37.0 7.1 **17.2** 0.7	 (40-74) (19-48) (3-9) **(0-6)** (0-1.5)
VES mm/h	11	<15
Sideremia mcg/dl	82	(50-165)
Screening celiachia	Neg	

Esami ormonali basali

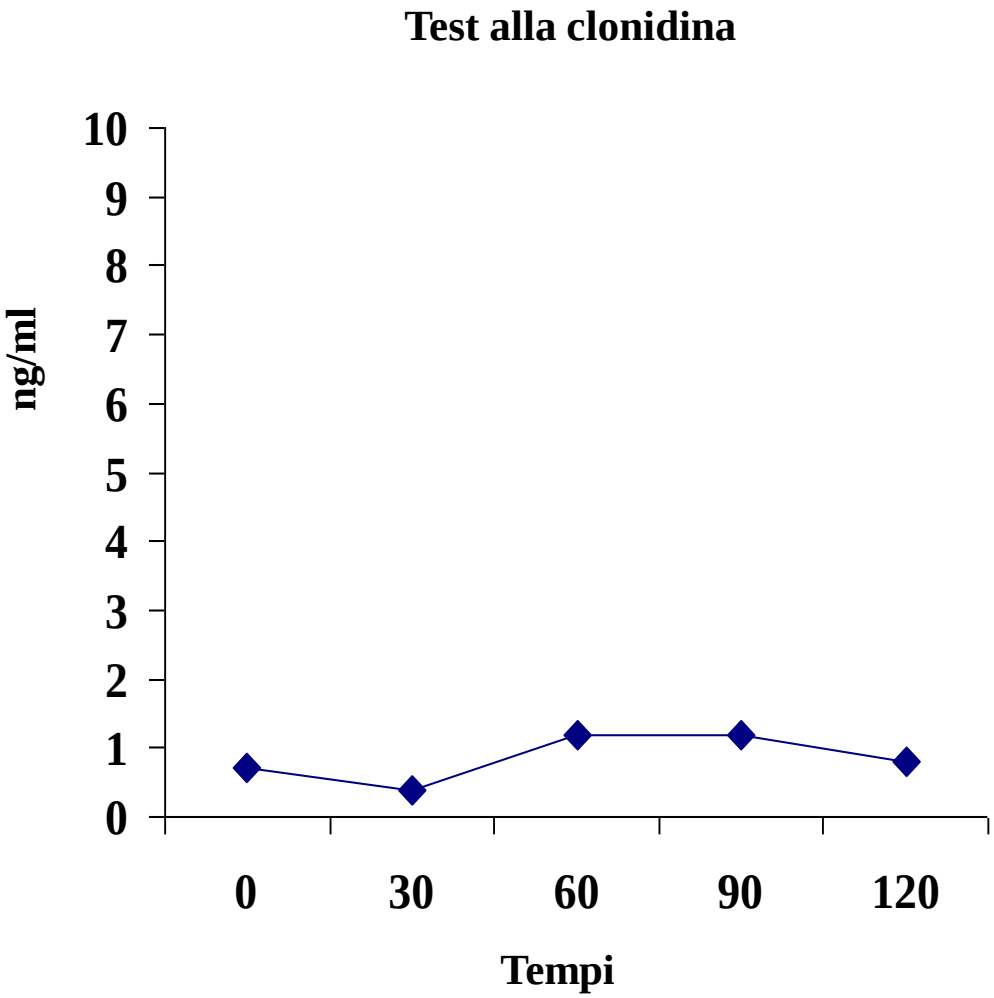


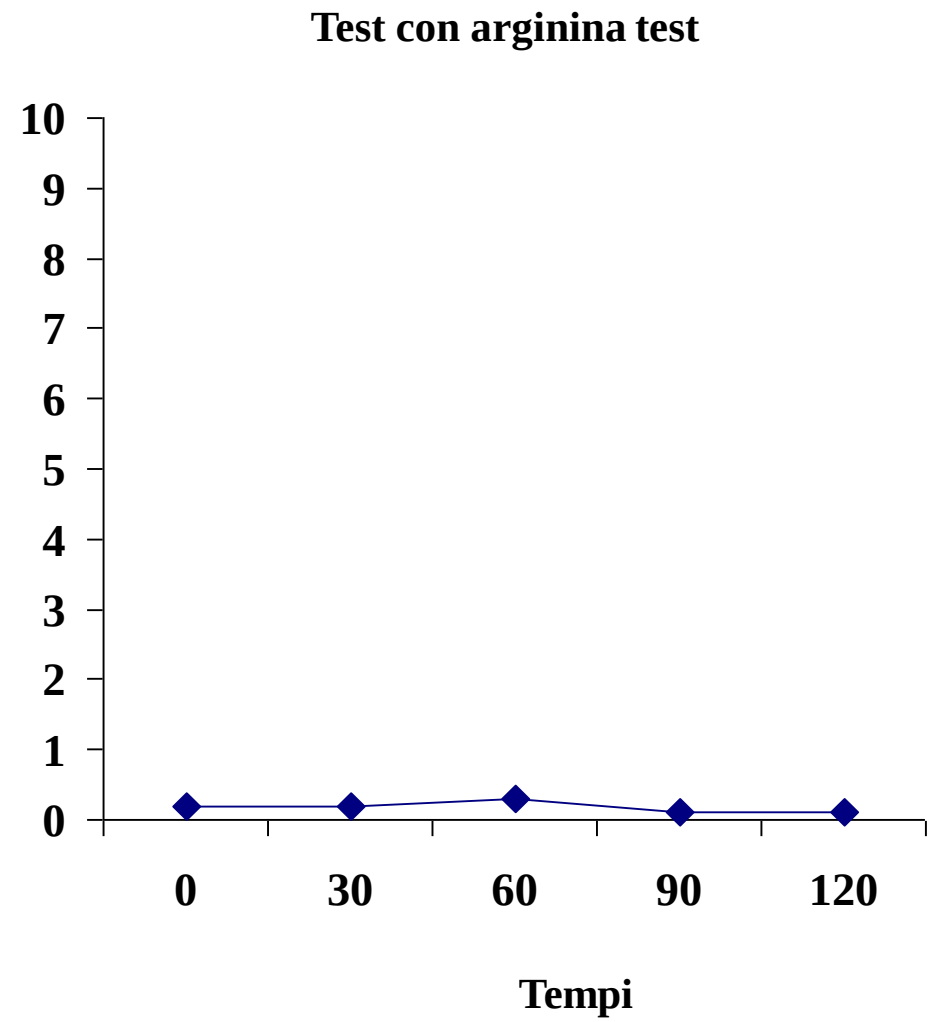
LH	0.4 U/L	(0.6-7)
FSH	0.1 U/L	(2-18)
Testosterone totale	1.02 nmol/L	(10-22)
ACTH	16.7 pg/ml	(<46)
Cortisolo	193 ng/ml	(70-210)
GH	<0.1 ng/ml	(<5)
IGF-1	53 ng/ml	(188-474)
TSH	0.39 U/L	(0.3-5)
FT4	9.0 pg/ml	(7-19)
PRL	15 ng/ml	(<15)

Quali esami diagnostici dinamici consiglierestе?

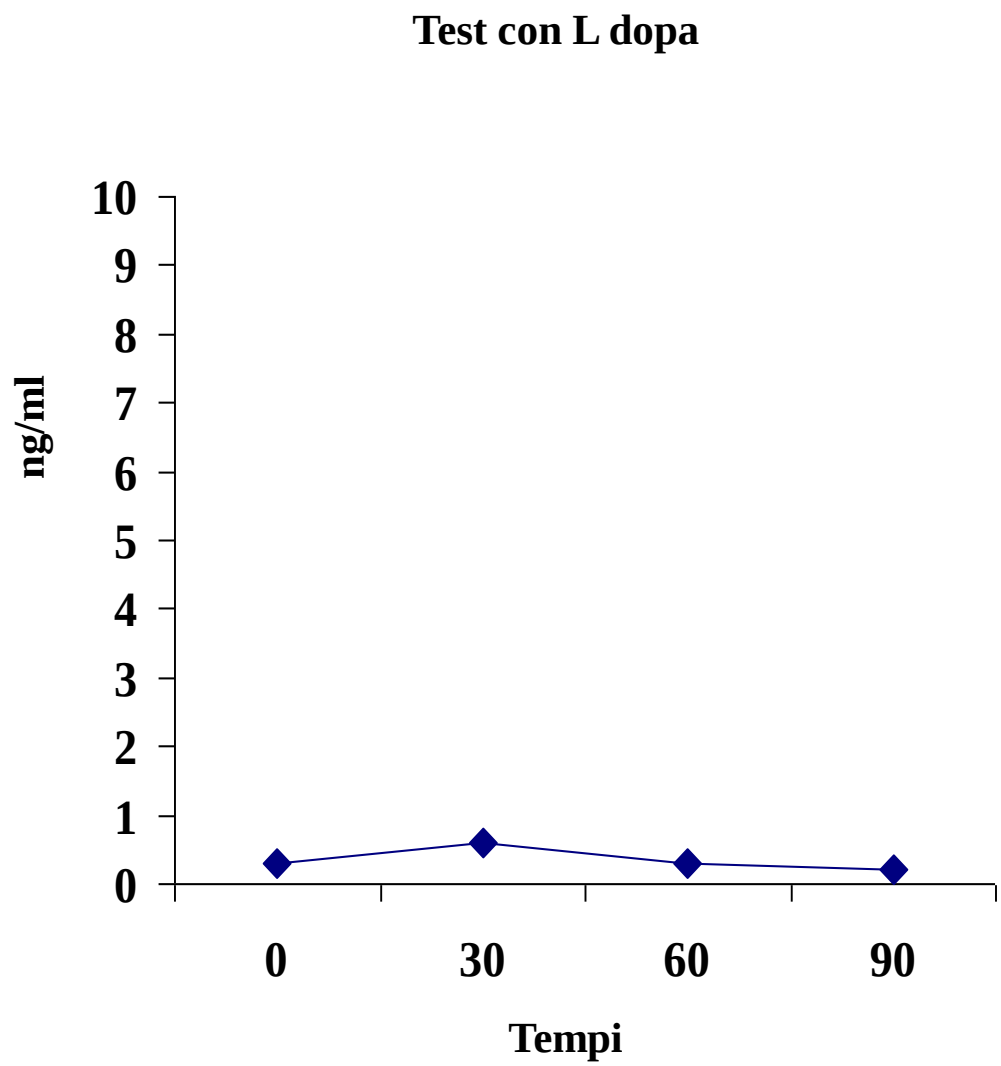
1. **Nulla, rassicuriamo e lo rivalutiamo a 3 mesi**
2. **Test clonidina**
3. **GH RH**
4. **GH-RH + arginina**
5. **L-dopa**

Test dinamici





Test dinamici



RMN encefalo

Presenza di processo occupante spazio ad estrinsecazione, prevalentemente soprasellare con calcificazioni intrasellari. La formazione occupa le cisterne soprasellari e si estende verso l'alto fino ad interessare il foramen bilateralmente.
Il terzo ventricolo è compresso e male apprezzabile.
L'iniezione endovenosa con mdc paramagnetico provoca uno sfumato enhancemen della periferia della lesione.
I ventricoli laterali sono modicamente dilatati

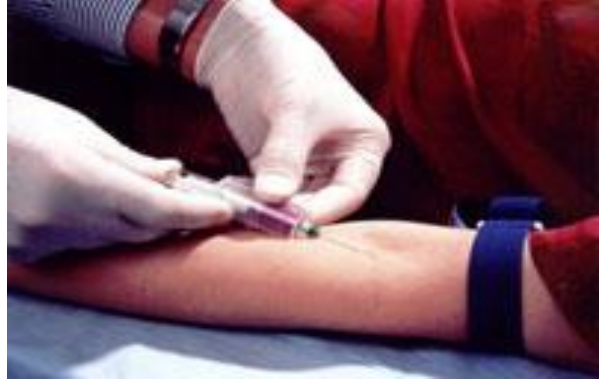
Asportazione completa del craniofaringioma

Panipopituitarismo e diabete insipido secondari

Terapia alla dimissione:

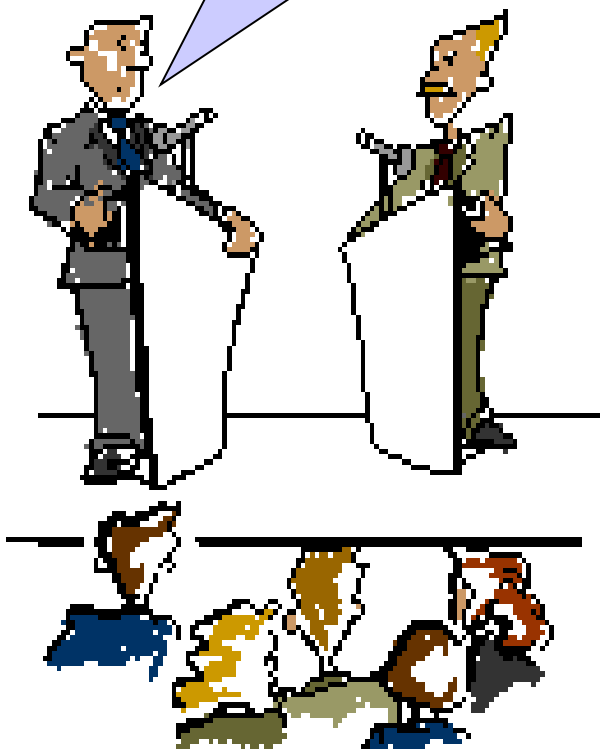
- **Cortone acetato ¼ x 2**
- **Minirin cp 0.2 mg + 0,15 mg+ 0,2 mg**
- **Eutirox 50 mcg/die**
- **Humatrope 6 mcg/die**

Esami ormonali basali



LH	<0.1 U/L	(0.6-7)
FSH	<0.3 U/L	(2-18)
Testosterone totale	<0.3 nmol/L	(10-22)
ACTH	<5 pg/ml	(<46)
Cortisolo	60 ng/ml	(70-210)
GH	<0.1 ng/ml	(<5)
IGF-1	48 ng/ml	(188-474)
TSH	0.05 U/L	(0.3-5)
FT4	6.9 pg/ml	(7-19)
PRL	<3 ng/ml	(<15)

Caro Danilo quali sono le attuali linee guida sulla diagnosi e terapia del deficit di GH in età pediatrica?



Diagnosi deficit di GH in età pediatrica

Test	Dose	Timing peak of GH
Arginine	0.5 g/kg I.V., over 30 min, maximum of 40 g	30–60 min
L-Dopa	125 mg if weight <13.5 kg	30–120 min
	250 mg if weight 13.5–31.5 kg	
	500 mg if weight >31.5 kg	
GHRH	1 or 2 mg/kg I.V. infusion over 1 min	15–30 min
Glucagon	0.03 mg/kg, maximum of 1 mg IM/SC	2–3 h
ITT	0.05–0.1 IU/kg I.V. bolus	30–60 min
Clonidine	5 mcg/kg, maximum of 250 mcg	60 min

Abbreviation: ITT, insulin tolerance test; GHRH, growth hormone releasing hormone

Richmond et al., Pituitary. 2008;11:115

In a child with clinical criteria for GHD, a peak GH concentration below 10 μg/L has traditionally been used to support the diagnosis. This value needs to be revised when using newer monoclonal-based assays and recombinant hGH reference preparations.

Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and aolescence: Summary Statment of the GH Reseach Society. JCEM 2000

Pituitary (2012) 15:301–310
DOI 10.1007/s11102-011-0372-6

A review of guidelines for use of growth hormone in pediatric and transition patients

David M. Cook · Susan R. Rose

Published online: 24 January 2012

This review will summarize the current guidelines for FDA-approved uses of GH among children and transition patients. A greater knowledge of these guidelines by medical providers will be instrumental in ensuring that patients with disorders of short stature are recommended for treatment and that they are treated appropriately.

Cook et al., Pituitary 2012; 15:301

Pituitary (2012) 15:301–310
DOI 10.1007/s11102-011-0372-6

A review of guidelines for use of growth hormone in pediatric and transition patients

David M. Cook · Susan R. Rose

Published online: 24 January 2012

The use of the GHRH/arginine test is not recommended with idiopathic isolated GHD of childhood-onset because it may result in a false-normal response in some cases of idiopathic GHD

Cook et al., Pituitary 2012; 15:301

Population Diagnosis (abbreviation) [reference(s)]	Criteria for growth hormone therapy	FDA-approved doses, mcg/kg/day
Pediatric patients		
Chronic renal insufficiency/ chronic kidney disease (CRI) [1, 27]	Growth failure associated with CRI up to time of renal transplantation. GH should be used in conjunction with optimal management of CRI	50
Growth hormone deficiency [1, 27, 33, 34, 49, 58]	Children with short stature who lack an adequate endogenous peak serum GH secretory response following challenge with a standard stimulus (<10 ng/mL)	22–50
	Children with unexplained short stature who pass a GH stimulation test (>10 ng/mL peak GH serum level), but who meet most of the following criteria: (1) height > 2.25 SD below the mean for age or > 2 SD below the mid-parental height percentile; (2) growth velocity < 25th percentile for bone age; (3) bone age > 2 SD below the mean for age; (4) low serum IGF-I and/or low serum IGFBP3; and/or (5) other clinical features suggestive of GHD	
Idiopathic short stature (ISS) [1, 27, 34, 49, 58]	Height SDS < −2.25, with growth rates unlikely to permit attainment of normal adult height	≤67
Noonan syndrome (NS) [11, 33]	Weight and length ≤ third centile	≤66
Prader-Willi syndrome (PWS) [10, 34, 58]	Early signs may include: prenatal growth retardation with median birth weight SDS of −1.37 (range −2.81 to +0.15; 20% have weight SDS < −2.0), and median birth length SDS of −0.46 (range −2.14 to +1.40); short stature is almost always observed after birth up to 2 years of age. Early diagnosis in infancy using accredited genetic testing allows early intervention with GH therapy, taking into account cautions and relative contraindications along with appropriate monitoring of GH replacement. Evaluation of IGF-I status and, if possible, GH status is recommended	34–50
	GH therapy may be started at 2 years of age or as young as 6–12 months of age	
SHOX gene haploinsufficiency (SHOX) [49]	Short stature or growth failure in children with test showing short stature homeobox-containing gene (SHOX) deficiency	50
Small for gestational age children (SGA) [8, 33, 34, 49]	Children with birth weight and/or length at least 2 SD < mean for gestational age	50–68
	Early intervention recommended for children 2–4 years of age with no evidence of catch-up growth before GH treatment	
Turner syndrome (TS) [6, 27, 33, 34, 49, 58]	Begin GH at the earliest age possible, as early as 9 months of age	47–67
Transition patients		
Growth hormone deficiency [1, 13, 27, 33, 34, 49, 58]	After documentation of persistent GHD, GH treatment may be continued after adult height is attained	25–100 (adolescents) 4–16 (adults)

GHD growth hormone deficiency, *IGF-I* insulin-like growth factor I, *IGFBP3* insulin-like growth factor binding protein 3, *SD* standard deviation, *SDS* standard deviation score

Diagnosi del deficit di GH nel bambino
Nota AIFA 39

Criteri diagnostici per la diagnosi di deficit di GH- Nota AIFA 2009

I: Parametri clinico-auxologici:

a) Statura <-3DS oppure statura <-2 DS e velocità di crescita/aa <-1 DS rispetto alla norma per età e sesso, misurata a distanza di almeno 6 mesi e con le stesse modalità;
oppure

b) Velocità di crescita/aa <-2DS o <-1,5 DS dopo 2 aa consecutivi, anche in assenza di bassa statura; nei primi due anni di vita sarà sufficiente fare riferimento alla progressiva decelerazione della velocità di crescita (la letteratura non fornisce a riguardo dati definitivi in termini di DS);
oppure

c) Malformazioni/lesioni ipotalamo-ipofisario dimostrate a livello neuro radiologico o difetti ipofisari multipli che comportino deficit di GH accertato in base ad una delle modalità del punto II;

II: Parametri di laboratorio:

a) risposta di GH < 10 µg/L a due test farmacologici eseguiti in giorni differenti (la risposta ad un solo test farmacologico >10 µg/L esclude la diagnosi di deficit di GH);
oppure
b) risposta di GH < 20 µg/L nel caso uno dei due test impiegati sia GHRH + arginina o GHRH +piridostigmina

Terapia deficit di GH in età pediatrica

Dose : 0.25-0.35 μg/Kg/day

0,25-0,50 μg/Kg/day

Efficacia terapia monitorata in base a:

- Variazione (Δ) della statura e della velocità di crescita
- Dosaggio IGF1
- Altri parametri (es. metabolici, osteosintesi) meno sensibili

Valutare i possibili effetti collaterali

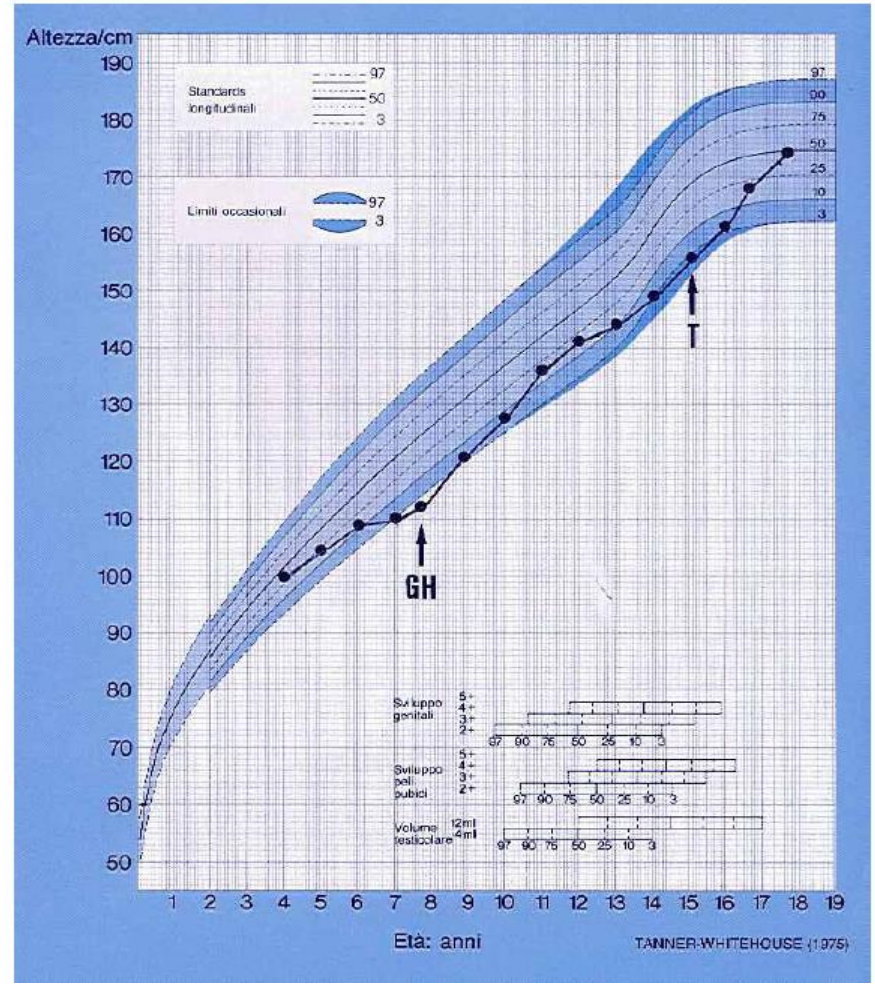
- Artralgia
- Ipertensione endocranica benigne
- Cefalea
- Ipotiroidismo
- Reazioni locali in sede di iniezione

- Lieve ipoglicemia
- Mialgia
- Rash
- Epifisiolisi femorale prossimale
- Peggioramento della scoliosi
- Malattia di Perthes

Cook et al., Pituitary 2012; 15:301

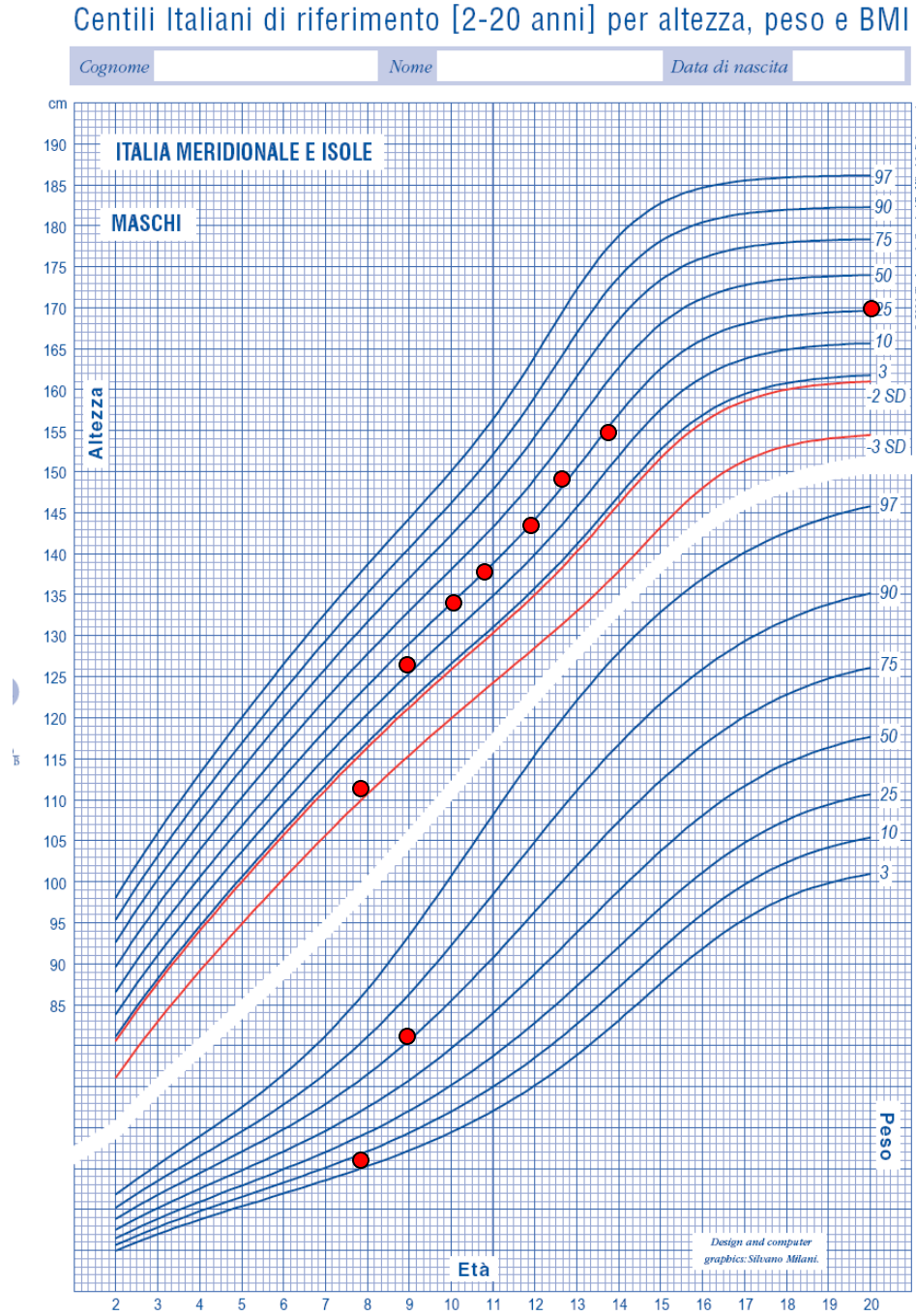
Tp con rhGH in età pediatrica: effetto sulla crescita

- **Appare essenziale "massimizzare" il guadagno staturale prima dell'inizio della pubertà**
- **Se la pubertà compare quando la statura non è ancora completa, è opportuno prendere in considerazione:**
  - **incremento delle dosi di GH**
  - **l'aggiunta di analoghi del GnRH al GH**
- **La valutazione del rapporto tra l'incremento dell'età staturale e l'incremento dell'età ossea rappresenta un indice sensibile per valutare l'efficacia della terapia con GH**



Cook et al., Pituitary 2012; 15:301

14 anni



Altezza bersaglio 173

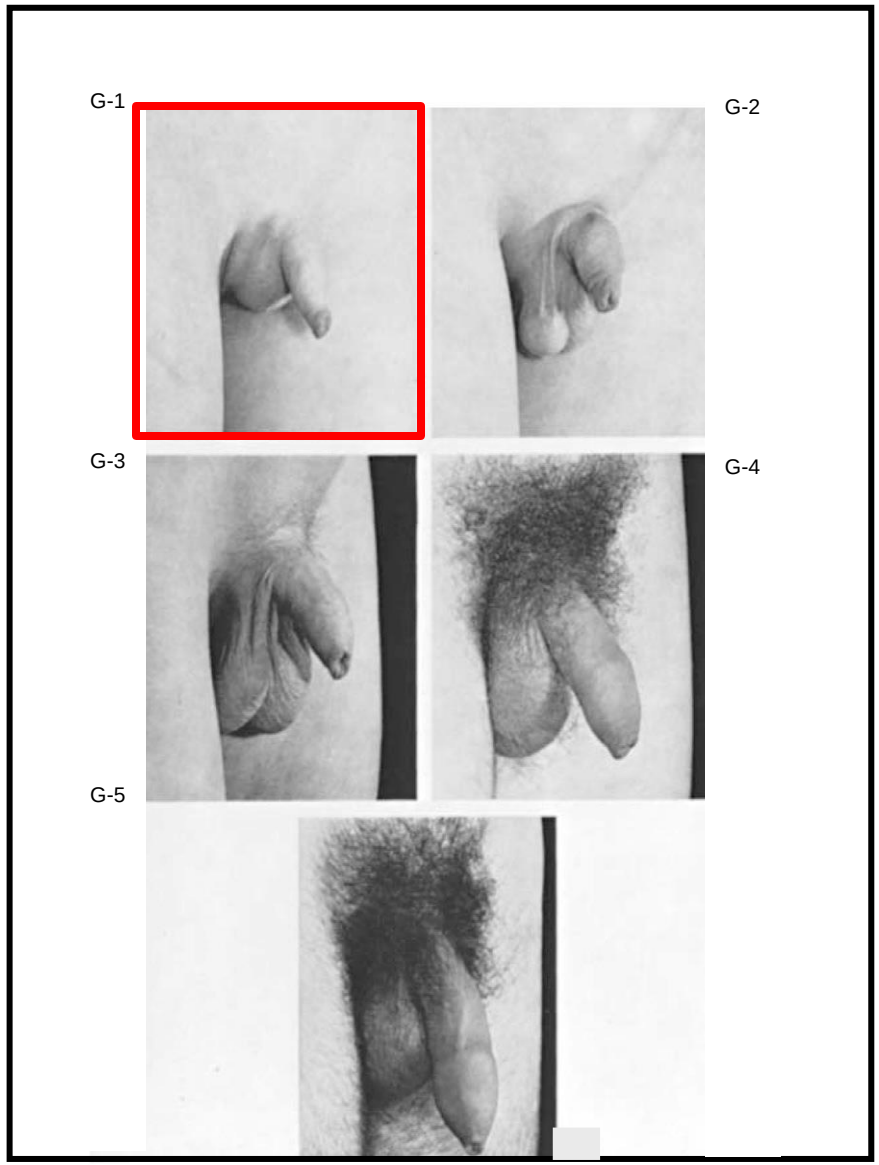

Giovanni e con la pubertà che si fa?…

Valutazione clinica

Peso 58.6 Kg **altezza 151.6 cm**

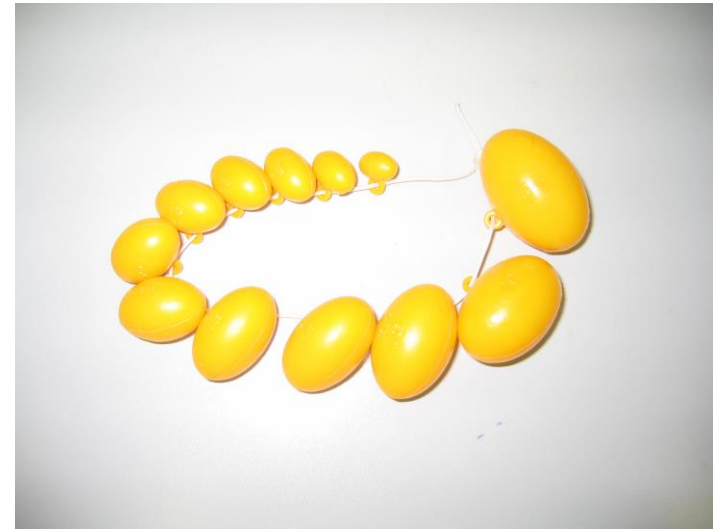
Pressione arteriosa 105/70 mmHg

Volume testicolare **dx 1 ml** **sn 1 ml (>12)** **Stadio di Tanner 1**



Tanner I

Prepubertal: testicular volume less than 1.5 ml; small penis of 3 cm or less



Maggi & Buvat Sex Med. 2013;10:285

Causes of male delayed puberty

1) Reversible (functional)

- **a) Systemic illness & other reversible conditions**
  - **• Systemic illness**
    - Cystic fibrosis
    - Asthma
    - Inflammatory bowel disease
    - Celiac disease
    - Juvenile rheumatoid arthritis
    - Sickle cell disease
    - Thalassemia
    - Hemosiderosis
    - Chronic renal disease
    - AIDS
    - Malignancies
  - **• Excessive energy expenditure, exercise**
  - **• Emotional deprivation**
  - **• Malnutrition**
  - **• Endocrinopathies**
    - Diabetes mellitus
    - Hypothyroidism
    - Hyperprolactinemia
    - Growth hormone deficiency
    - Cushing syndrome
    - Obesity
- **b) Constitutional delay of puberty**
- **c) Hypogonadotropic (secondary) hypogonadism (10%)**

2) Irreversible (permanent)

- **c) Hypogonadotropic (secondary) hypogonadism (90%)**
- **d) Hypergonadotropic (primary) hypogonadism (100%)**

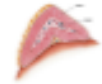
Maggi & Buvat Sex Med. 2013;10:285

Costitutional Delay of Puberty

"Healthy individulas who spontaneously enter puberty after the age of 13 for girls and 14 for boys"

Extreme physiological variant of the normal velocity of development

Retarded bone age, delayed adrenarche, and delayed gonadarche



Family history : mother or father or siblings with delayed puberty

No one test distinguishes between costitutional delay and hypogonadotropic hypogonadism

Diagnosis of exclusion

Maggi & Buvat Sex Med. 2013;10:285

Quali sono i segni clinici che possono suggerire un ritardo costituzionale di crescita?

1. **Volume testicolare > 4 cc**
2. **Familiarità**
3. **Valori di testosterone > 0.7 nmol/L (0.2 ng/ml)**
4. **Normale risposta a LH-RH**
5. **Tutti i precedenti**

I livelli di testosterone possono essere usati come segno predittore di pubertà: un valore maggiore di 0.7 nmol/L (0.2 ng/ml; 20 ng/dl) indica un volume testicolare superiore a 4 mL entro 12 mesi nel 77% ed entro 15 mesi 100%.

Maggi & Buvat Sex Med. 2013;10:285

Cosa consigliate per l'induzione della pubertà?

1. **LH**
2. **Testosterone**
3. **LH+FSH**
4. **FSH**
5. **Non saprei**

•**Trattamento con testosterone:** circa il 15 -25 % della dose abituale dell'adulto è sufficiente per ottenere una normale virilizzazione e una normale crescita nel tempo, senza indurre un chiusura precoce delle cartilagini di cogniugazione (EBM level lb).

•**Trattamento con gonadotropine:** 1250–5000 IU hCG in associazione con 12.5–150 IU hMG 3 volte settimana

Maggi & Buvat J Sex Med. 2013;10:285

Hormonal induction of puberty in FEMALE

- Oral estrogen formulations:
  Ethinyl estradiol: 2.5–5 μg/day (=50–100 ng/kg/day); the dose should be increased gradually to adult dose (20–25 μg/day)
  Micronized 17β-estradiol: 5 μg/kg/day; the dose should be increased gradually to adult dose (minimum effective adult dose, 2 mg/day)
  Conjugated equine estrogens: ~0.3 mg/day, then 0.625 to 1.25 mg/day[†]
- Transdermal estrogen formulations (adult dose):
  17β-Estradiol
  - patch: 25–100 μg/24 h
  - gel: 25–100 μg/24 h
- Depot estrogen formulations:
  17β-Estradiol: 0.2 mg/month, increasing 0.2 mg every 6 months until 1.0 mg, then 0.5 mg every 6 months (maximum, 3.0 mg/month)

In subjects with uterus +

- Progestins[‡] (cyclic therapy, 10–14 days/period):
  Medroxyprogesterone acetate: 5–10 mg/day
  Dydrogestrone: 10–20 mg/day
  Norethisterone: 0.7–10.5 mg/day
  Levonorgestrel: 60–90 μg/day

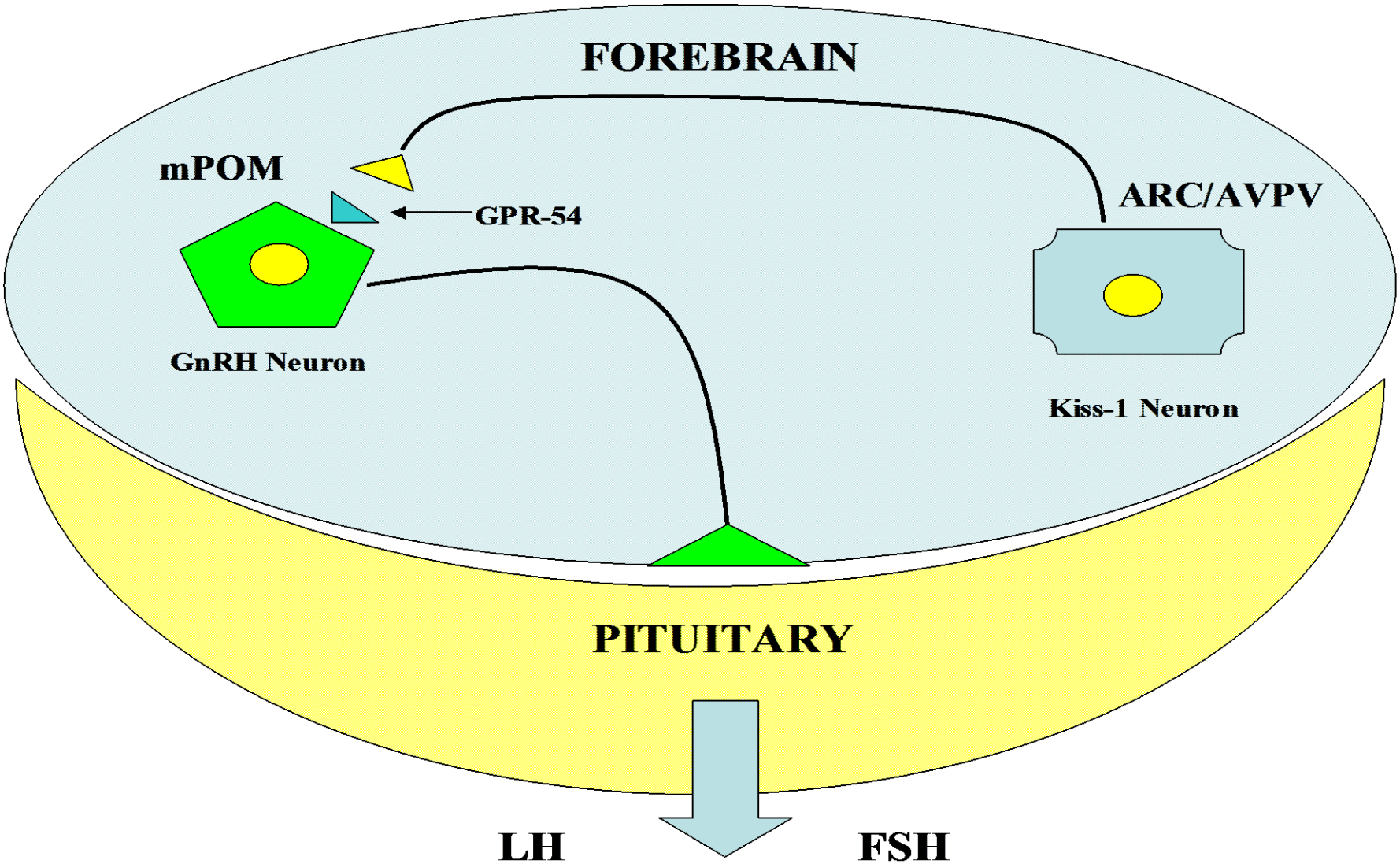
Bertelloni et al Gyn End 2008, 24: 339-46

Advantages of gonadotropins vs testosterone in inducing pubertal development

	Gonadotropins	Testosterone
Promote increases in growth spurt	+++	+++
Induce the development of secondary sexual characteristics	+++	+++
Bone maturation and epiphyseal closure	+++	+++
Testis growth	+++	---
Induce spermatogenesis	++	---
Reverse hypogonadism	+	+
Costs	+++	+

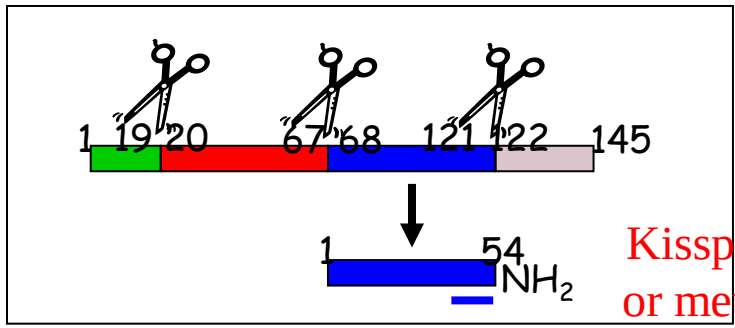
Maggi & Buvat Sex Med. 2013;10:285

Kiss-1 GPR-54 pathway: probably plays a key role in puberty timing



KiSS-1/GPR54

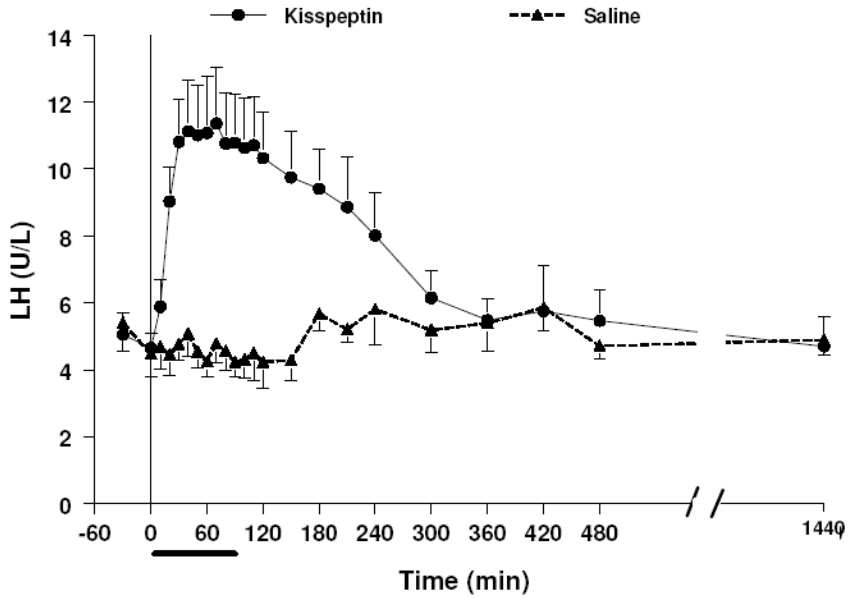
KiSS-1 protein



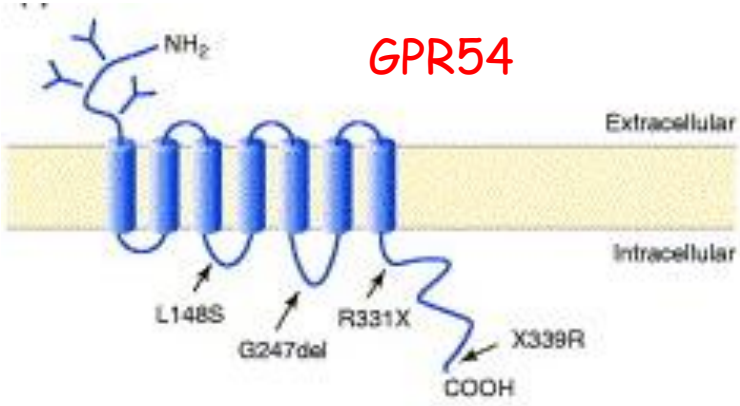
Kisspeptin
or metastin

Central or peripheral administration of kisspeptin stimulates the HPG axis and increases circulating concentrations of LH and FSH in rodents and human males

Navarro et al. Endocrinology, 146:156, 2005
Navarro et al Endocrinology, 146:1689, 2005
Dhillo et al. J Clin Endocrinol Metab 90:6609, 2005



Dhillo et al. J Clin Endocrinol Metab 2005



Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54

Nicolas de Roux*†‡, Emmanuelle Genin§, Jean-Claude Carel¶, Fumihiko Matsuda‖, Jean-Louis Chaussain¶, and Edwin Milgrom*

*Institut National de la Santé et de la Recherche Médicale Unité 135, Unité de Recherches Hormones Gènes et Reproduction, Hôpital de Bicêtre, 94275 Le Kremlin-Bicêtre, France; †Institut National de la Santé et de la Recherche Médicale Unité 584, Hormone Targets, Faculté de Médecine Necker Enfants Malades, 75015 Paris, France; §Institut National de la Santé et de la Recherche Médicale Unité 535, Génétique Epidémiologique et Structure des Populations Humaines, Hôpital de Bicêtre, 94275 Le Kremlin-Bicêtre, France; ¶Service d'Endocrinologie Pédiatrique, Hôpital Saint Vincent de Paul, 75014 Paris, France; and ‖Centre National de Genotypage, 2 Rue Gaston Cremieux, 91057 Evry, France

Communicated by Etienne-Emile Baulieu, College de France, Le Kremlin-Bicêtre Cedex, France, July 14, 2003 (received for review June 16, 2003)

PNAS, 2003

Loss of function mutations of GPR54 gene are associated with lack of puberty onset and hypogonadotropic hypogonadism, without anosmia, in humans and mice

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The GPR54 Gene as a Regulator of Puberty

Stephanie B. Seminara, M.D., Sophie Messager, Ph.D., Emmanouella E. Chatzidaki, B.Sc., Rosemary R. Thresher, Ph.D., James S. Acierno, Jr., B.S., Jenna K. Shagoury, B.S., Yousef Bo-Abbas, M.D., Wendy Kuohung, M.D., Kristine M. Schwinof, M.A., Alan G. Hendrick, Ph.D., Dirk Zahn, Ph.D., John Dixon, B.A., Ursula B. Kaiser, M.D., Susan A. Slaugenhaupt, Ph.D., James F. Gusella, Ph.D., Stephen O'Rahilly, M.D., Mark B.L. Carlton, Ph.D., William F. Crowley, Jr., M.D., Samuel A.J.R. Aparicio, B.M., B.Ch., Ph.D., and William H. Colledge, Ph.D.

NEJM 2003

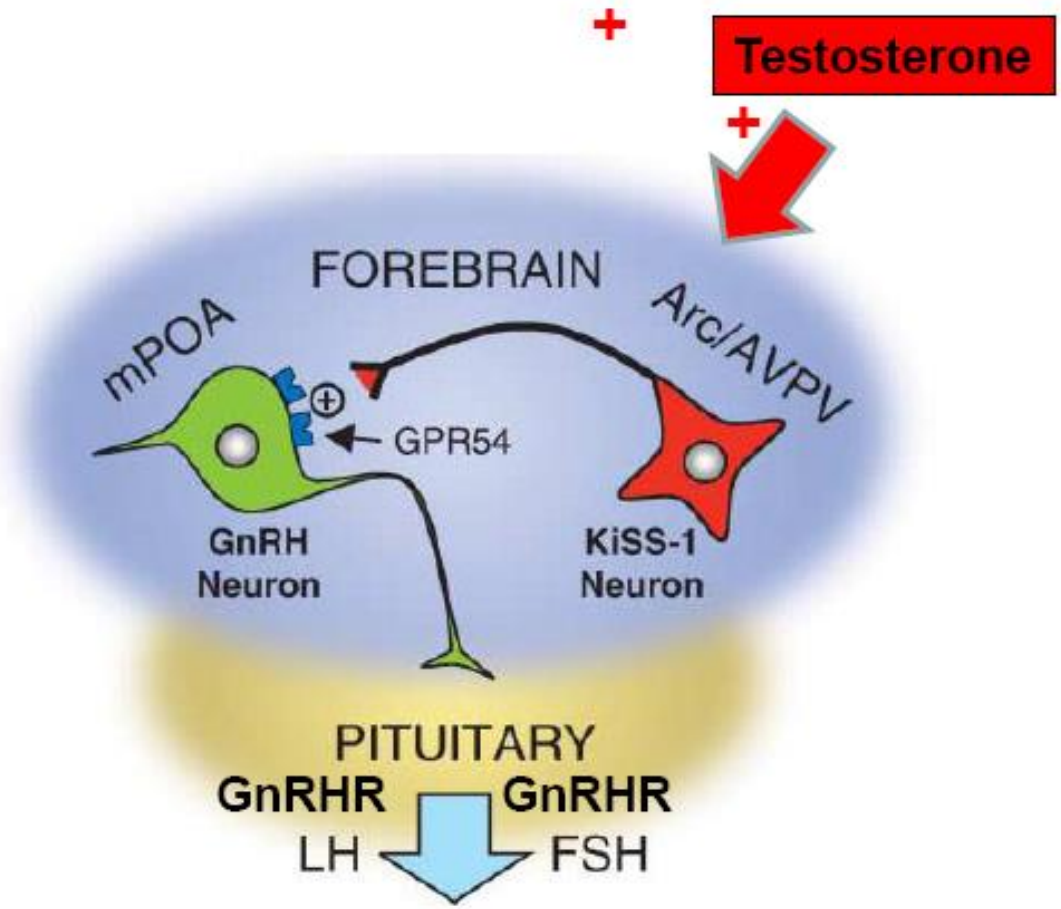
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A *GPR54*-Activating Mutation in a Patient with Central Precocious Puberty

Milena Gurgel Teles, M.D., Suzy D.C. Bianco, Ph.D., Vinicius Nahime Brito, M.D., Ericka B. Trarbach, Ph.D., Wendy Kuohung, M.D., Shuyun Xu, M.D., Stephanie B. Seminara, M.D., Berenice B. Mendonca, M.D., Ursula B. Kaiser, M.D., and Ana Claudia Latronico, M.D.

Teles et al., N Engl J Med. 2008



Reversible Kallmann syndrome

Pitteloud et al., JCE&M 2005, 90: 1317
Raivio et al., N Engl J Med 2007, 357:863
Ribeiro et al Eur J Endocrinol 2007 , 285

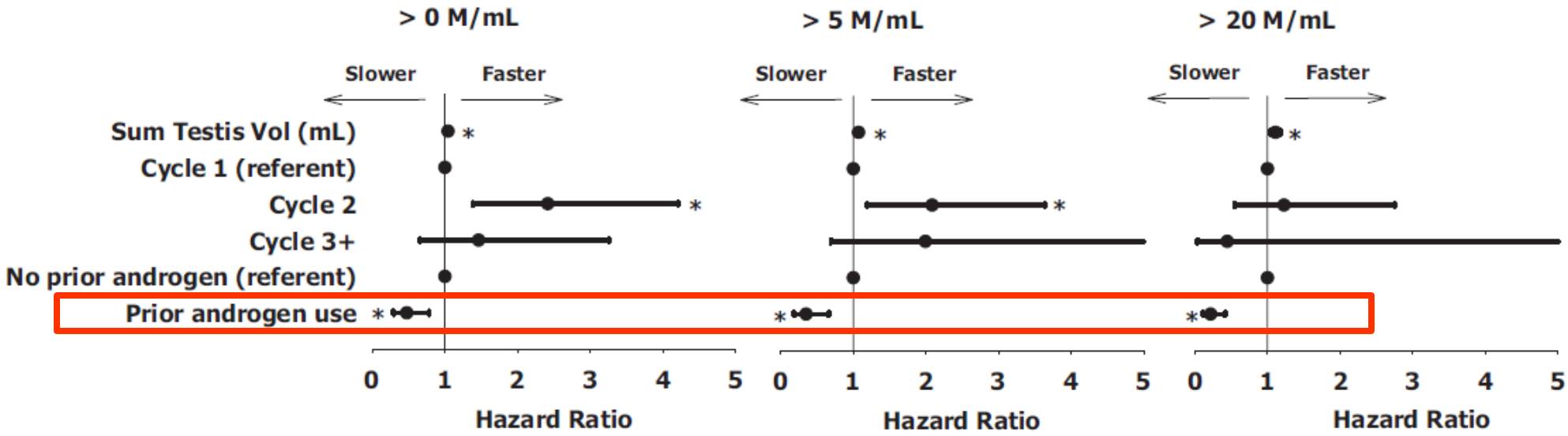
ORIGINAL ARTICLE

Endocrine Care

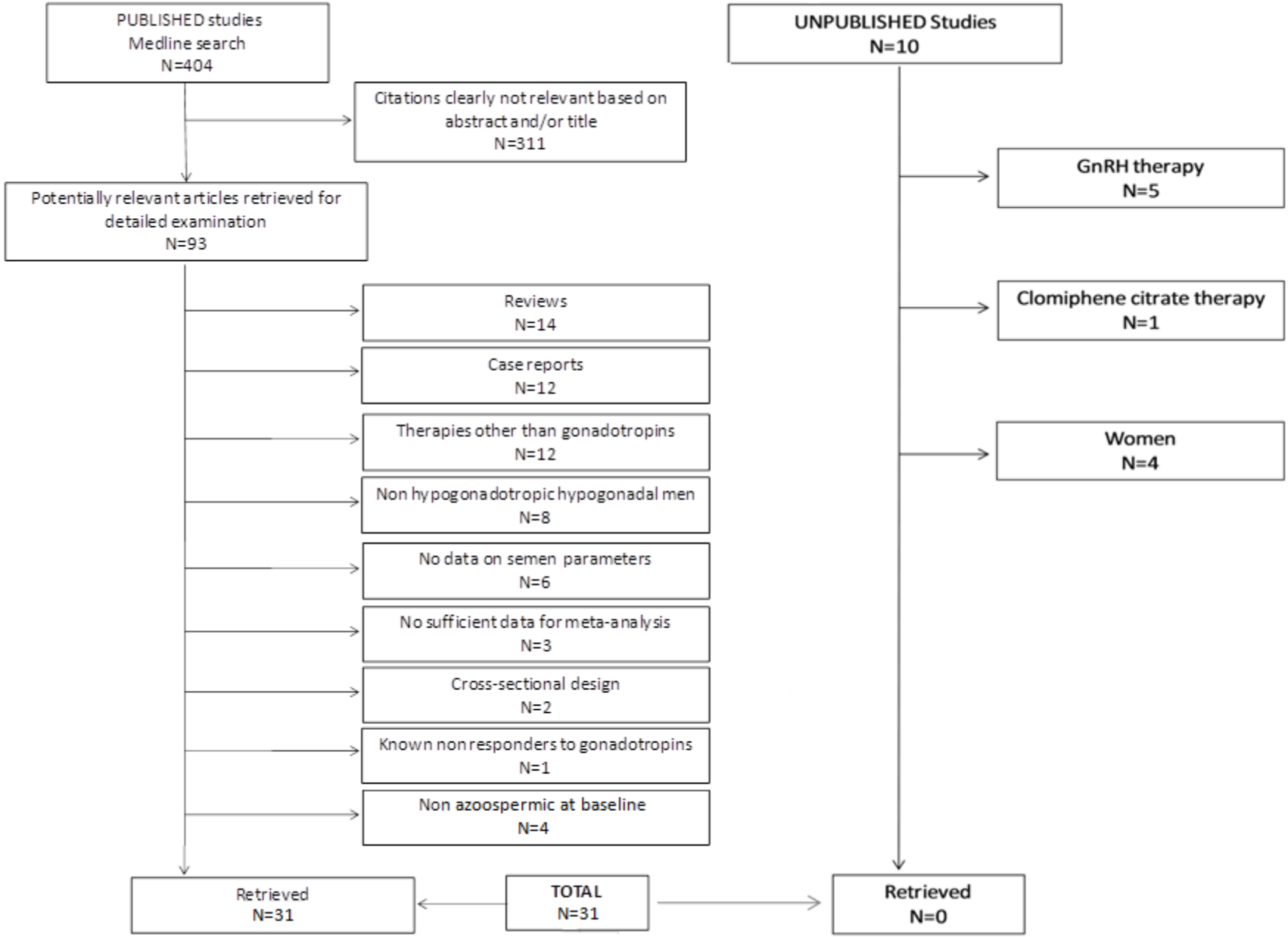
Induction of Spermatogenesis and Fertility during Gonadotropin Treatment of Gonadotropin-Deficient Infertile Men: Predictors of Fertility Outcome

Peter Y. Liu, H. W. Gordon Baker, Veena Jayadev, Margaret Zacharin, Ann J. Conway, and David J. Handelsman

75 men, with 72 desiring fertility, was treated at two academic andrology centers for a total of 116 courses of therapy from 1981–2008

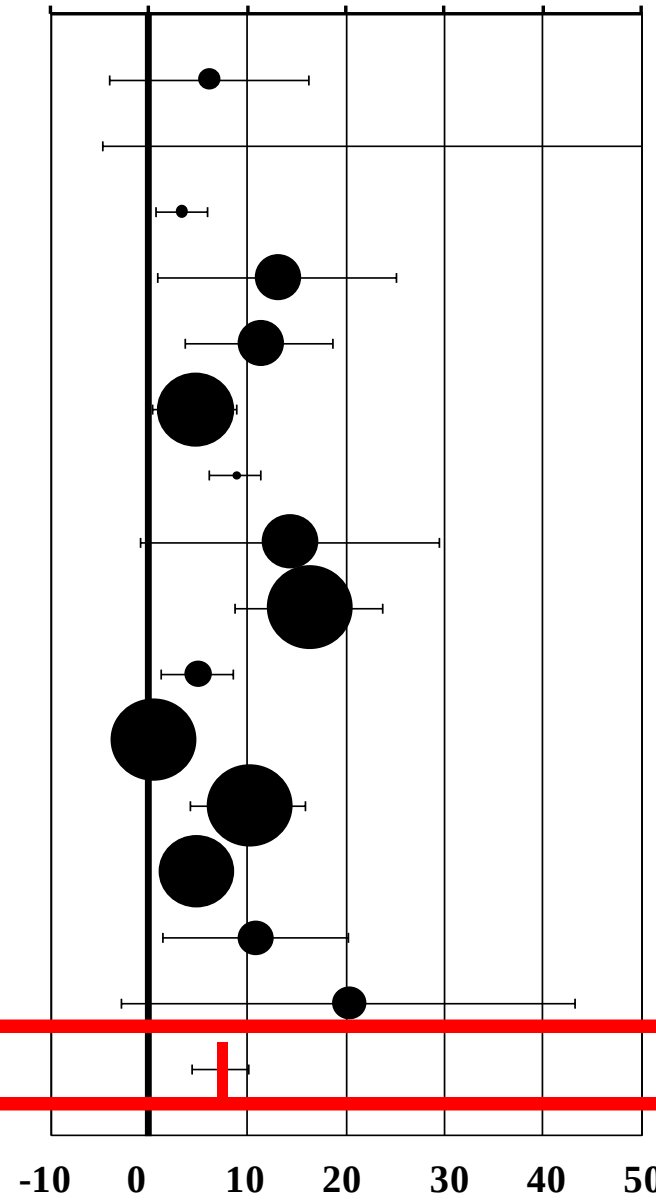


Liu et al., J Clin Endocrinol and Metab 2009;94:801



Rastrelli et al., 2013 manuscript in preparation

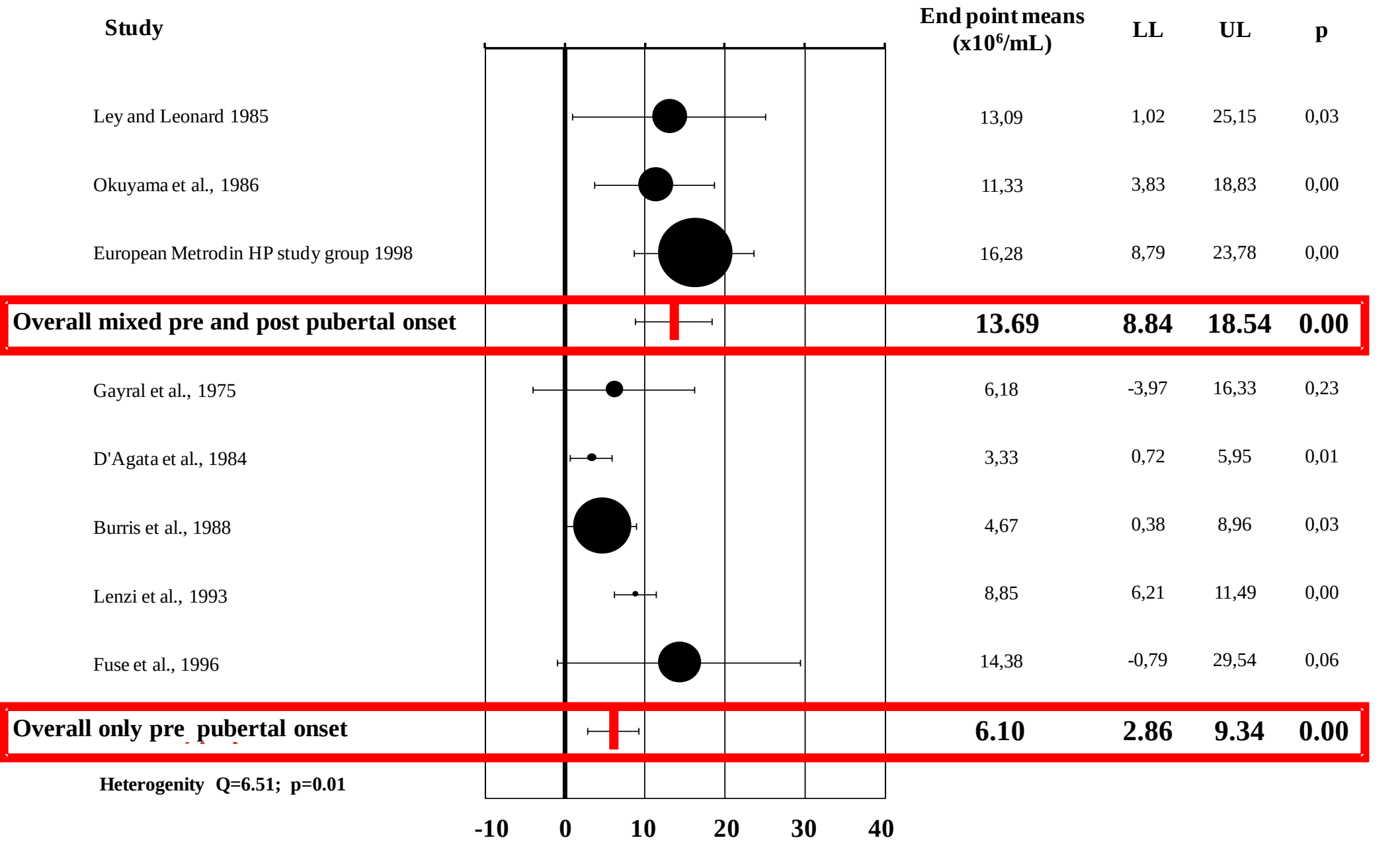
Mean sperm count (with 95% confidence interval [CI]) after gonadotropin therapy



Study	End point means (x10⁶/mL)	LL	UL	p
Gayral et al., 1975	6,18	-3,97	16,33	0,23
Levalle et al., 1983	76,33	-4,66	157,33	0,06
D'Agata et al., 1984	3,33	0,72	5,95	0,01
Ley and Leonard 1985	13,09	1,02	25,15	0,03
Okuyama et al., 1986	11,33	3,83	18,83	0,00
Burris et al., 1988	4,67	0,38	8,96	0,03
Lenzi et al., 1993	8,85	6,21	11,49	0,00
Fuse et al., 1996	14,38	-0,79	29,54	0,06
European Metrodin HP study group 1998	16,28	8,79	23,78	0,00
Carani et al., 1999	4,97	1,37	8,57	0,01
Bakircioglu et al., 2007	0,45	-0,33	1,23	0,26
Matsumoto et al., 2009	10,17	4,33	16,02	0,00
Efesoy et al., 2009	4,77	2,14	7,40	0,00
Oldereid et al., 2010	10,85	1,45	20,25	0,02
Milsom et al., 2012	20,33	-2,71	43,37	0,08
Overall	**7.40**	**4.54**	**10.26**	**0.00**

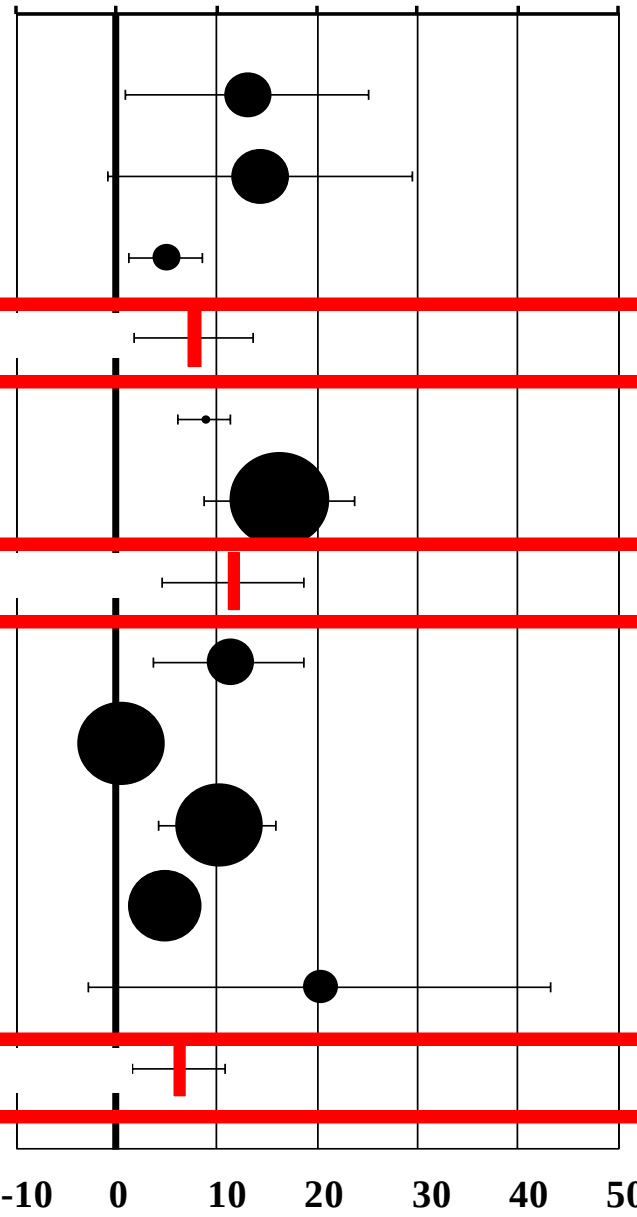
Rastrelli et al., 2013 manuscript in preparation

Mean sperm count (with 95% confidence interval [CI]) after gonadotropin therapy



Rastrelli et al., 2013 manuscript in preparation

Mean sperm count (with 95% confidence interval [CI]) after gonadotropin therapy

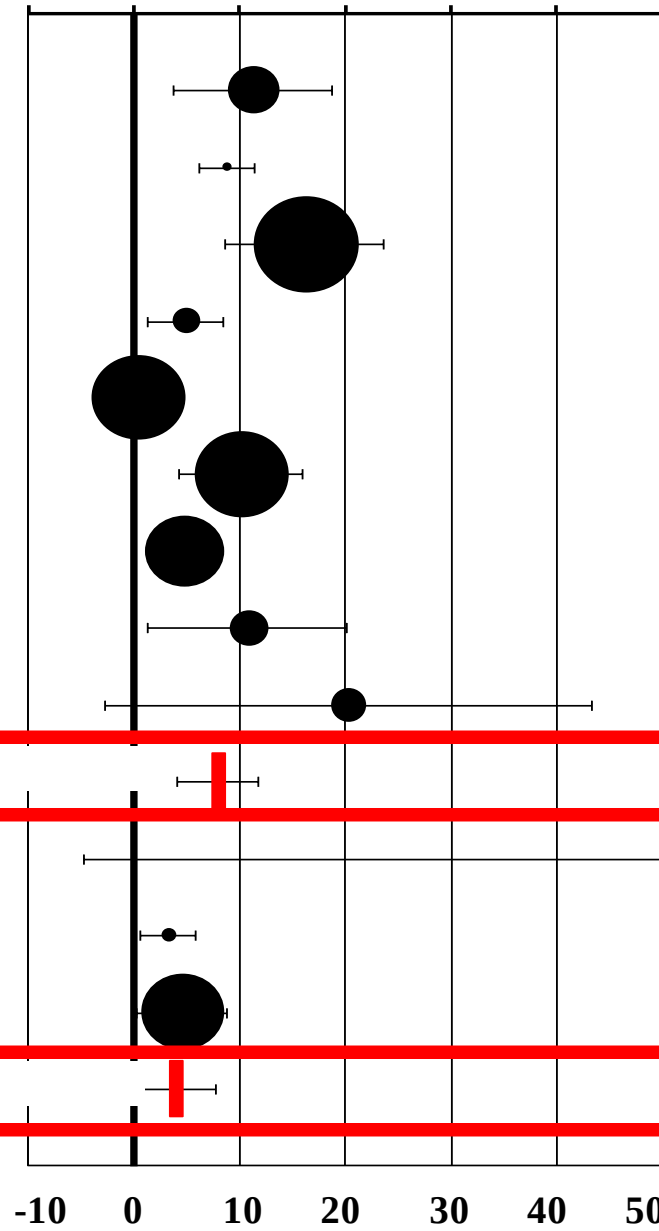


Study	End point means (x10⁶/mL)	LL	UL	p
Ley and Leonard 1985	13,09	1,02	25,15	0,03
Fuse et al., 1996	14,38	-0,79	29,54	0,06
Carani et al., 1999	4,97	1,37	8,57	0,01
Overall urinary derived FSH	**7.78**	**1.80**	**13.75**	**0.01**
Lenzi et al., 1993	8,85	6,21	11,49	0,00
European Metrodin HP study group 1998	16,28	8,79	23,78	0,00
Overall purified FSH	**11.71**	**4.62**	**18.79**	**0.00**
Okuyama et al., 1986	11,33	3,83	18,83	0,00
Bakircioglu et al., 2007	0,45	-0,33	1,23	0,26
Matsumoto et al., 2009	10,17	4,33	16,02	0,00
Efesoy et al., 2009	4,77	2,14	7,40	0,00
Milsom et al., 2012	20,33	-2,71	43,37	0,08
Overall recombinant FSH	**6.27**	**1.59**	**10.94**	**0.01**

Heterogenity Q=1.578; p=0.454

Rastrelli et al., 2013 manuscript in preparation

Mean sperm count (with 95% confidence interval [CI]) after gonadotropin therapy

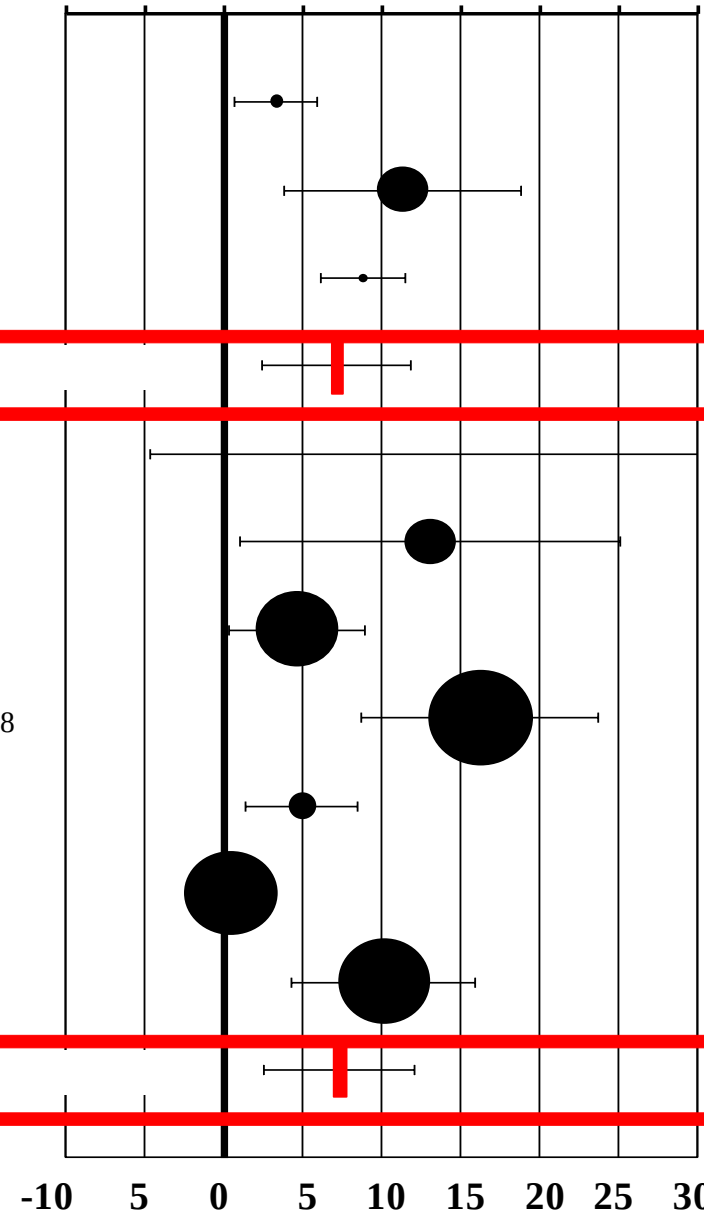


Study	End point means ($x10^6$/mL)	LL	UL	p
Okuyama et al., 1986	11,33	3,83	18,83	0,00
Lenzi et al., 1993	8,85	6,21	11,49	0,00
European Metrodin HP study group 1998	16,28	8,79	23,78	0,00
Carani et al., 1999	4,97	1,37	8,57	0,01
Bakircioglu et al., 2007	0,45	-0,33	1,23	0,26
Matsumoto et al., 2009	10,17	4,33	16,02	0,00
Efesoy et al., 2009	4,77	2,14	7,40	0,00
Oldereid et al., 2010	10,85	1,45	20,25	0,02
Milsom et al., 2012	20,33	-2,71	43,37	0,08
Overall hCG+FSH	**7.98**	**4.12**	**11.83**	**0.00**
Levalle et al., 1983	76,33	-4,66	157,33	0,06
D'Agata et al., 1984	3,33	0,72	5,95	0,01
Burris et al., 1988	4,67	0,38	8,96	0,03
Overall only hCG	**4.03**	**0.25**	**7.81**	**0.04**

Heterogenity Q=2.058; p=0.151

Rastrelli et al., 2013 manuscript in preparation

Mean sperm count (with 95% confidence interval [CI]) after gonadotropin therapy

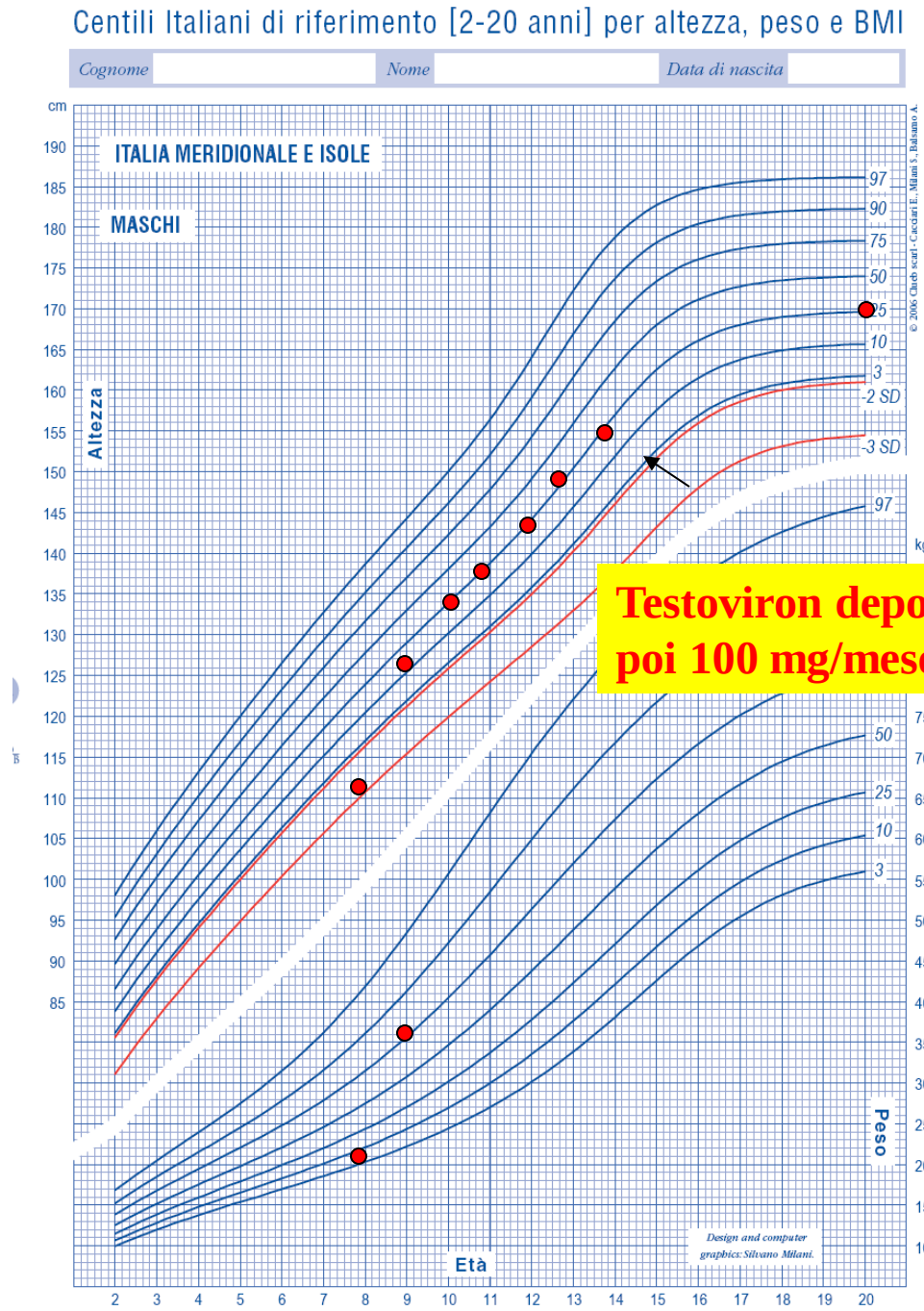


Study	End point means (x10⁶/mL)	LL	UL	p
D'Agata et al., 1984	3,33	0,72	5,95	0,01
Okuyama et al., 1986	11,33	3,83	18,83	0,00
Lenzi et al., 1993	8,85	6,21	11,49	0,00
Overall no previous TRT	**7.18**	**2.50**	**11.87**	**0.00**
Levalle et al., 1983	76,33	-4,66	157,33	0,06
Ley and Leonard 1985	13,09	1,02	25,15	0,03
Burris et al., 1988	4,67	0,38	8,96	0,03
European Metrodin HP study group 1998	16,28	8,79	23,78	0,00
Carani et al., 1999	4,97	1,37	8,57	0,01
Bakircioglu et al., 2007	0,45	-0,33	1,23	0,26
Matsumoto et al., 2009	10,17	4,33	16,02	0,00
Overall previous TRT	**7.38**	**2.61**	**12.14**	**0.00**

Heterogenity Q=0.003; p=0.955

Rastrelli et al., 2013 manuscript in preparation

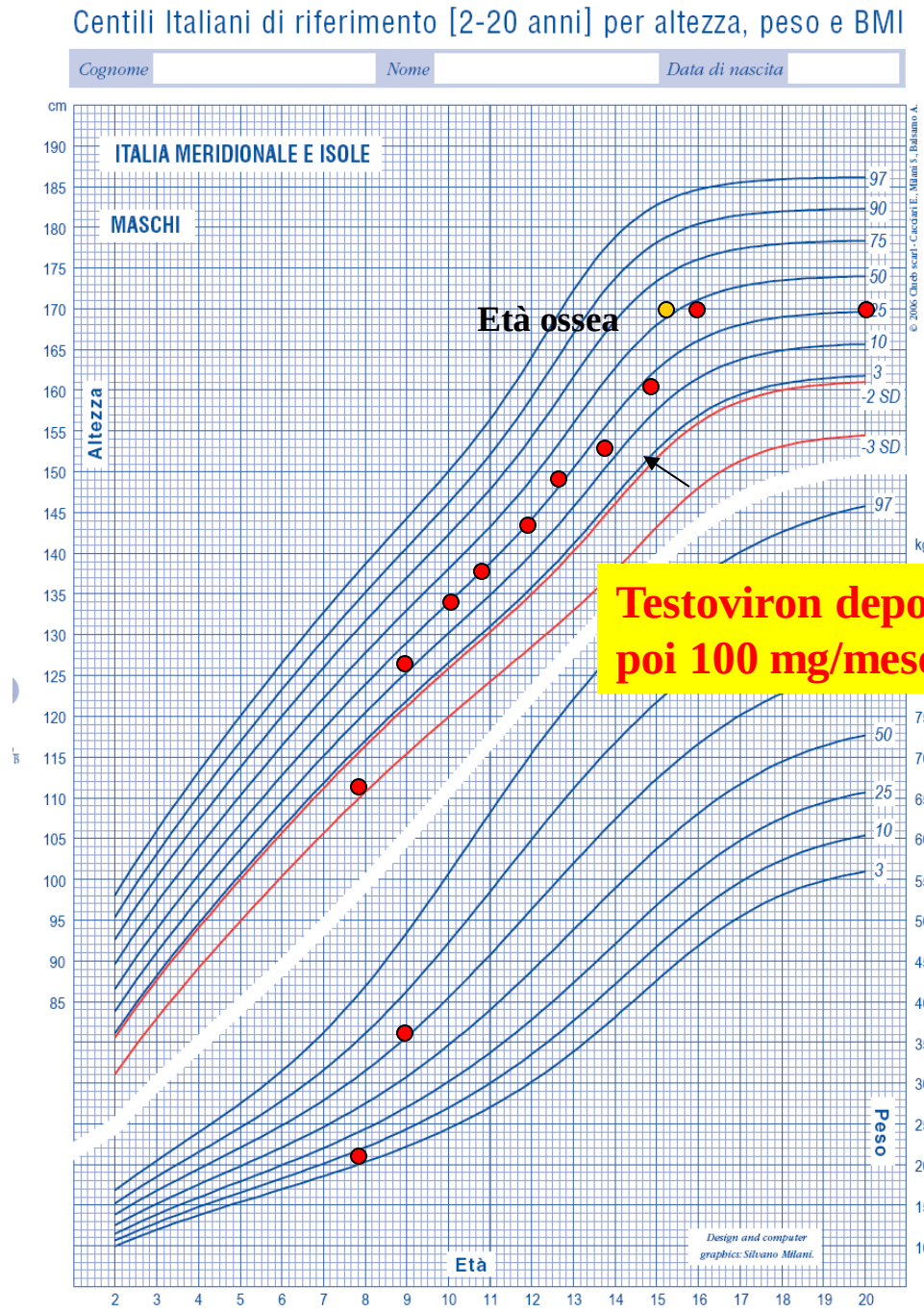
14 anni



Altezza bersaglio 173

Testoviron depot 50 mg/mese per 2 mesi poi 100 mg/mese

16 anni



Altezza bersaglio 173

Testoviron depot 50 mg/mese per 2 mesi poi 100 mg/mese


Caro dottore ho conosciuto una ragazzina… siamo insieme da alcuni mesi.
Non abbiamo ancora avuto rapporti completi ma durante la stimolazione genitale mi sento poco eccitato

Valutazione clinica

Peso 95 Kg Altezza 178 cm BMI 29.9 kg/m^2 circonferenza vita 107 cm

Pressione arteriosa 130/80 mmHg

Normale sviluppo dei genitali esterni e distribuzione pilifera, Tanner 4

Volume testicolare dx 3 ml sm 4 ml (>12)

No Varicocele
Prostata piccola

Cosa suggerite?

1. PDE5i

2. Dapoxetina

3. Setralina

4. Aumentare la dose di testosterone

5. Mandiamolo da Corona che lui ci capisce di problemi di sessualità

Psychobiological Correlates of Delayed Ejaculation in Male Patients With Sexual Dysfunctions

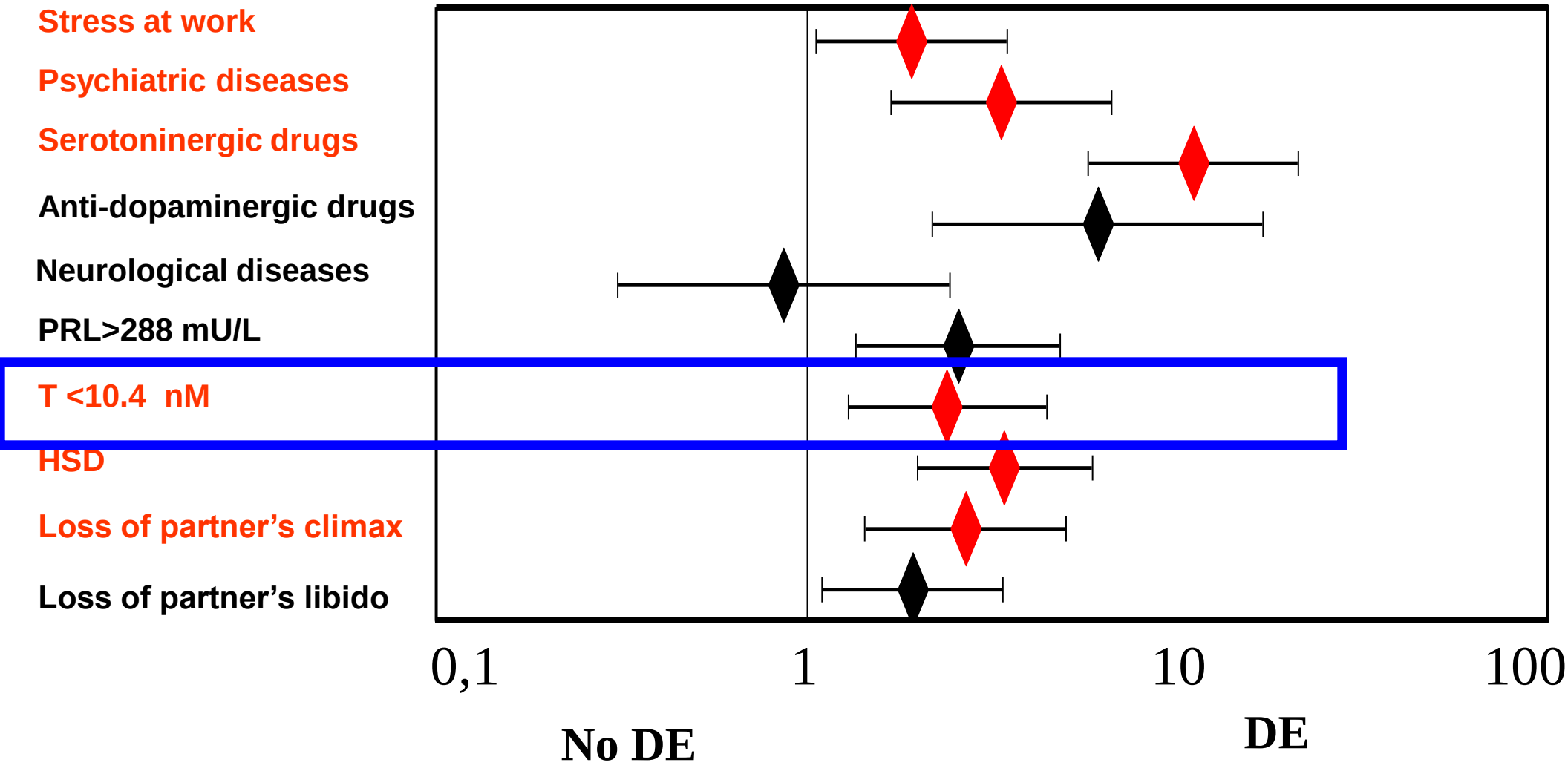
GIOVANNI CORONA,*† EDOARDO MANNUCCI,‡ LUISA PETRONE,* ALESSANDRA D. FISHER,* GIANCARLO BALERCIA,§ GIUSEPPE DE SCISCIOLO,|| ALESSANDRO PIZZOCARO,¶ ROBERTA GIOMMI,# VALERIO CHIARINI,† GIANNI FORTI,* AND MARIO MAGGI*

*From the *Andrology Unit, Department of Clinical Physiopathology, University of Florence, Italy; †Endocrinology Unit, Maggiore-Bellaria Hospital Bologna, Italy; ‡Diabetes Section Geriatric Unit, Department of Critical Care, University of Florence, Italy; §Endocrinology Unit, Polytechnic University of Marche Ancona, Italy; ||Spinal Unit, Neurophysiopathology Service, University of Florence, Italy; ¶Humanitas Clinical Institute, Rozzano, Milan, Italy; and #International Institute of Sexology, Florence, Italy.*

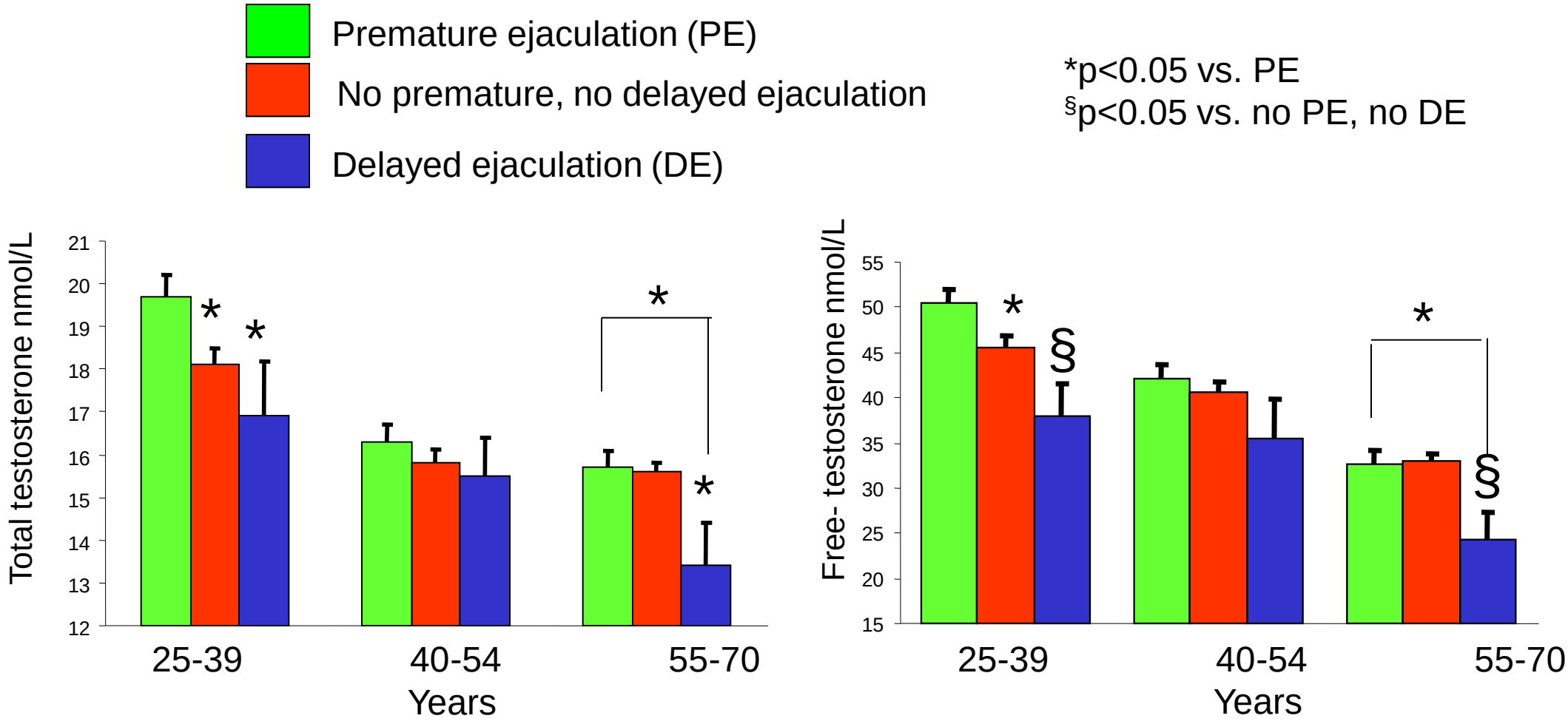
n=1632; mean age 50.1±12.0 years

Corona et al. J Androl. 2006;27:453

Relative risk for the parameters correlated to delayed ejaculation (DE) after adjustment for confounding factors

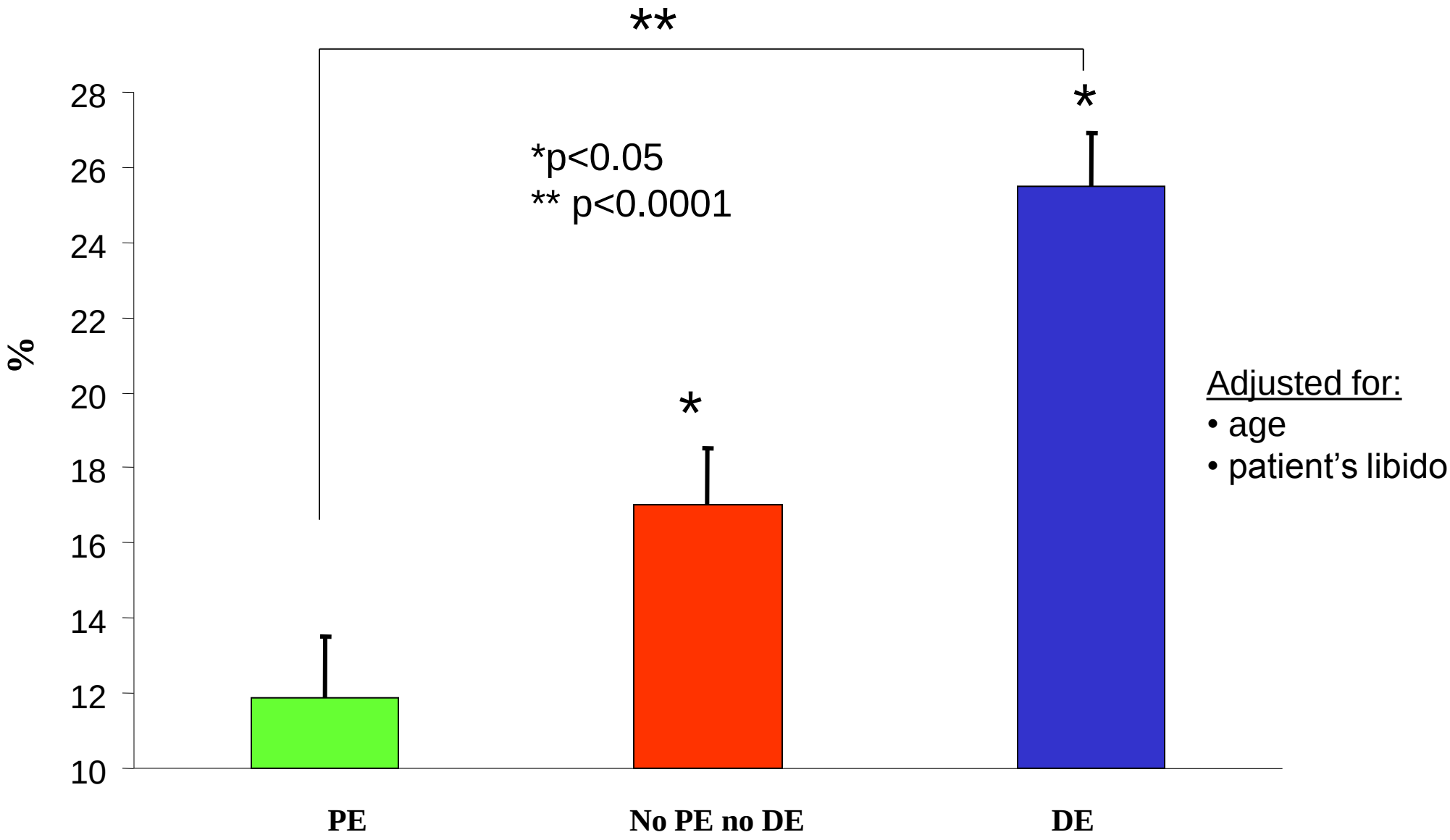


Corona et al. J Androl. 2006;27:453

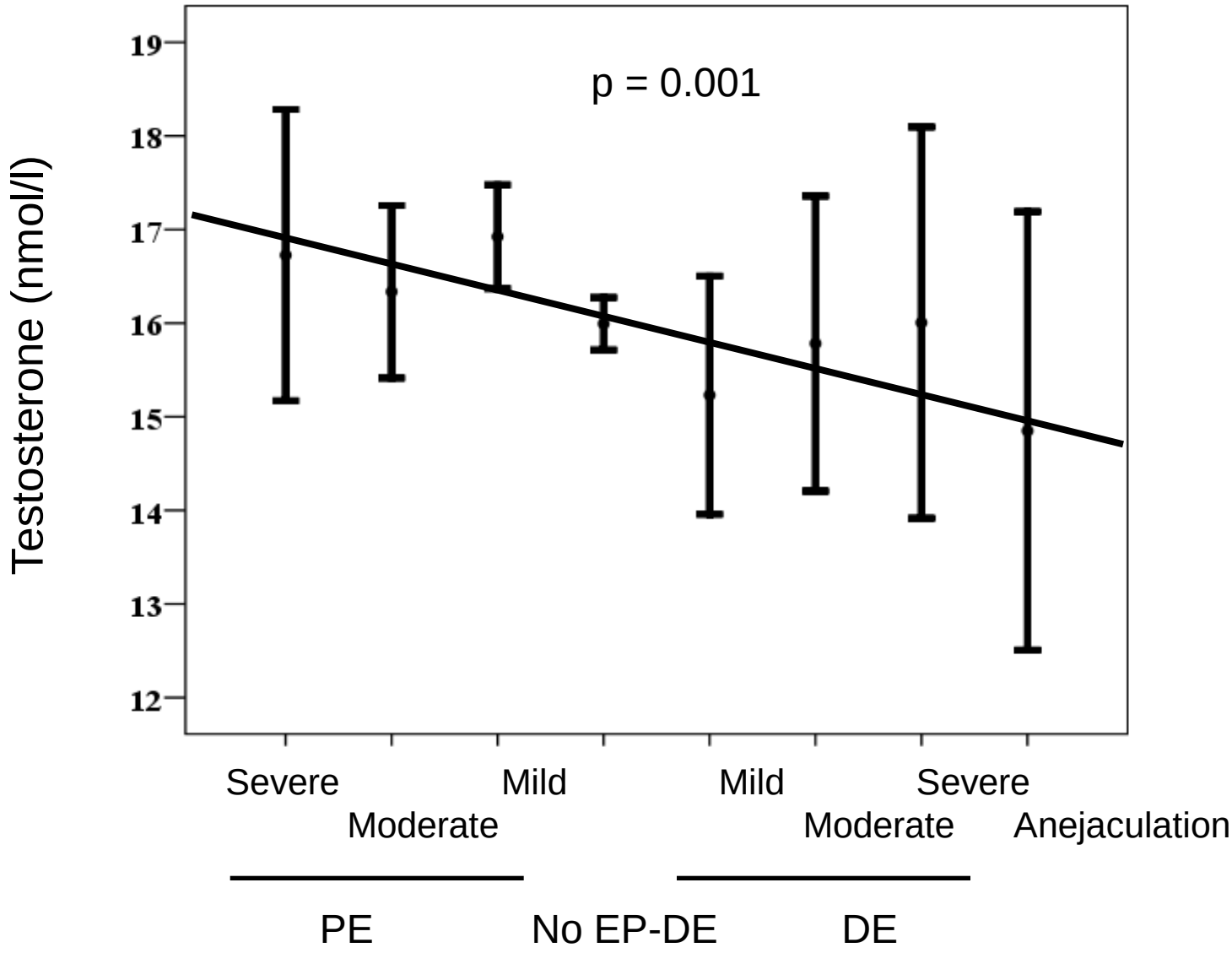


Corona et al. J Sex Med. 2008;5:1991

Adjusted prevalence of hypogonadism (TT < 10.4 nmol/l) in patients with premature, delayed or no premature or delayed ejaculation

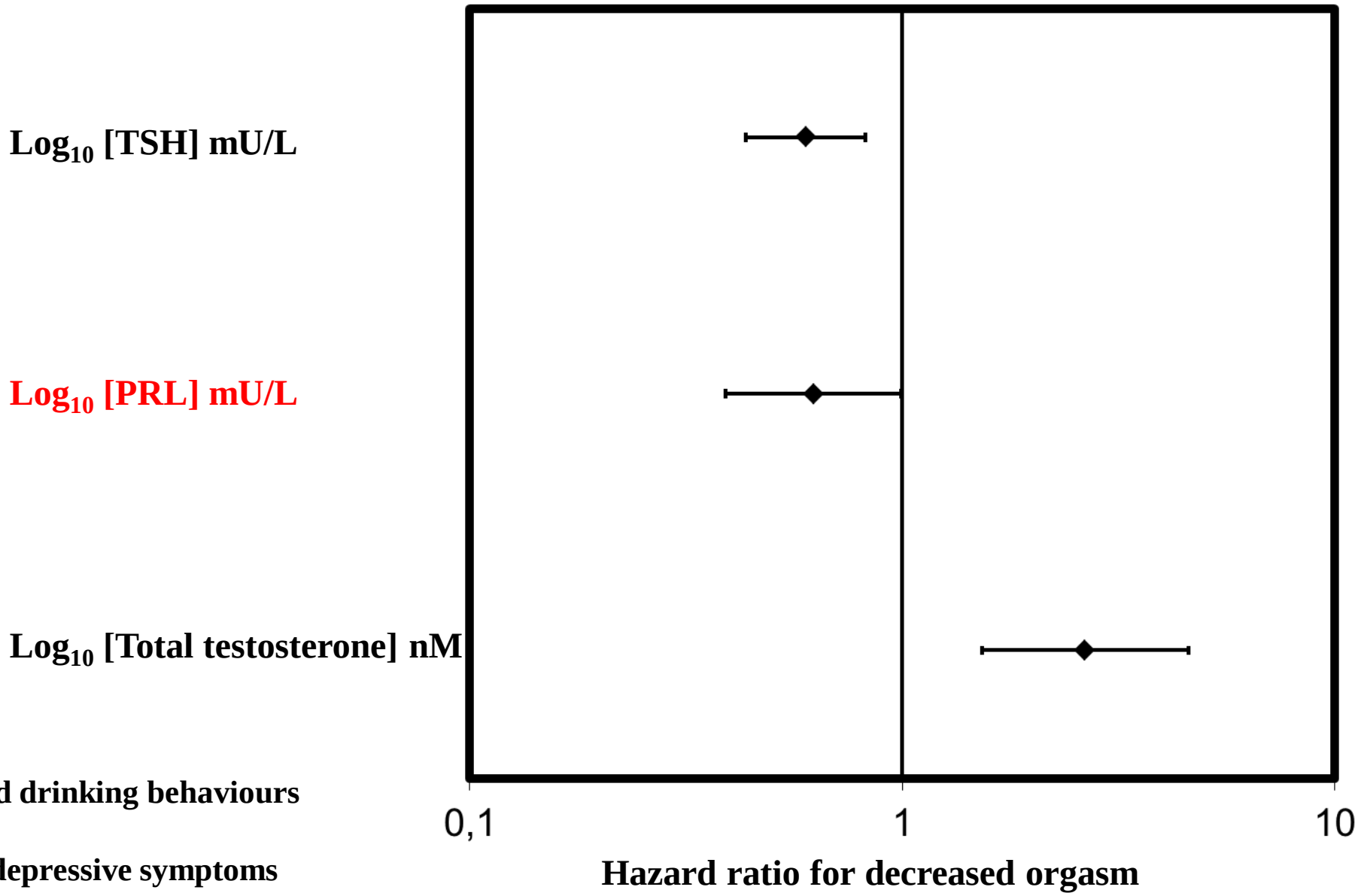


Corona et al. J Sex Med. 2008;5:1991



Corona et al. Int J Androl. 2010;33:1

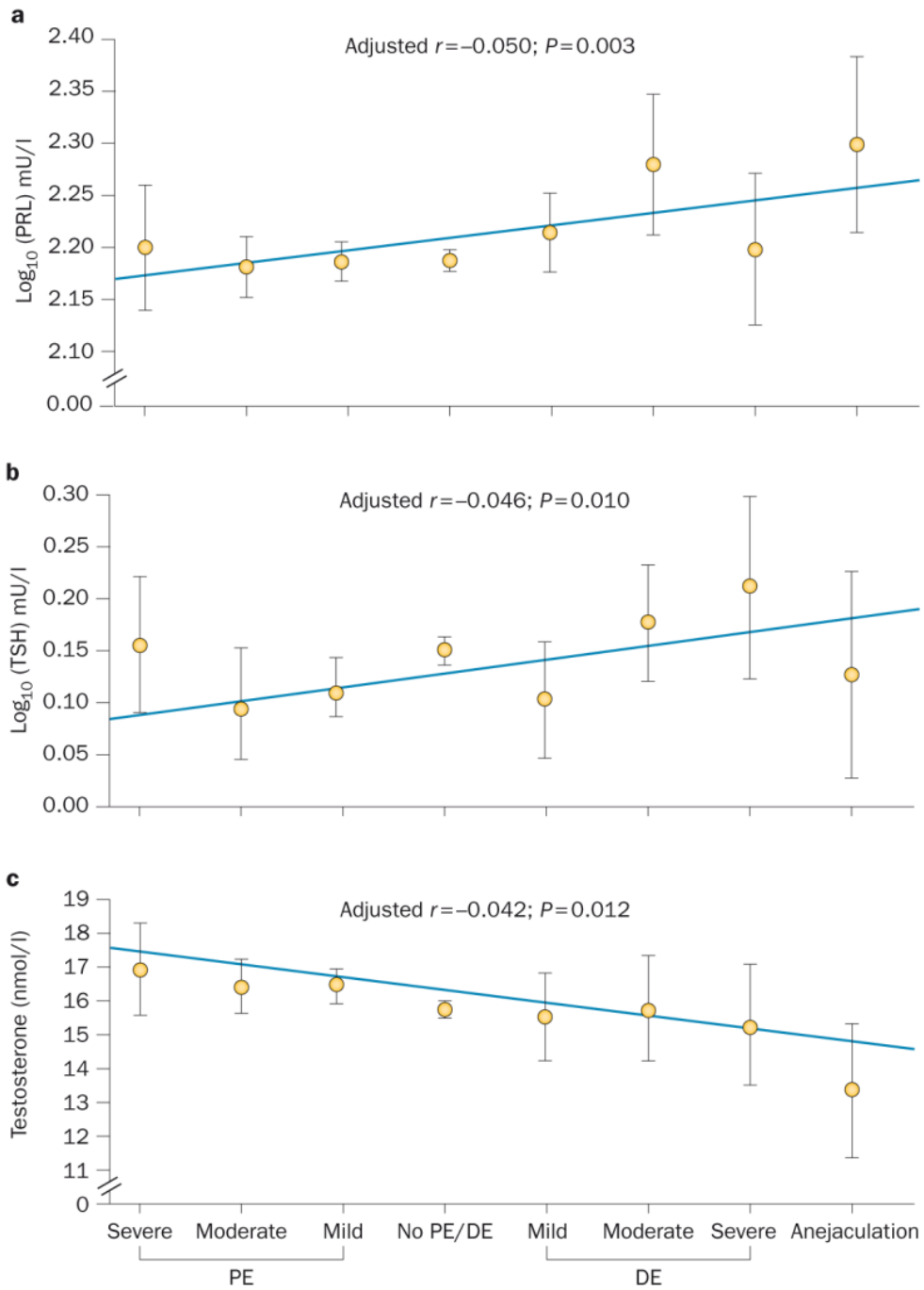
Hazard ratio for premature ejaculation according to the hormonal milieu in 1962 subjects with sexual dysfunction (w/o hyperprolactinemia and medication) at the University of Florence, Italy



Adjusted for:

- Age
- Smooking and drinking behaviours
- ED severity
- Anxiety and depressive symptoms
- Psychiatric disease

Corona et al., Nat Rev Urol. 2012;9:508



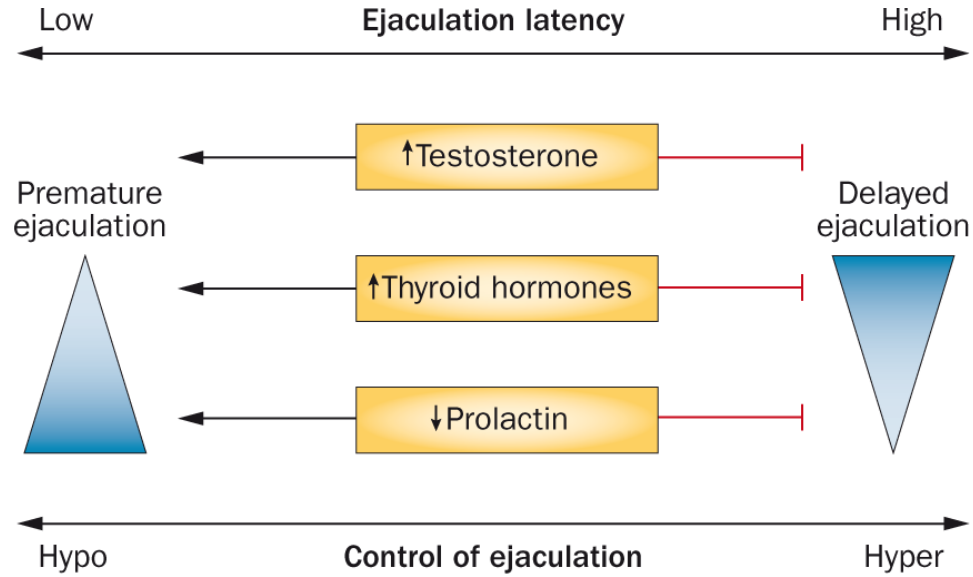


Figure 4 | The hormonal regulation of the ejaculatory continuum.

Corona et al., Nat Rev Urol. 2012;9:508

Come possiamo spiegare queste associazioni?

Research Report

Behavioral effects of pubertal anabolic androgenic steroid exposure in male rats with low serotonin

Yonas B. Keleta[a], Augustus R. Lumia[b], George M. Anderson[c], Marilyn Y. McGinnis[a,*]

[a]Department of Biology, University of Texas at San Antonio, San Antonio, 6900 N. Loop 1604 West, San Antonio, TX 78249, USA
[b]Texas State University, Department of Psychology, San Marcos, TX 78666, USA
[c]Child Study Center, Yale University, School of Medicine, New Haven, CT, USA

Chronic Testosterone exposure significantly ($p<0.05$) reduces 5-HT levels in striatum and 5-HIAA in both hypothalamus and striatum in a rat model

Keleta et al. Int J Androl. 2007;1132:1029

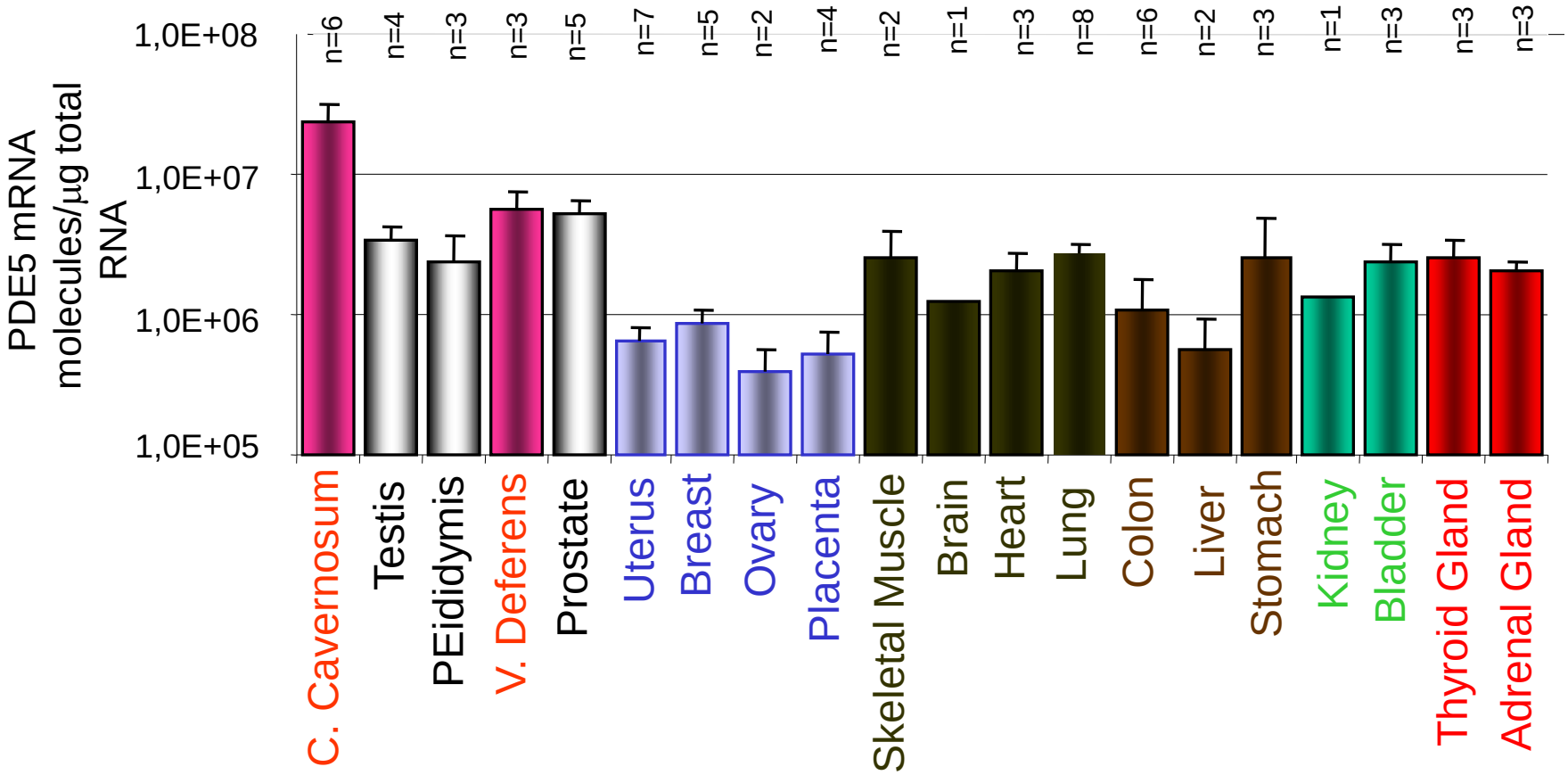
0013-7227/04/$15.00/0
Printed in U.S.A.

Endocrinology 145(5):2253–2263

doi: 10.1210/en.2003-1699

Androgens Regulate Phosphodiesterase Type 5 Expression and Functional Activity in Corpora Cavernosa

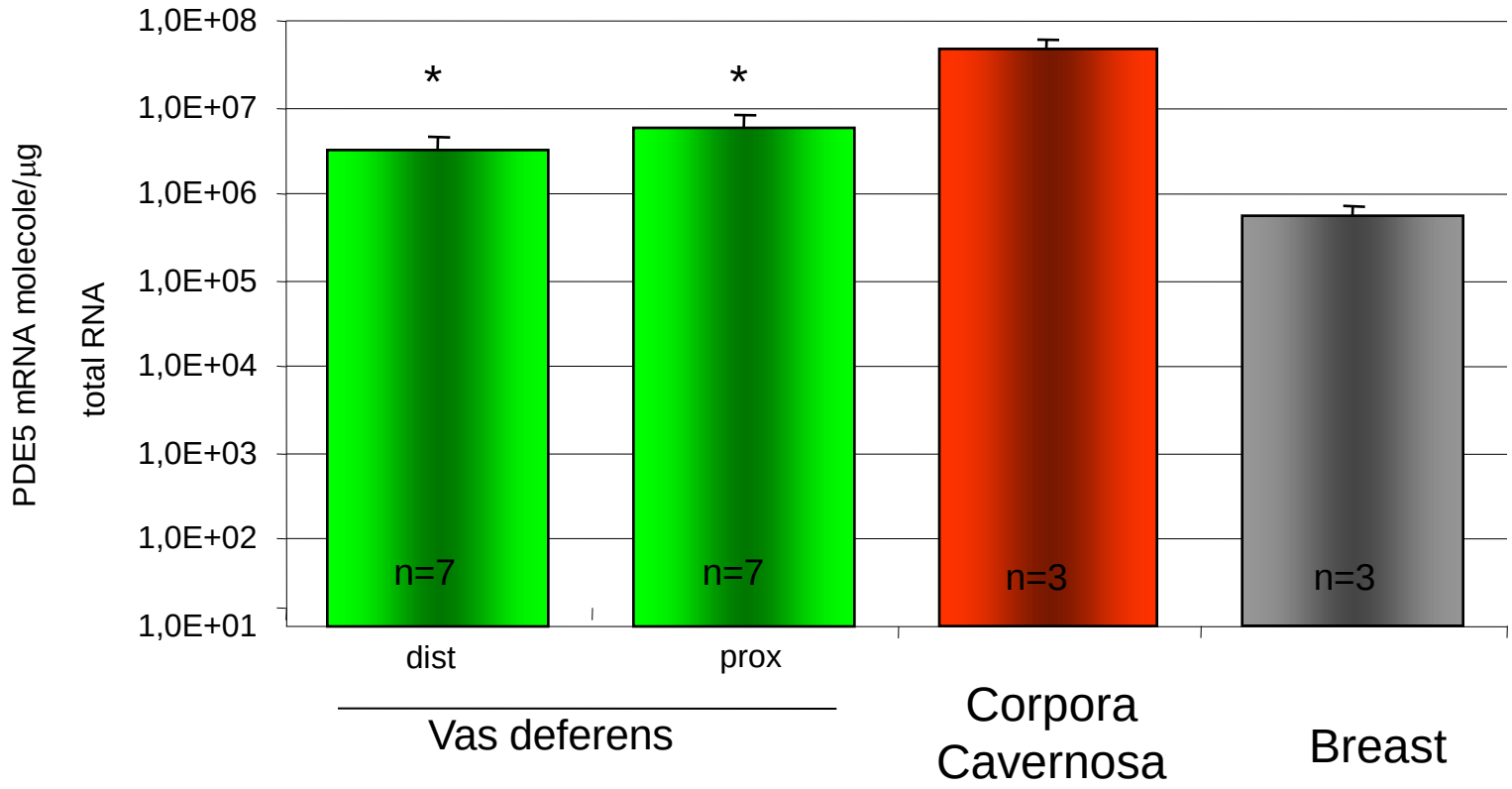
ANNAMARIA MORELLI, SANDRA FILIPPI, ROSA MANCINA, MICHAELA LUCONI, LINDA VIGNOZZI, MIRCA MARINI, CLAUDIO ORLANDO, GABRIELLA BARBARA VANNELLI, ANTONIO AVERSA, ALESSANDRO NATALI, GIANNI FORTI, MAURO GIORGI, EMMANUELE A. JANNINI, FABRIZIO LEDDA, AND MARIO MAGGI



Molecular Human Reproduction Vol.11, No.2 pp. 107–115, 2005
Advance Access publication January 7, 2005 doi:10.1093/molehr/gah143

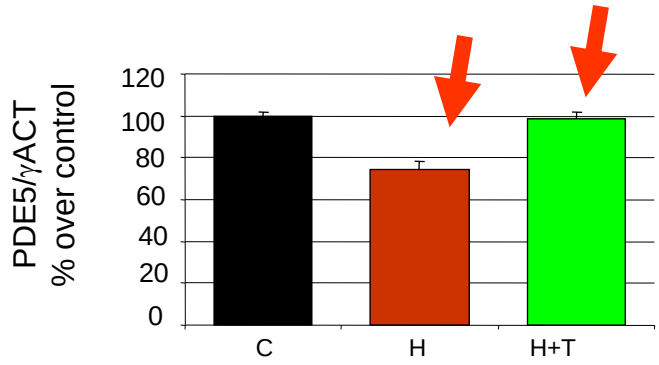
Expression and functional activity of phosphodiesterase type 5 in human and rabbit vas deferens

R.Mancina[1]*, S.Filippi[2]*, M.Marini[3], A.Morelli[1], L.Vignozzi[1], A.Salonia[5], F.Montorsi[5], N.Mondaini[4], G.B.Vannelli[3], S.Donati[1], F.Lotti[1], G.Forti[1] and M.Maggi[1,6]



Testosterone regulates PDE5 gene expression …

…and enzyme activity



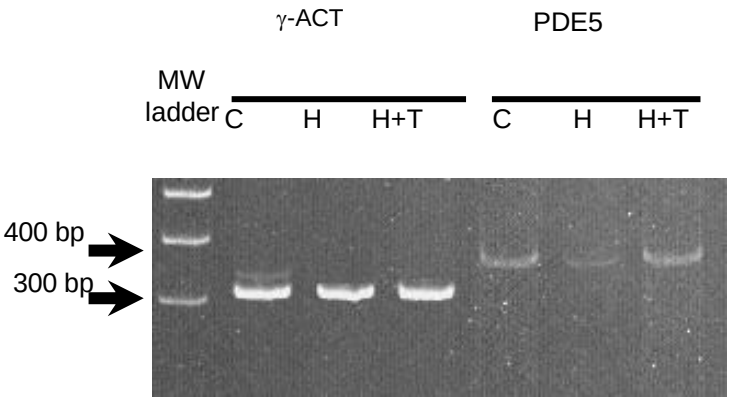
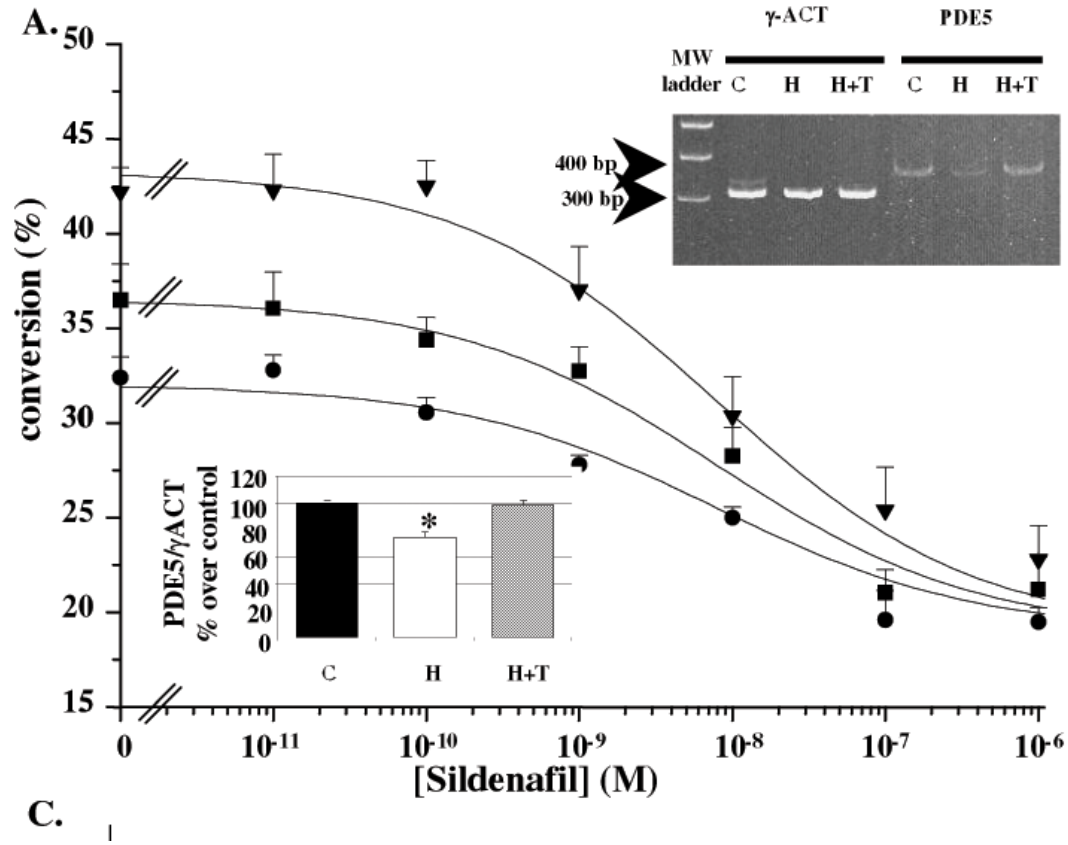


Figure 4



Mancina et al. Mol. Hum Reprod. 2005;11:107

CONCLUSIONS

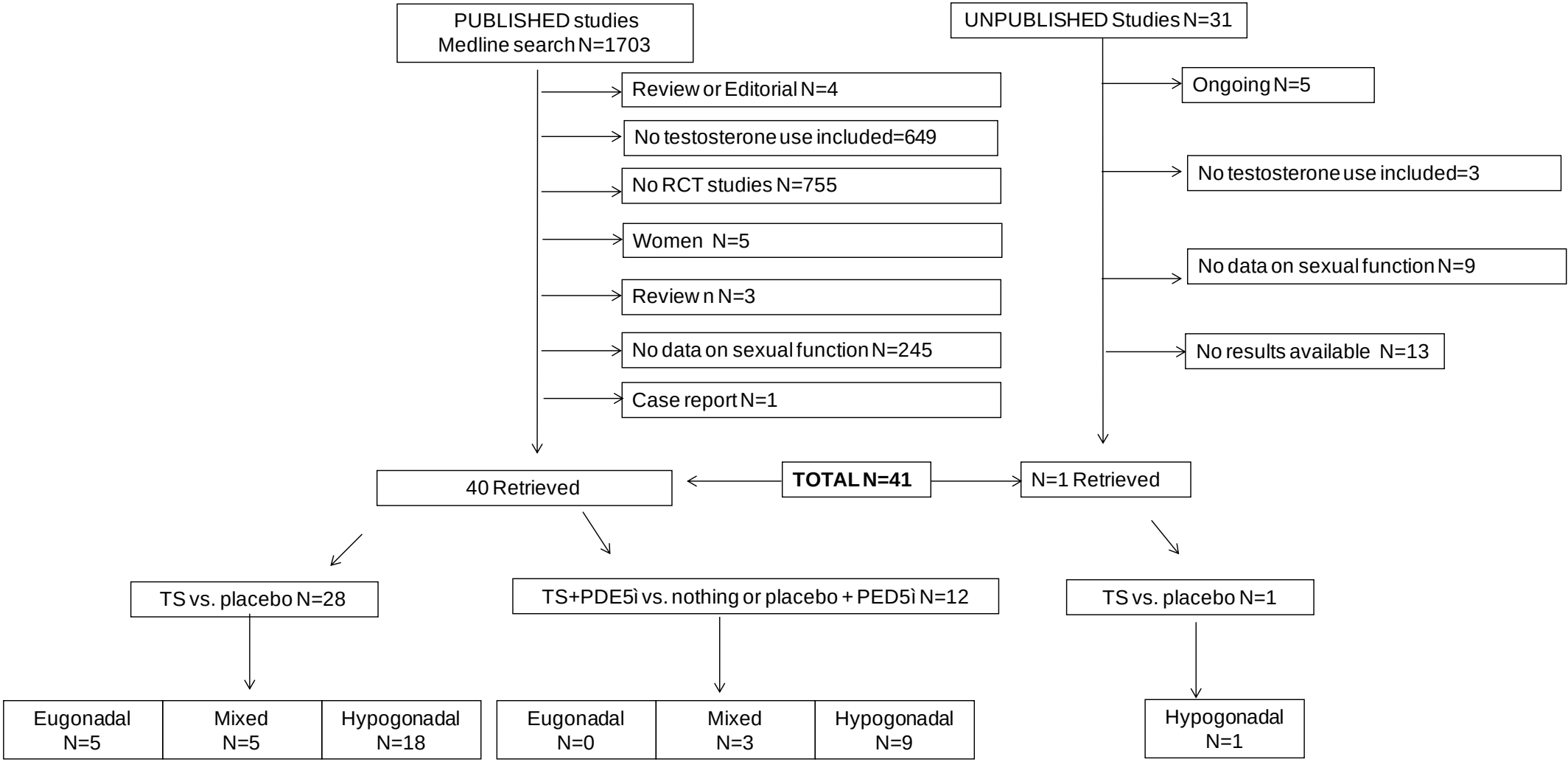
Lower Testosterone → Lower PDE5 expression

↓

Lower cGMP degradation

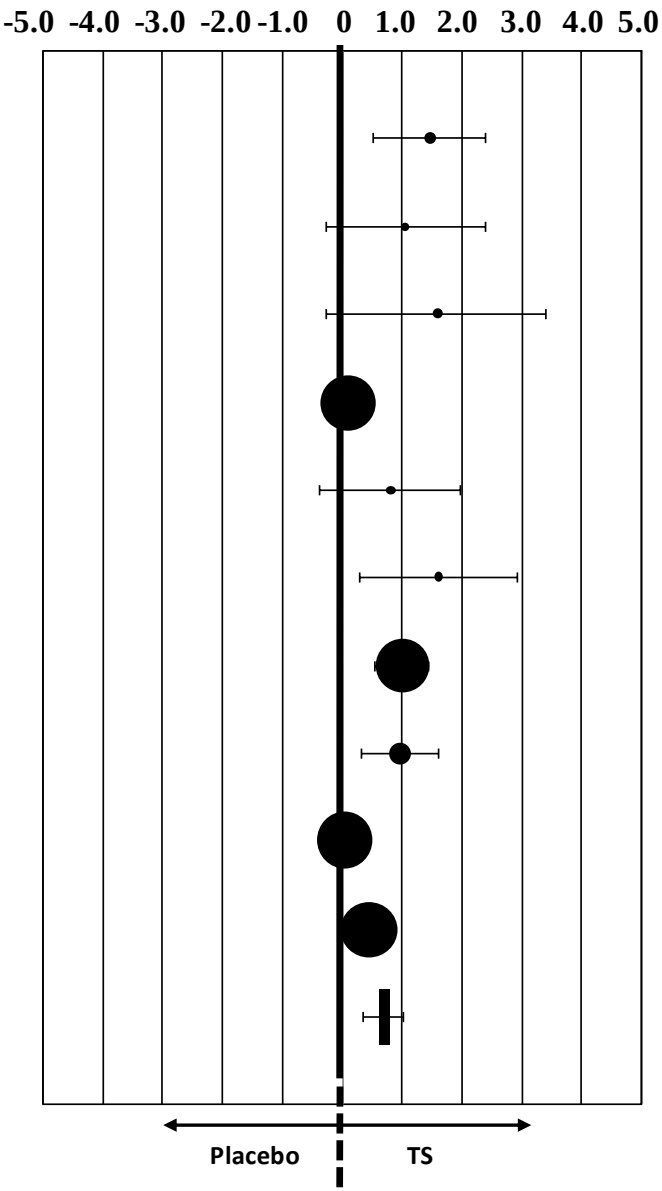
↙

Lower male genitalia tract contractility → Higher ejaculation timing



Corona et al., 2013 submitted

Orgasm component standardized



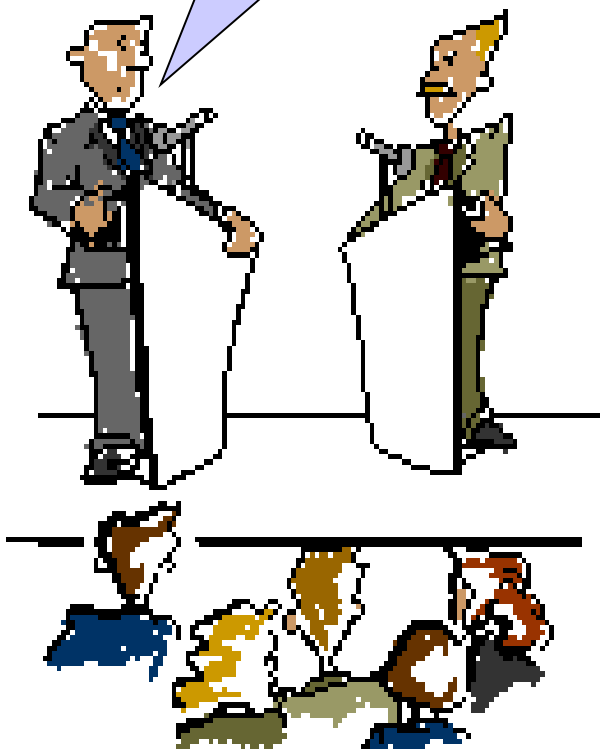
Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
Skakkebaek et al., 1981	1,46	0,52	2,40	0,00
Davidson et al., 1979	1,06	-0,26	2,39	0,12
Kwan et al., 1983	1,58	-0,26	3,41	0,09
Gluud et al., 1988	0,11	-0,27	0,49	0,58
Carani et al., 1990	0,79	-0,38	1,97	0,19
Schiavi et al., 1997	1,62	0,30	2,94	0,02
Cavallini et al., 2004	1,00	0,54	1,46	0,00
Chaing et al., 2009	0,97	0,31	1,62	0,00
Jones et al., 2011	0,05	-0,24	0,34	0,74
Hackett et al., 2013	0,42	0,13	0,72	0,00
Overall	0,68	0,34	1,02	0,00

Corona et al., 2013 submitted


Non ti preoccupare sono cose che capitano, specie le prime volte…
Provate ad aumentare la dose a 250 mg ogni 3 settimane


Dottore ora si che va bene!!!
Ho organizzato una uscitina con casa libera… non lo dica alla mamma…

Caro Danilo ma con il GH che si fa a questo punto?



Cosa suggerite?

1. **Proseguire con la stessa dose di GH**
2. **Aumentare la dose alla terapia dell'adulto**
3. **Sospendere orami è alto quanto i genitori**
4. **Rivalutiamo il deficit di GH per vedere se è guarito**
5. **Non saprei**

DEFICIT DI GH
"Fase di transizione"

Periodo di tempo compreso tra il raggiungimento della statura finale e l'età del giovane adulto, durante il quale si raggiunge la "stabilizzazione" di vari processi maturativi metabolici ed endocrini (massa ossea e muscolare, composizione corporea, sistema cardiovascolare, ecc..). Tale periodo si prolunga per circa 6-7 anni (soggetti di età compresa tra i 16 e i 25 anni).

↓

I soggetti GHD in fase di transizione, se non trattati, presentano alterazioni nella regolazione di questi processi

Cook et al., Pituitary 2012; 15:301

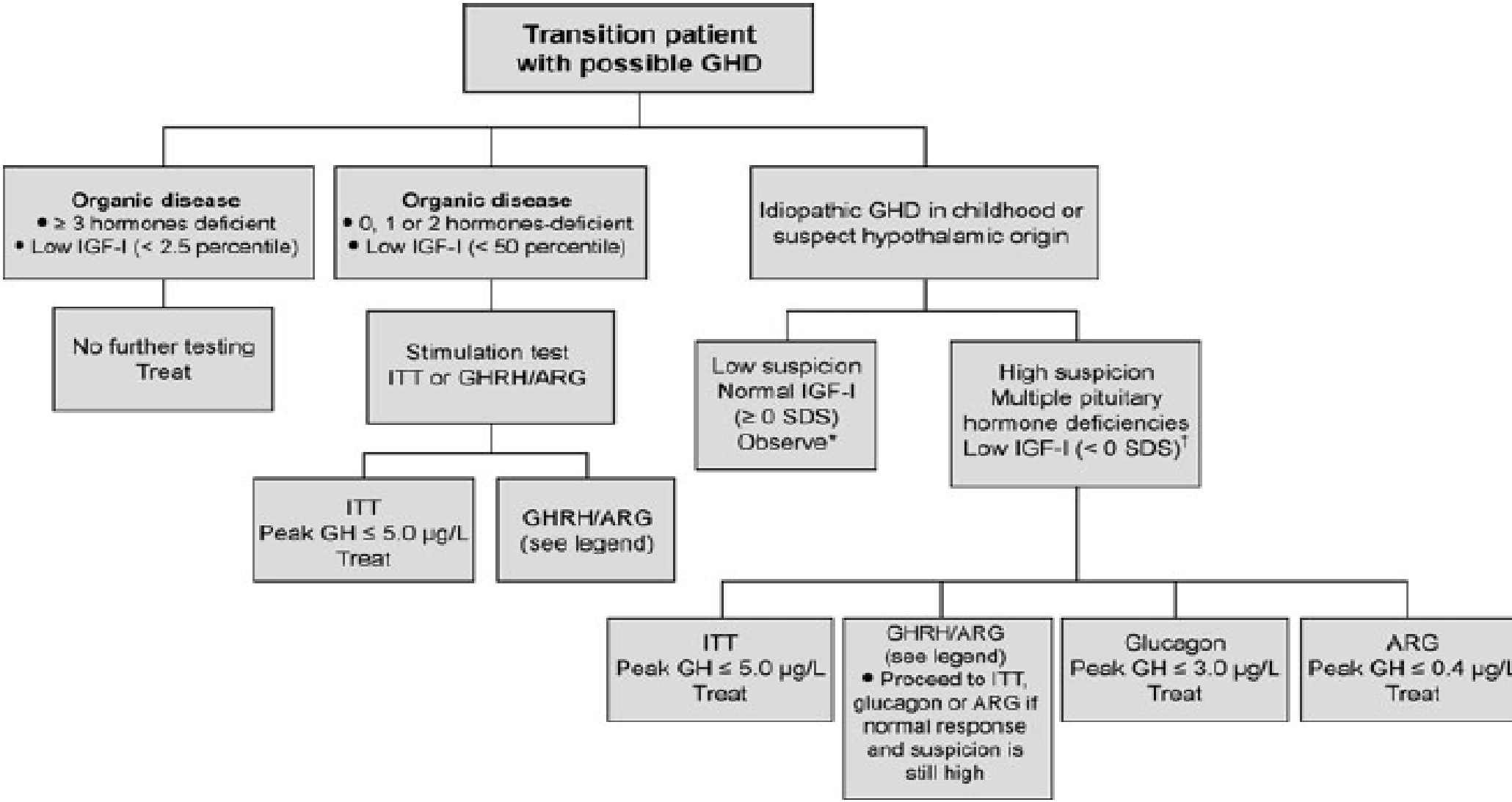
GHD nella fase di transizione

"RETESTING"

1. Dopo il raggiungimento della statura finale devono essere identificati i pazienti che devono continuare la terapia con GH.
2. Il deficit si conferma in circa il 30% dei pazienti GHD trattati durante l'infanzia.

Cook et al., Pituitary 2012; 15:301

Flowchart re-testing GHD fase di transizione



Cook et al., Pituitary 2012; 15:301

SPECIAL FEATURE

Clinical Practice Guideline

Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline

Mark E. Molitch, David R. Clemmons, Saul Malozowski, George R. Merriam, and Mary Lee Vance

Recommendation 2.3

We recommend that because of the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-I level at least 1 month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing. (1/⊕⊕⊕◯)

Molitch et al., J Clin Endocrinol Metab 2011;96:1587

Cutt-off per la definizione di GHD dopo stimolo nella fase di transizione

Society	Year	ITT (ng/mL)	GHRH/Arginine (ng/mL)[a]	Arginine (ng/mL)	Glucagon (ng/mL)
GRS [59]	1998	<3	None given	None given	None given
AACE [60]	2003	<5	<5	<5	<5
Endocrine Society [29]	2006	<5.1	<4.1	<1.4	None given
GRS [61]	2007	<3	<4, 8, 11 (BMI dependent)	Not approved	<3
AACE [12]	2009	<5	<4, 8, 11 (BMI dependent)	<0.45	<3
Endocrine Society [13]	2011	<5	<4.1	None given	None given

AACE American Association of Clinical Endocrinologists, *BMI* body mass index, *GRS* The Growth Hormone Research Society, *ITT* insulin tolerance test

[a] Not widely used in the US; for childhood-onset growth hormone deficiency, the cutoff range for the GHRH/arginine test is 15.1–20.3 mcg/L [62, 63]

Cook et al., Pituitary 2012; 15:301

Terapia deficit GH durante la fase di transizione

- Subito prima della pubertà la posologia può essere aggiustata alle dosi approvate di 25-100 μg/Kg/die
- Durante la pubertà la posologia può essere proseguita all'equivalente di 0,7 mg/Kg/settimana
- All'inizio della fase di transizione si consiglia di proseguire con 0,8-1 mg/die

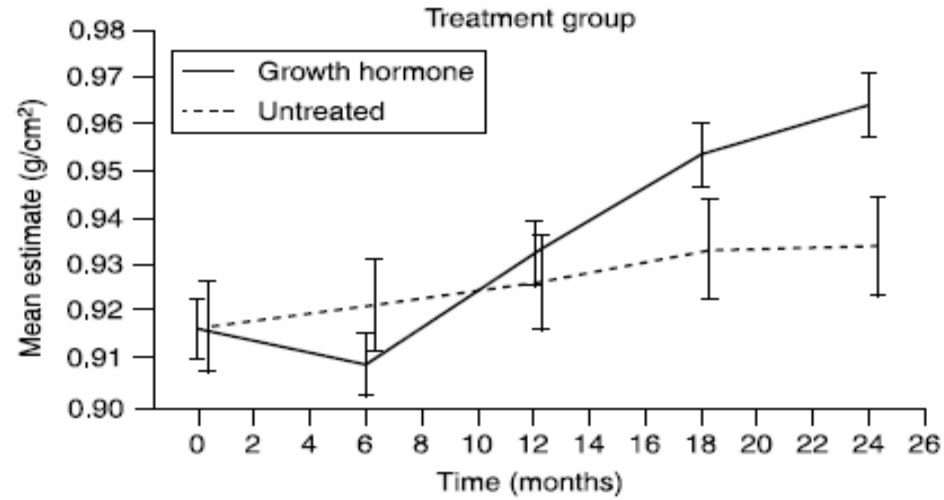
Come per l'adulto durante la fase di transizione il monitoraggio della terapia si avvale del dosaggio dell' IGF1 i cui valori devono essere compresi nel range di normalità e non superare il limite superiore della norma (0SD <IGF1> +2SD)

Cook et al., Pituitary 2012; 15:301

Terapia deficit GH durante la fase di transizione

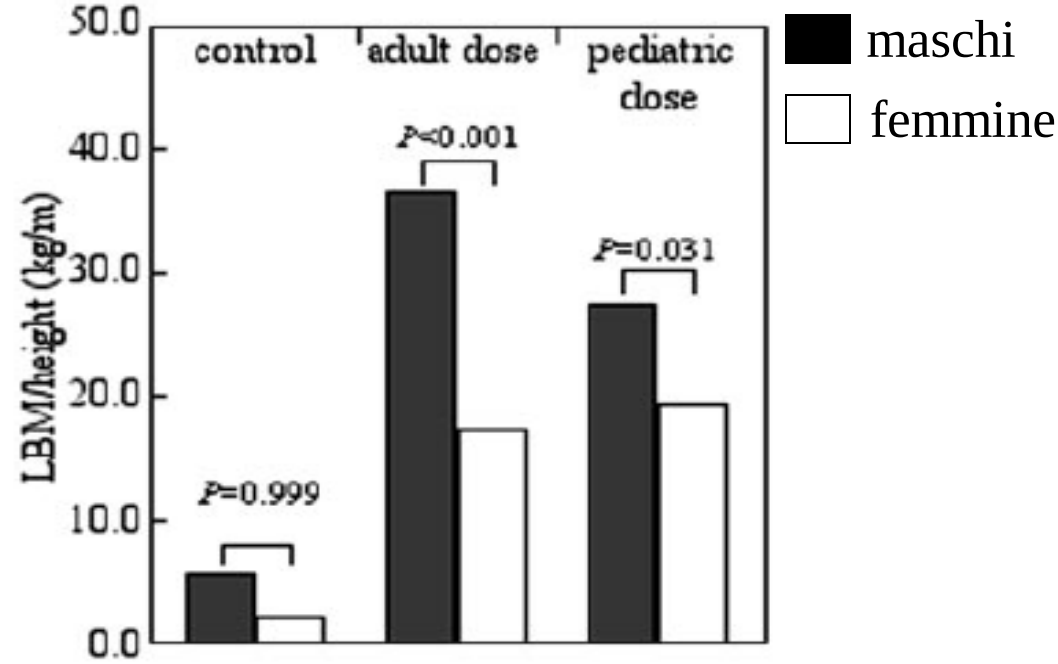
Incremento della massa ossea

Conway et al., Eur J Endocrinol. 2009;160: 899



Dose di GH condiziona modifiche della composizione corporea

Attanasio et al., J Endocrinol and Metab. 2004;89:48579



SPECIAL FEATURE

Clinical Practice Guideline

Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline

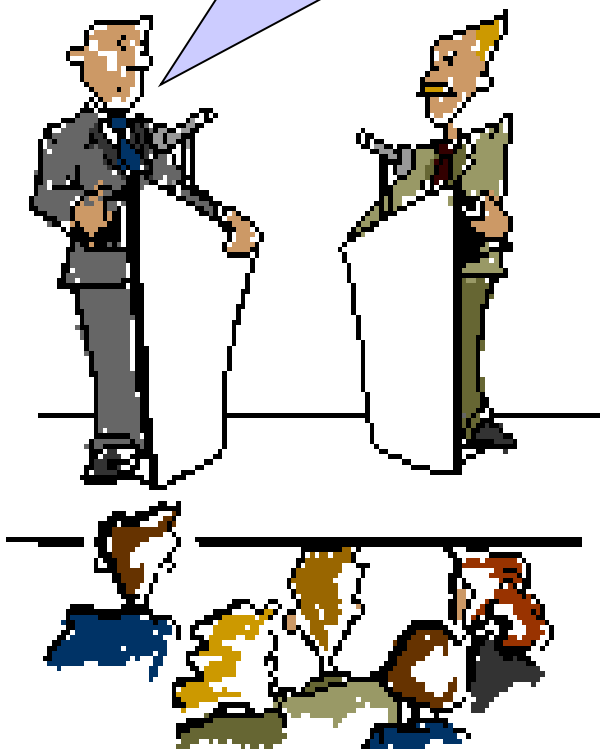
Mark E. Molitch, David R. Clemmons, Saul Malozowski, George R. Merriam, and Mary Lee Vance

Recommendation 3.3

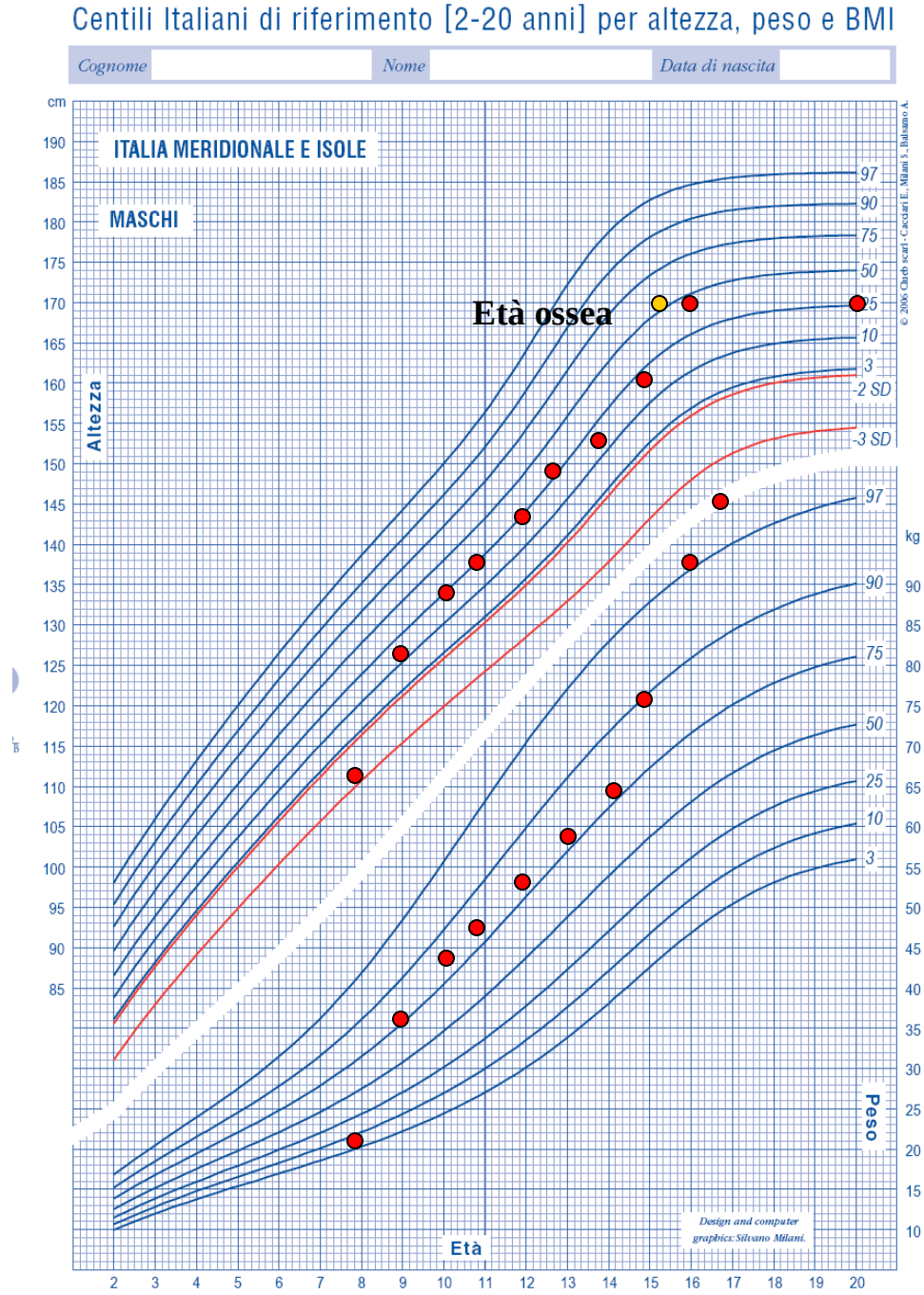
We recommend after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period (1/⊕⊕◯◯)

Molitch et al., J Clin Endocrinol Metab 2011;96:1587

Caro Danilo questo paziente ci sta creando molti problemi…
Hai visto come è variato il peso?
Cosa ci puoi dire a riguardo?

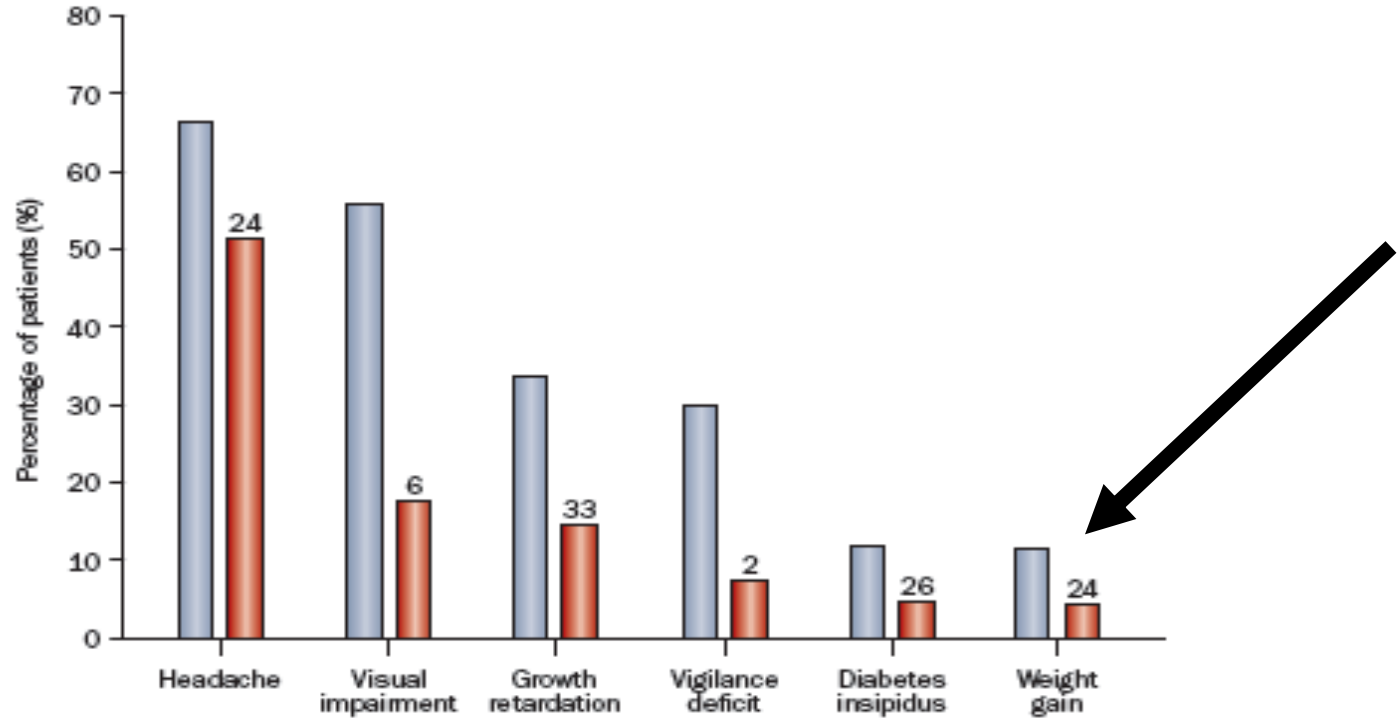


17 anni



Altezza bersaglio 173

Obesità in pazienti con Craniofaringioma alla diagnosi: 0.13 casi per 100,000 soggetti/anno

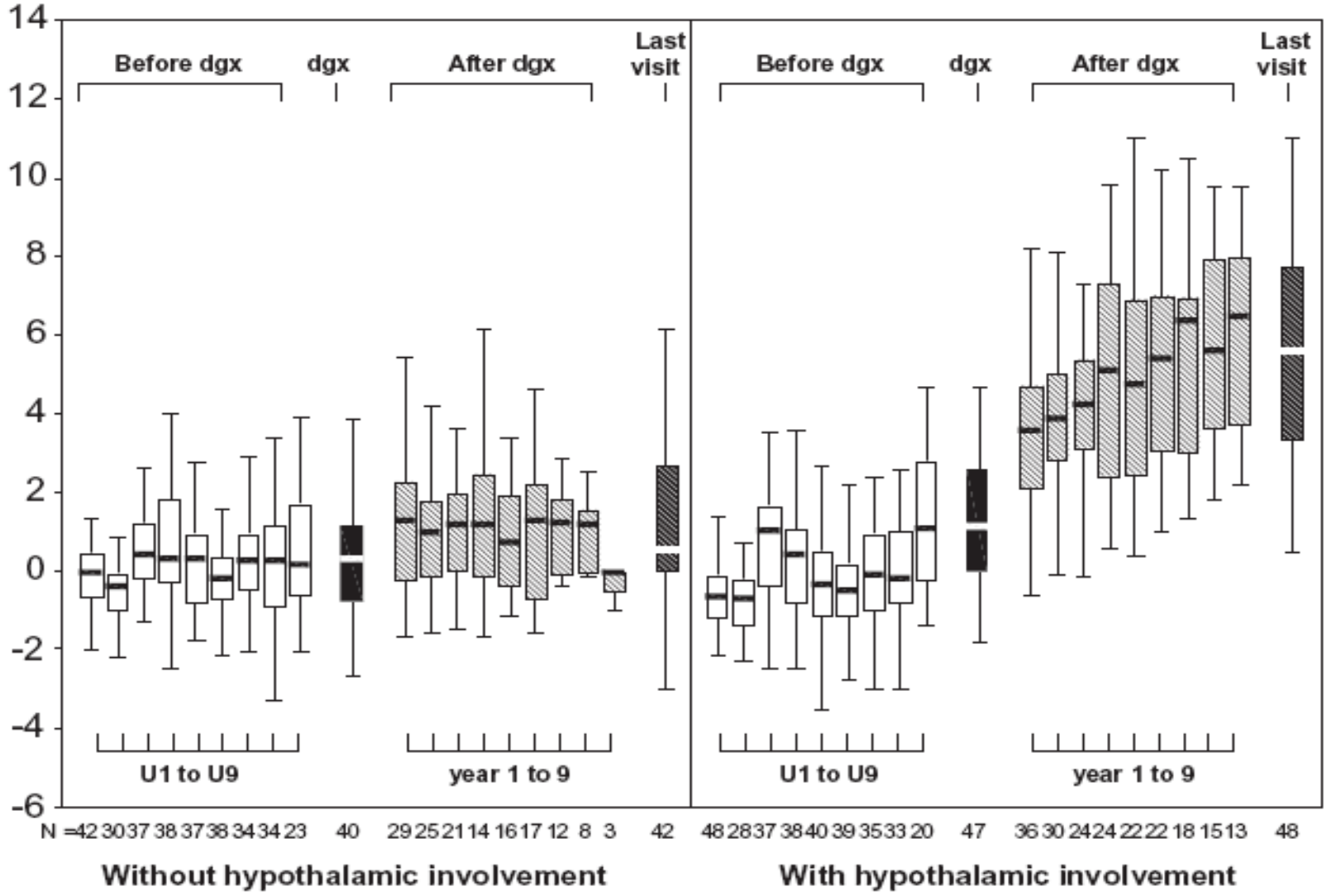


Percentuale di paz. che presentavano le manifestazioni prima della diagnosi

Percentuale di paz. che presentavano il sintomo come prima manifestazione

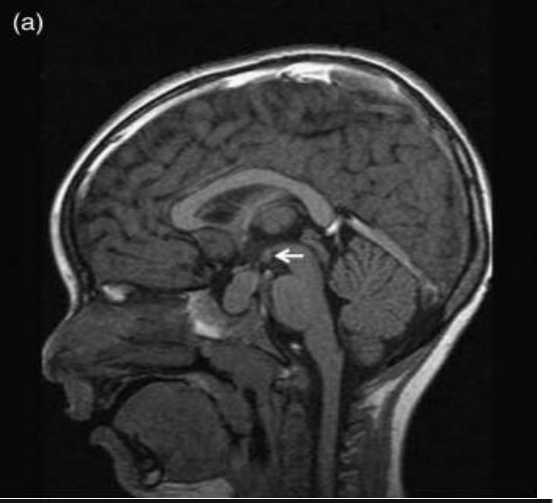
Mueller et al. Nat Rev Endocrinol 2010; 6:609

CRANIOFARINGIOMI NEL BAMBINO/ADOLESCENTE: EFFETTO SUL PESO

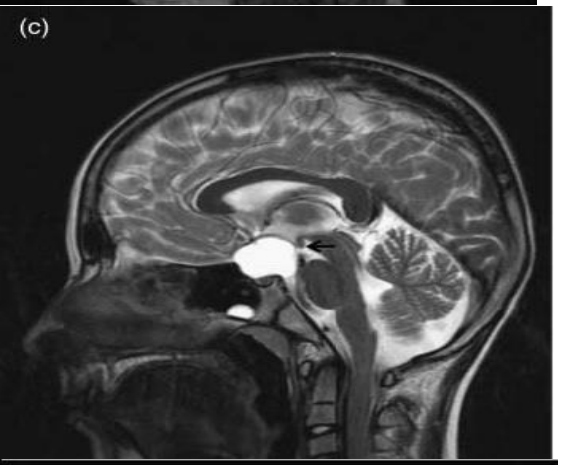


Bereket et al., Ob Rev 2012; 13:780

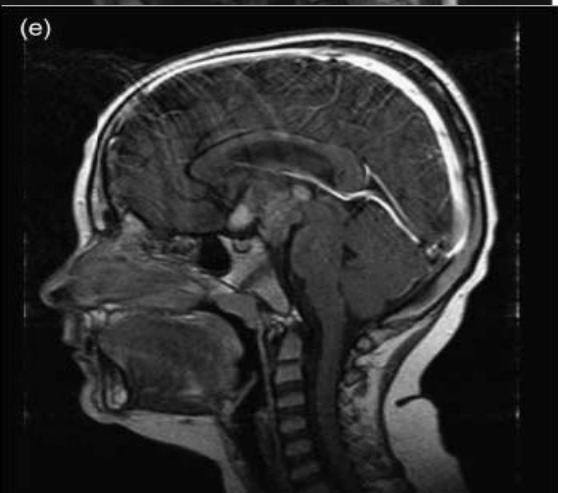
ESTENSIONE LESIONE: FATTORE DI RISCHIO PRINCIPALE SVILUPPO OBESITA'



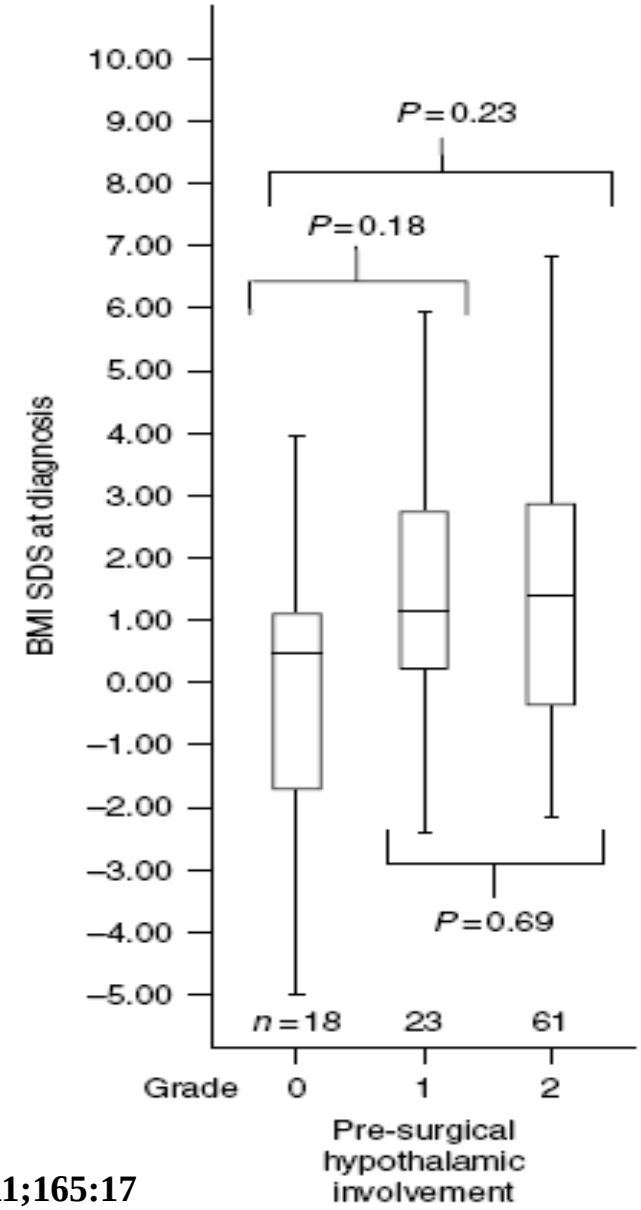
GRAD0 0:
NO COINVOLGIMENTO/LESIONE IPOTALAMO



GRADO 1:
COINVOLGIMENTO/LESIONE IPOTALAMO ANTERIORE SENZA COINVOLGERE I CORPI MAMMILLARI E L'AREA IPOTALAMICA INTORNO AD ESSI

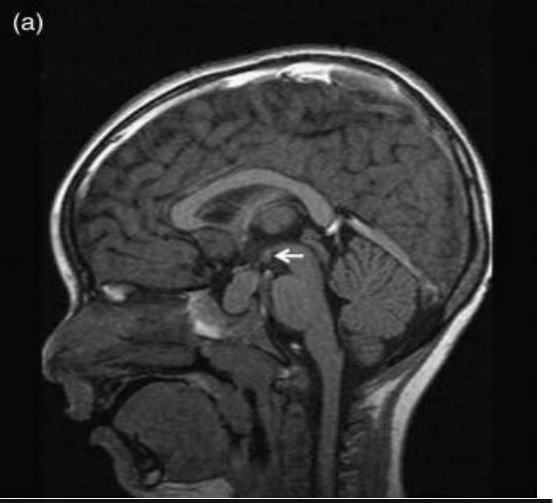


GRAD0 2:
COINVOLGIMENTO/LESIONE IPOTALAMO ANTERIORE E POSTERIORE, ES. COIVOLGIMENTO CORPI MAMMILLARI O AREE IPOTALAMICHE AL DI SOPRA DI ESSI



Mueller HL et al Eur J Endocrinol 2011;165:17

ESTENSIONE LESIONE: FATTORE DI RISCHIO PRINCIPALE SVILUPPO OBESITA'



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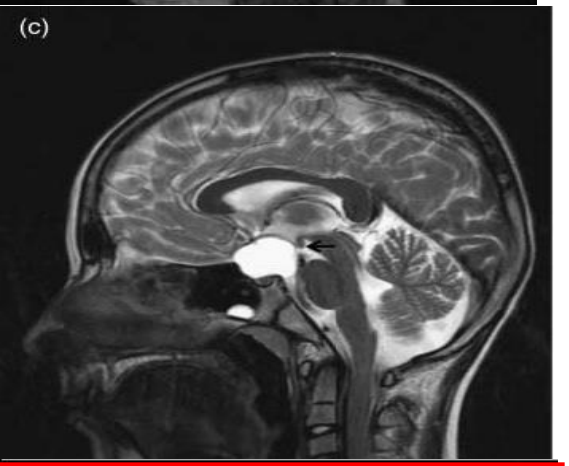
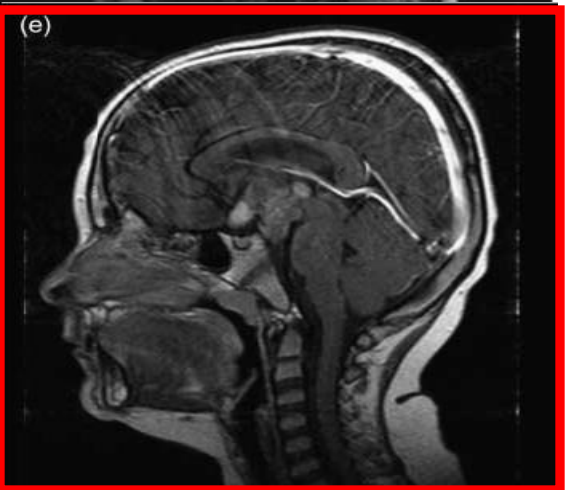
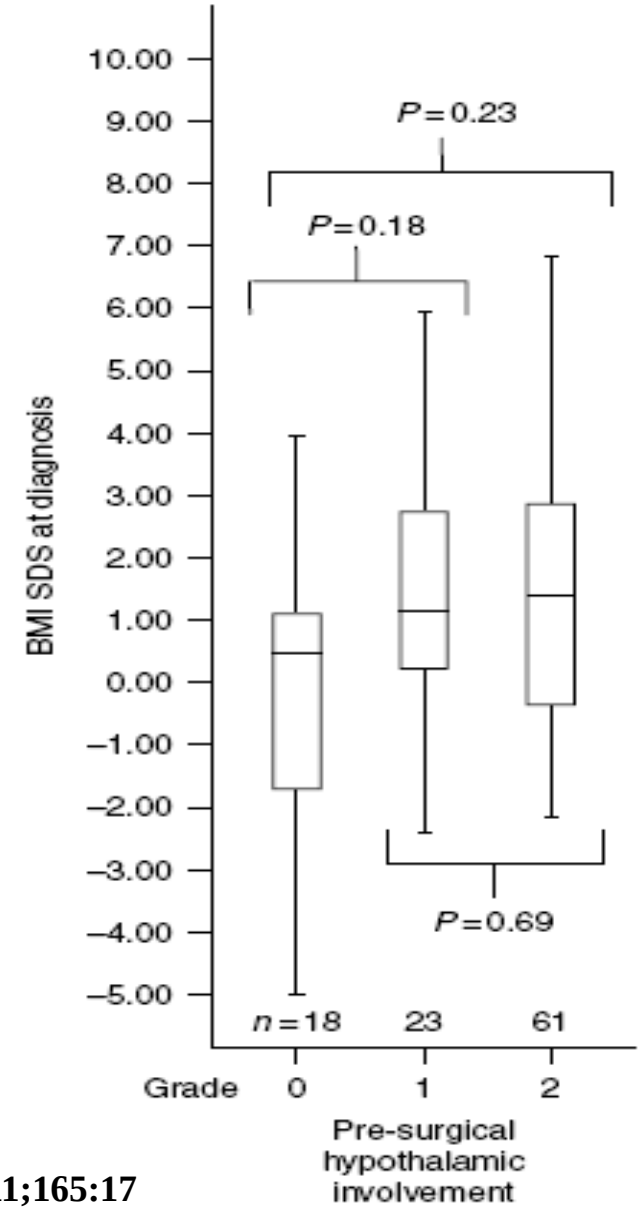
NO COINVOLGIMENTO/LESIONE IPOTALAMO



GRADO 1:
COINVOLGIMENTO/LESIONE IPOTALAMO ANTERIORE SENZA COINVOLGERE I CORPI MAMMILLARI E L'AREA IPOTALAMICA INTORNO AD ESSI

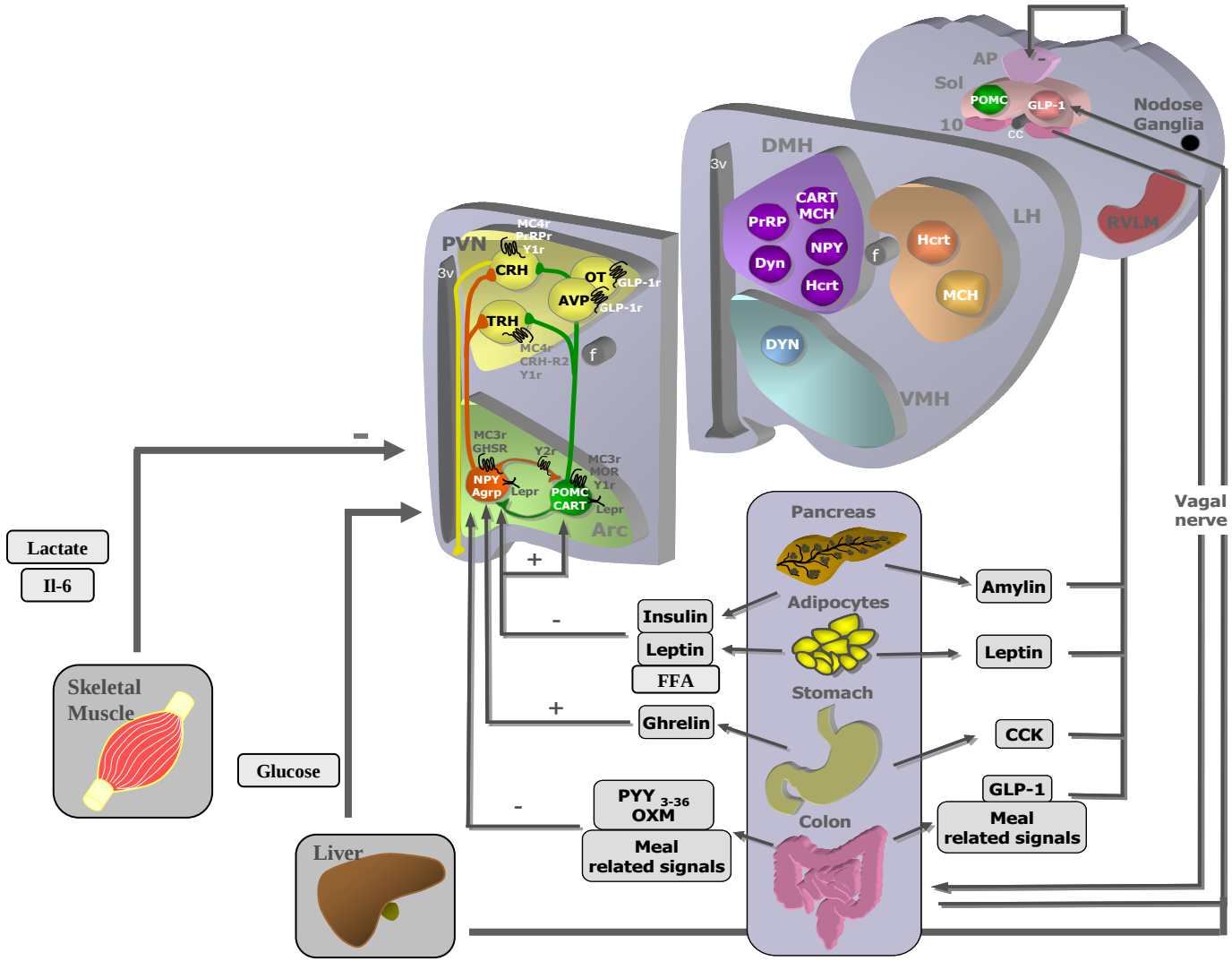


GRAD0 2:
COINVOLGIMENTO/LESIONE IPOTALAMO ANTERIORE E POSTERIORE, ES. COIVOLGIMENTO CORPI MAMMILLARI O AREE IPOTALAMICHE AL DI SOPRA DI ESSI



Mueller HL et al Eur J Endocrinol 2011;165:17

Ruolo dell'ipotalamo nel bilancio energetico



Bagnol Curr Opin Drug Discov Devel. 2004;7:665

L'IPERFAGIA NON E' SEMPRE PRESENTE. POSSIBILE AUMENTO PONDERALE IN PRESENZA DI RIDOTTO INTROITO CALORICO

Group	BMI in (kg/m²)	BMI SDS	Age (yr)	Total daily energy-intake (kcal)[a]	Fat (% of total energy intake)[b]	Carbohydrates (% of total energy intake)	Proteins (% of total energy intake)	Fibers (g/d)	n
Intrasellar CP	21.6 ± 3.2	2.8 ± 2.3	10.8 ± 2.4	1916 ± 677	35.0 ± 5.3	50.9 ± 5	15.3 ± 2.6	17.6 ± 5.0	12
Hypothalamic CP	26.3 ± 7.4	4.3 ± 4.4	12.7 ± 2.9	2075 ± 877	33.0 ± 6.3	53.6 ± 6.5	13.9 ± 2.5	18.5 ± 9.9	15
Controls	18.5 ± 3.2	0.6 ± 1.7	11.3 ± 2.7	2476 ± 815	37.9 ± 5.7	51.6 ± 6.1	14.5 ± 2.2	19.8 ± 7.7	1027

The factor group (intrasellar CP, hypothalamic CP, controls) significantly influenced total daily energy intake ([a] $P = 0.002$) and the percentage of fat intake ([b] $P = 0.0007$). Values are the mean ± SD.

Harz et al. J Clin Endocrinol & Metab 2003;88:5227

I PAZIENTI CON CRANIOFARINGIOMA IPOTALAMICO HANNO GENERALMENTE UNA RIDOTTA ATTIVITA' FISICA

Group	n sex (m/f)	Age (yr)	BMI (kg/m^2)	BMI SDS[a]	Movement (cpm)		
					Total movement counts	Movement counts during leisure time	Movement counts at school/university/work[b]
Patients with CP in ambulatory setting	9 (5/4)	19.2 ± 3.9	28.1 ± 8.4	2.9 ± 3.0 (−0.3 to 8	228.1 ± 66.5[c]	345.3 ± 109.2	234.6 ± 56.4 (5)
Controls in ambulatory setting	11 (6/5)	18.5 ± 5.4	27.2 ± 7.8	2.7 ± 2.7 (−0.5 to 7.2)	281.7 ± 64.8	425.2 ± 143.6	383.9 ± 133.8 (9)
Patients with CP in clinical setting	10 (5/5)	13.7 ± 3.8	27.6 ± 5.1	4.2 ± 2.1 (1.5–8.6)	227.6 ± 50.9[d]	381.2 ± 106.5[e]	311.5 ± 108.4
Obese controls in clinical setting	15 (6/9)	14.1 ± 2.5	30.7 ± 4.4	5.2 ± 1.9 (2.1–8.3)	298.5 ± 81.4	545.6 ± 158.6	330.8 ± 117.2

CP patients had a lower total movement count per minute than did controls in th outpatient set ng ([c] $P = 0.08$) and a significantly lower average count than did obese controls in the clinical setting (total average: [d] $P = 0.0$; leisure ti e: [e] $P = 0.002$).

[a] Range is in *parentheses*.

[b] Number of subjects is in *parentheses*.

Harz et al. J Clin Endocrinol & Metab 2003;88:5227

E SOPRATTUTTO I PAZIENTI CON OBESITA' IPOTALAMICA PRESENTANO UNA RIDOTTA SPESA ENERGETICA

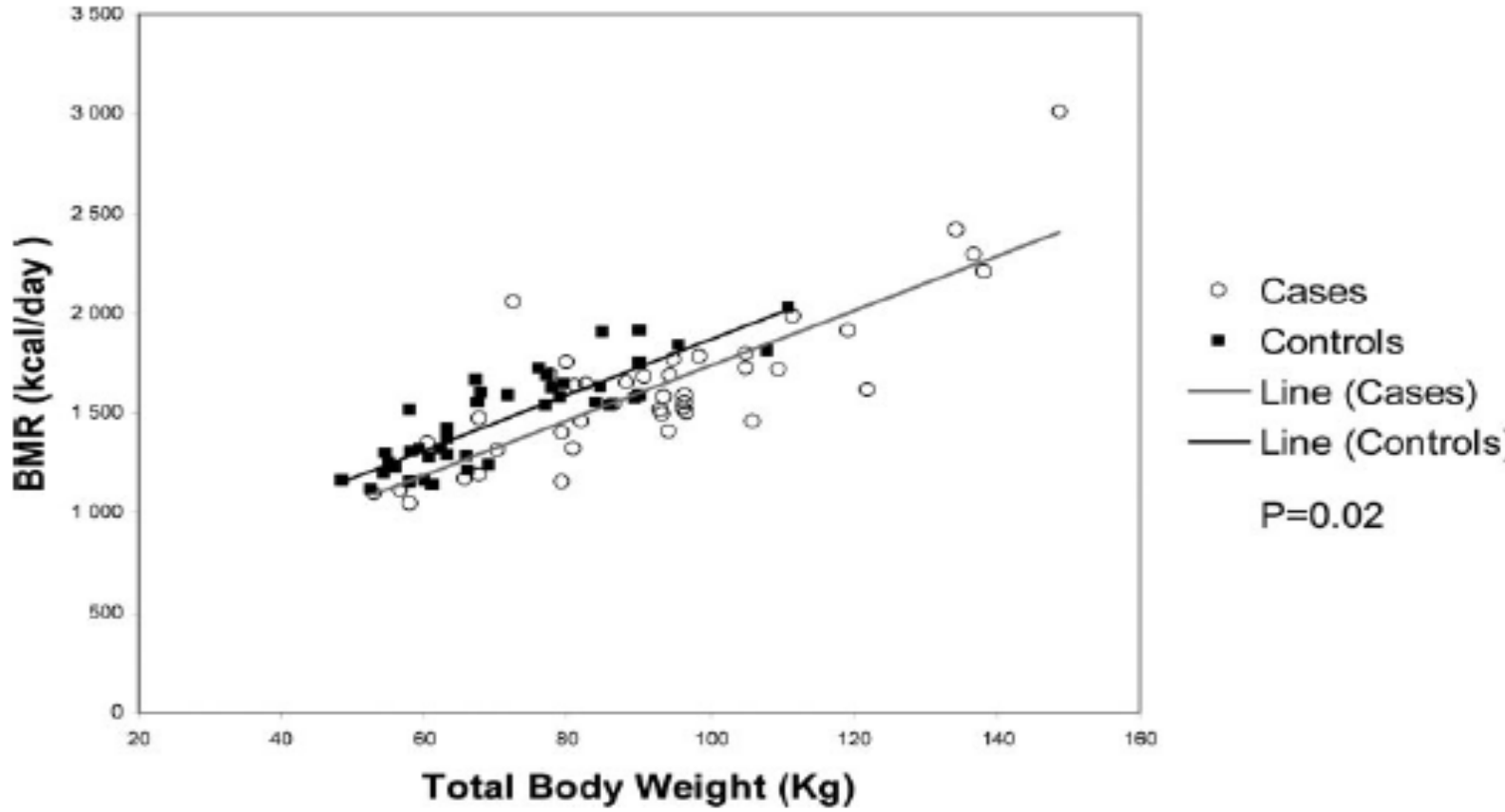
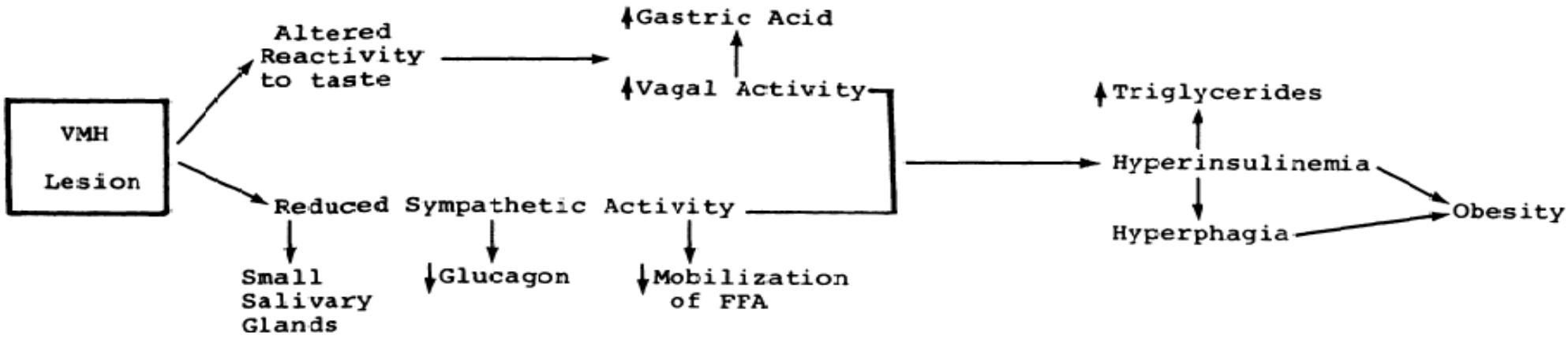


FIG. 1. Linear association between total body weight (kilograms) and BMR (kilocalories/day) among patients and controls. Patients had significantly lower BMR compared with controls after adjustment for sex and total body weight in linear regression analysis (mean difference, −90 kcal/24 h; 95% CI, −160 to −10; $P = 0.02$).

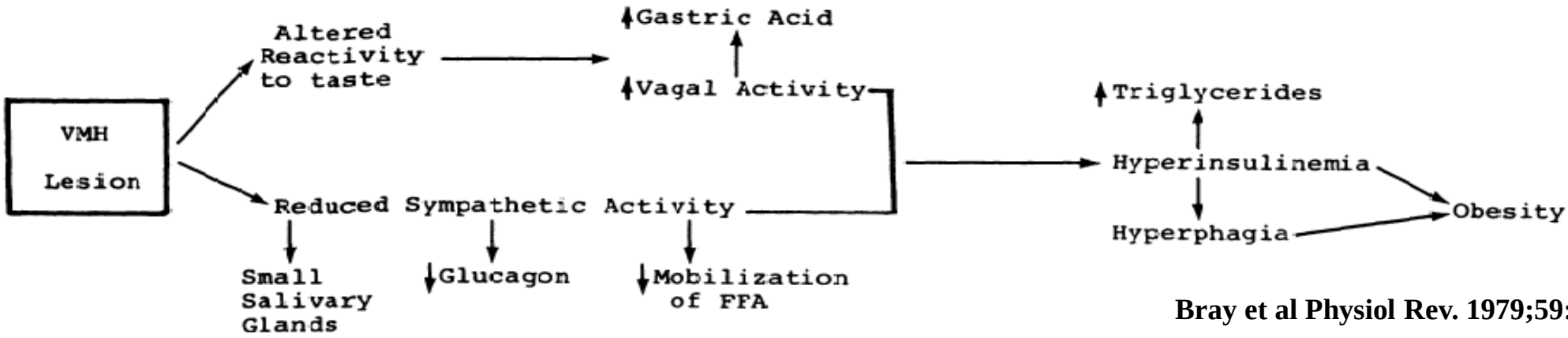
Kim RJ et al. Childs Nerv Syst; 2010; 26:913

LE IPOTESI AUTONOMICHE



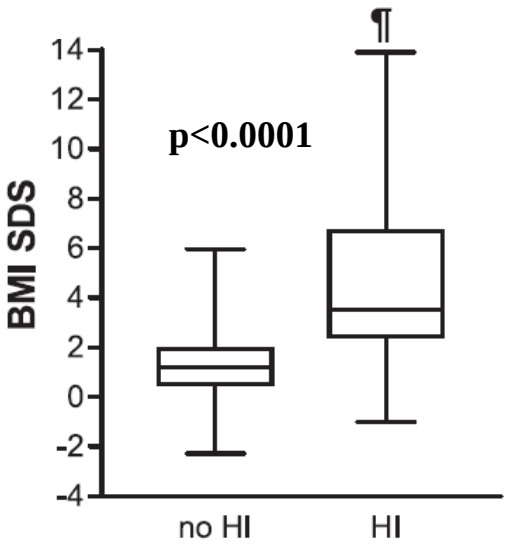
Bray et al Physiol Rev. 1979;59:719

LE IPOTESI AUTONOMICHE

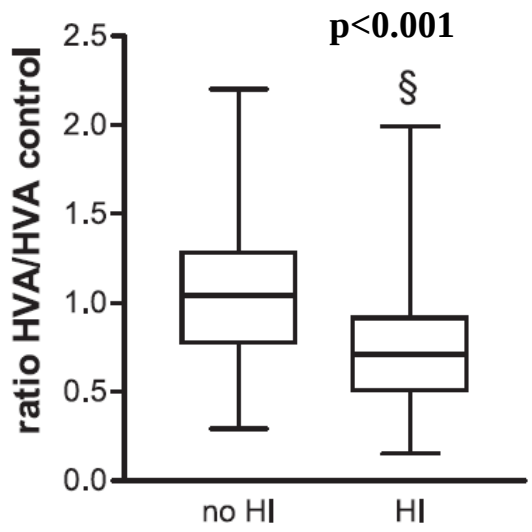


Bray et al Physiol Rev. 1979;59:719

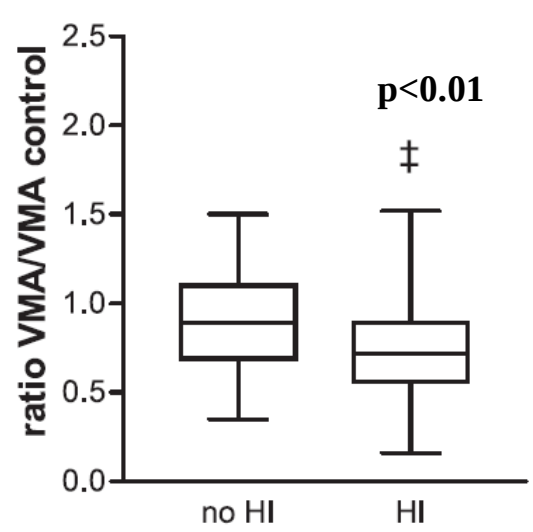
BMI



HVA



VMA



Roth et al Pediatr Res. 2007;61:496

TP MEDICA: Dextroamfetamina

ARTICLE

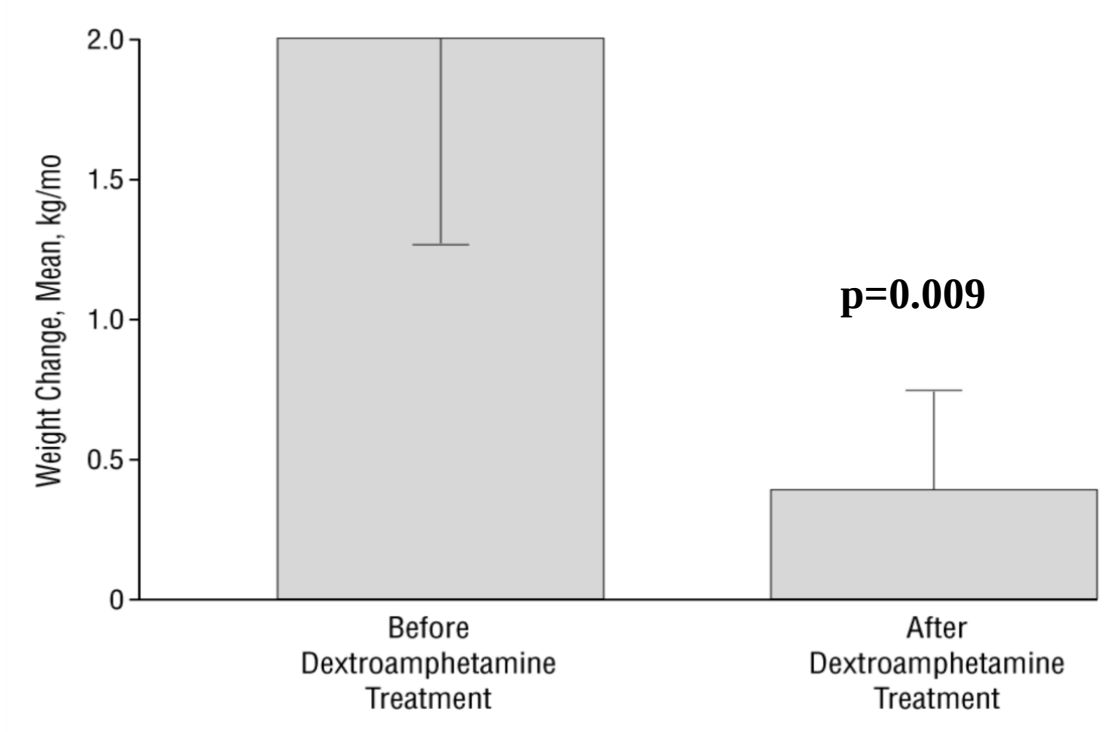
The Use of Dextroamphetamine to Treat Obesity and Hyperphagia in Children Treated for Craniopharyngioma

Patrick W. Mason, MD, PhD; Nicolas Krawiecki, MD; Lillian R. Meacham, MD

Patient No./ Age, y/Sex	Time From Surgery to Protocol, mo	Hypothalamic Scale*	Hormonal Deficiencies	Maximum Daily Dosage of Dextroamphetamine Sulfate/Time of Day Taken
1/8.5/M	9	Grade 2	Thyroid, adrenal, and diabetes insipidis	7.5 mg/AM 7.5 mg/noon 5 mg/PM
2/6.0/F	7	Grade 2	Thyroid, adrenal, and diabetes insipidis	7.5 mg/AM 5 mg/noon 2.5 mg/PM
3/9.8/F	14	Grade 2	Thyroid and growth hormone	5 mg/AM 5 mg/noon 2.5 mg/PM
4/9.0/M	10	Grade 2	Thyroid, adrenal, and diabetes insipidis	7.5 mg/AM 7.5 mg/noon 2.5 mg/PM
5/8.2/M	12	Grade 2	Thyroid, adrenal, and diabetes insipidis	7.5 mg/AM 5 mg/noon 2.5 mg/PM

Mason et al Arch Pediatr Adolesc Med. 2002;156:887

TP MEDICA: Dextroamfetamina



Mason et al Arch Pediatr Adolesc Med. 2002;156:887

0013-7227/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(6):2586–2592

doi: 10.1210/jc.2002-030003

Octreotide Therapy of Pediatric Hypothalamic Obesity: A Double-Blind, Placebo-Controlled Trial

ROBERT H. LUSTIG, PAMELA S. HINDS, KAREN RINGWALD-SMITH, ROBBIN K. CHRISTENSEN, SUE C. KASTE, RANDI E. SCHREIBER, SHESH N. RAI, SHELLY Y. LENSING, SHENGJIE WU, AND XIAOPING XIONG

Patients were randomized in a double-blind fashion to receive either octreotide (n=9) or placebo (n=9) sc for 6 months in an escalating dosage schedule,

- starting with injection volumes to deliver 5 mcg/kg/d (divided into three daily doses),
- bimonthly increments of 5mcg/kg/d to a maximum dosage of 15 mcg/kg/d

Lustig et al., J Clin Endocrinol & Metab 2003; 88:2586

Tp MEDICA: Octreotide

Parameter	Month 0		Month 6		Change		*P*
	Octreotide	Placebo	Octreotide	Placebo	Octreotide	Placebo	
Weight (kg)	98.5 ± 9.2	102.7 ± 6.8	100.0 ± 9.5	111.9 ± 7.5			
BMI (kg/m^2)	37.4 ± 2.5	36.8 ± 1.2	37.2 ± 2.5	39.0 ± 1.4	−0.2 ± 0.2	+2.2 ± 0.5	<0.001 *t* test
Caloric intake (kcal/d)	1994 ± 226	2342 ± 959	1818 ± 277	2325 ± 451	−200 ± 103	+102 ± 513	NS
Leptin (ng/ml)	45.3 ± 8.2	34.7 ± 4.7	32.8 ± 5.1	29.1 ± 4.4	−12.4 ± 6.9	−5.5 ± 4.6	NS
Fasting glucose (mM)	4.37 ± 0.25	3.91 ± 0.43	5.22 ± 0.37	3.98 ± 0.23	+0.85 ± 0.29	+0.07 ± 0.28	0.076 *t* test 0.022 median test
Peak glucose (mM)	8.36 ± 0.61	6.87 ± 0.38	9.65 ± 1.06	6.99 ± 1.86	+1.29 ± 0.64	+0.12 ± 0.42	NS
Glucose response (mM)	3.98 ± 0.48	3.04 ± 0.44	4.43 ± 0.73	3.00 ± 0.44	+0.45 ± 0.55	−0.06 ± 0.21	NS
Fasting insulin (pM)	209.6 ± 35.4	264.6 ± 48.5	198.5 ± 84.8	200.1 ± 33.3	−11.2 ± 66.2	−64.6 ± 52.6	NS
Peak insulin (pM)	1472 ± 159	2215 ± 354	966 ± 277	2322 ± 468	−506 ± 369	+147 ± 238	NS
Insulin response (pM)	1181 ± 155	1905 ± 352	764 ± 250	2122 ± 451	−417 ± 304	+216 ± 215	0.110 *t* test 0.034 median test

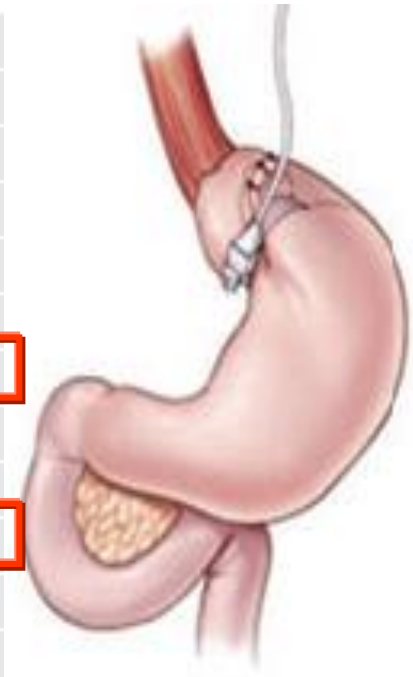
P values are in reference to the change from months 0–6 between octreotide and placebo groups. To convert glucose concentrations from mM to mg/dl, multiply by 18; to convert insulin concentrations from pM to μU/ml, multiply by 0.1394.

Lustig et al., J Clin Endocrinol & Metab 2003; 88:2586

Tp chirurgica: bendaggio gastrico

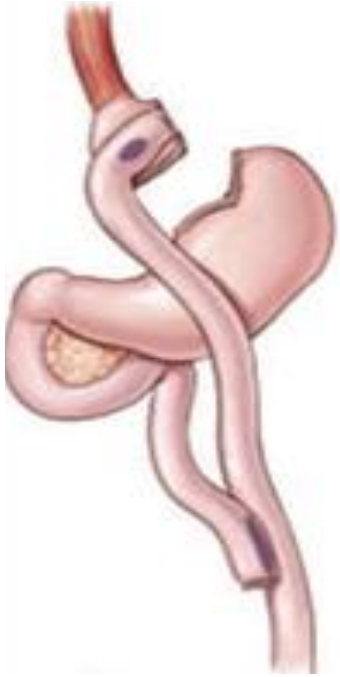
Table 1 Patients' characteristics, age and body mass index (BMI) at the time of craniopharyngioma diagnosis, at the time of laparoscopic gastric banding (LAGB), at the time of greatest weight loss after LAGB and at latest follow-up visit after LAGB. *Patient #4 had gastric sleeve resection 2.2 years after LAGB.

patient #		1	2	3	4
gender	f/m	f	m	f	f
age at diagnosis	years	2	13	12	20
BMI at diagnosis	kg/m^2	17.3	27.4	26.9	21.6
BMI at diagnosis	SDS	−0.9	+4.5	+4.7	+0.2
age at LAGB	years	13.8	17.5	21.5	23.7
BMI at LAGB	kg/m^2	46.4	44.9	51.9	40.0
BMI at LAGB	SDS	+10.9	+10.4	+11.4	+6.2
age at nadir BMI after LAGB	years	15.8	17.9	22.5	24.5
nadir BMI after LAGB	kg/m^2	38.1	42.8	42.6	36.2
nadir BMI after LAGB	SDS	+6.9	+9.4	+7.7	+4.9
age at latest visit	years	22.9	22.7	28.6	30.8
BMI at latest visit	kg/m^2	49.6	53.6	53.6	42.7
BMI at latest visit	SDS	+10.2	+13.9	+10.2	+6.3



Müller et al., Klin Pediatr. 2007; 219:323

A ROUX-EN-Y GASTRIC BYPASS



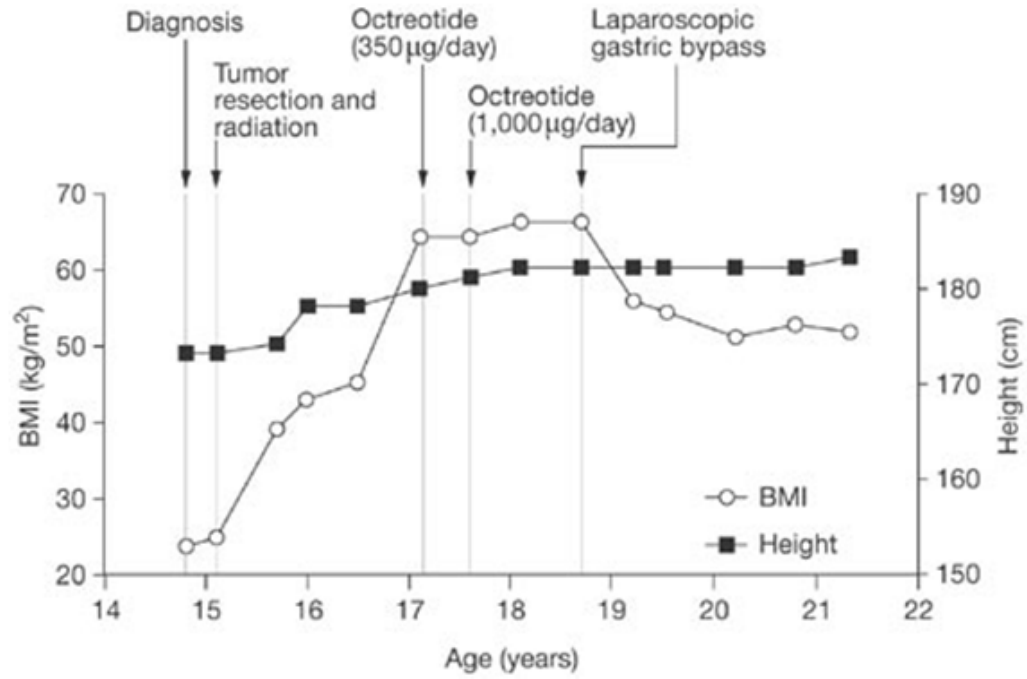
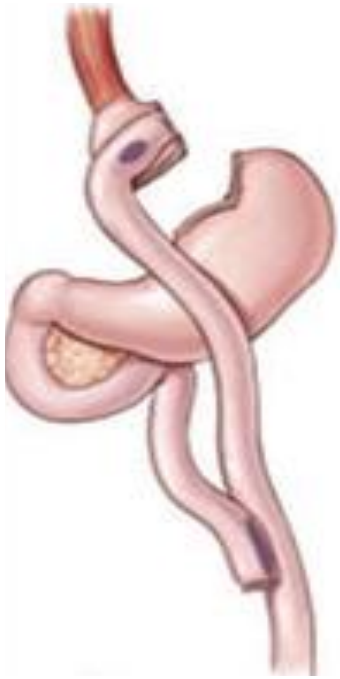
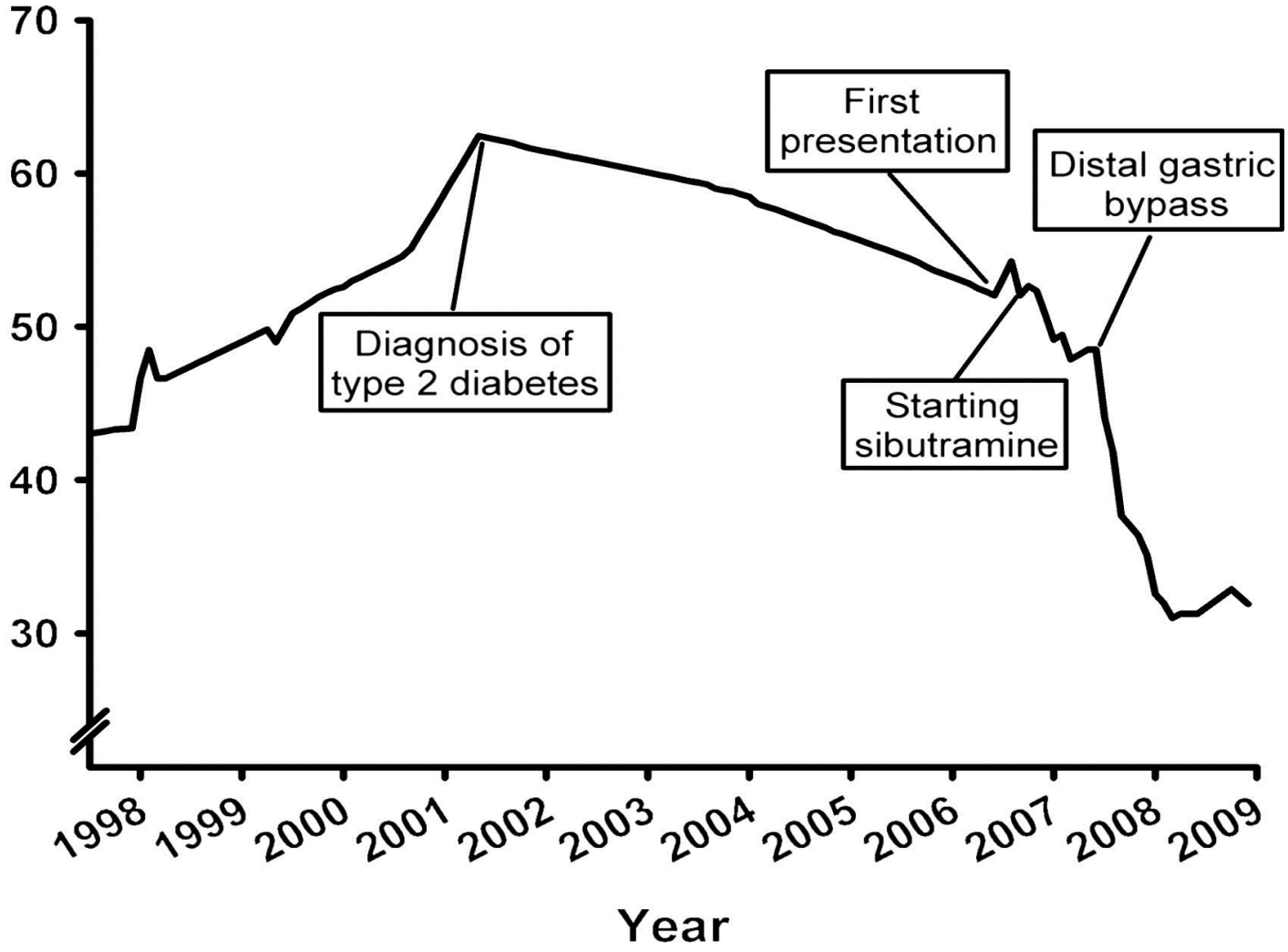


Figure 2. BMI changes of the patient and clinical events over time
At the time of gastric bypass surgery, the patient's BMI was 67 kg/m^2, his weight was 223.5 kg, and his excess weight was 150 kg, representing 204% over ideal weight for his gender and age. At the longest available follow-up (2.5 years following operation) the patient had a weight loss of 49 kg; that represents 22% of his initial weight or 33% of his initial excess weight.

Inge et al. Nat Clin Pract Endocrinol Metab. 2007; 3:606

Distal gastric bypass operation





Schultes et al. Eur J Endocrinol 2009;161:201

Conclusioni obesità ipotalamica

- Modificazione degli stili di vita
- Attività fisica (se possibile)
- Tp farmacologica solo se combinata con le modifiche dello stile di vita
- Chirurgia solo in caso di fallimento della terapia comportamentale e farmacologica
- No chirurgia di tipo restrittivo se iperfagia o disturbi comportamento alimentare

Pagotto U 2013 in press

Giovanni e con il GH e il testosterone nell'età adulta che si fa?

Ho sentito notizie allarmati sia per il GH sia per il testosterone…
Ci sai dare notizie rassicuranti?

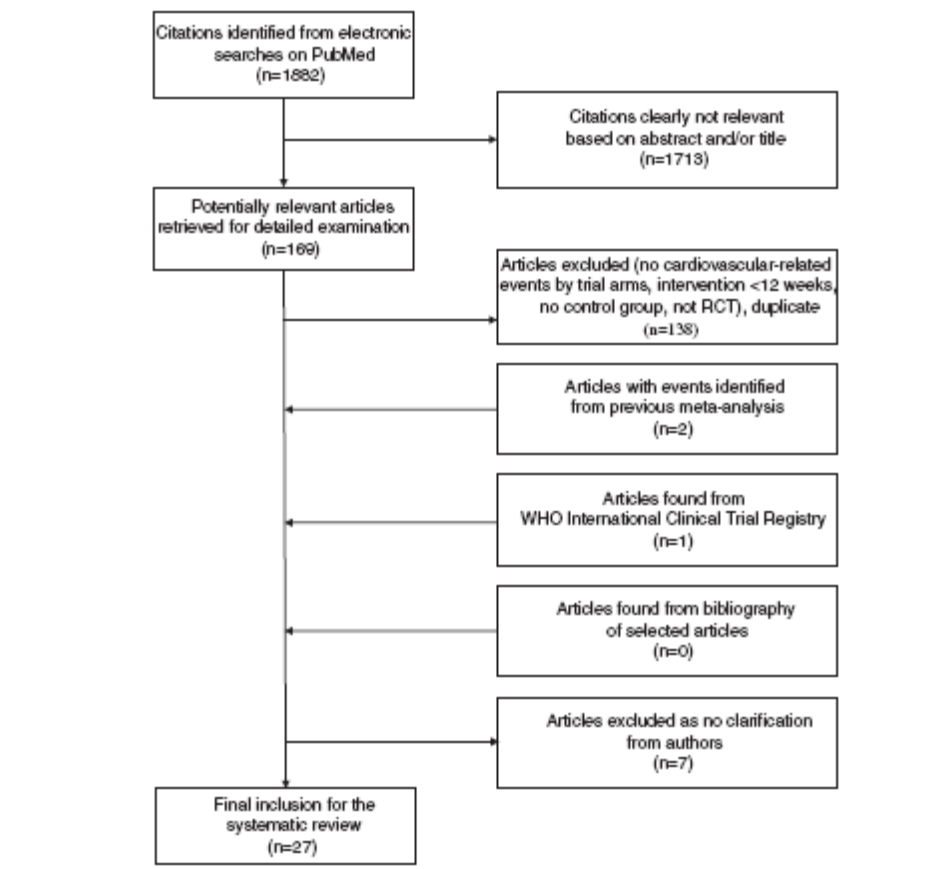
Xu et al. BMC Medicine 2013, 11:108
http://www.biomedcentral.com/1741-7015/11/108

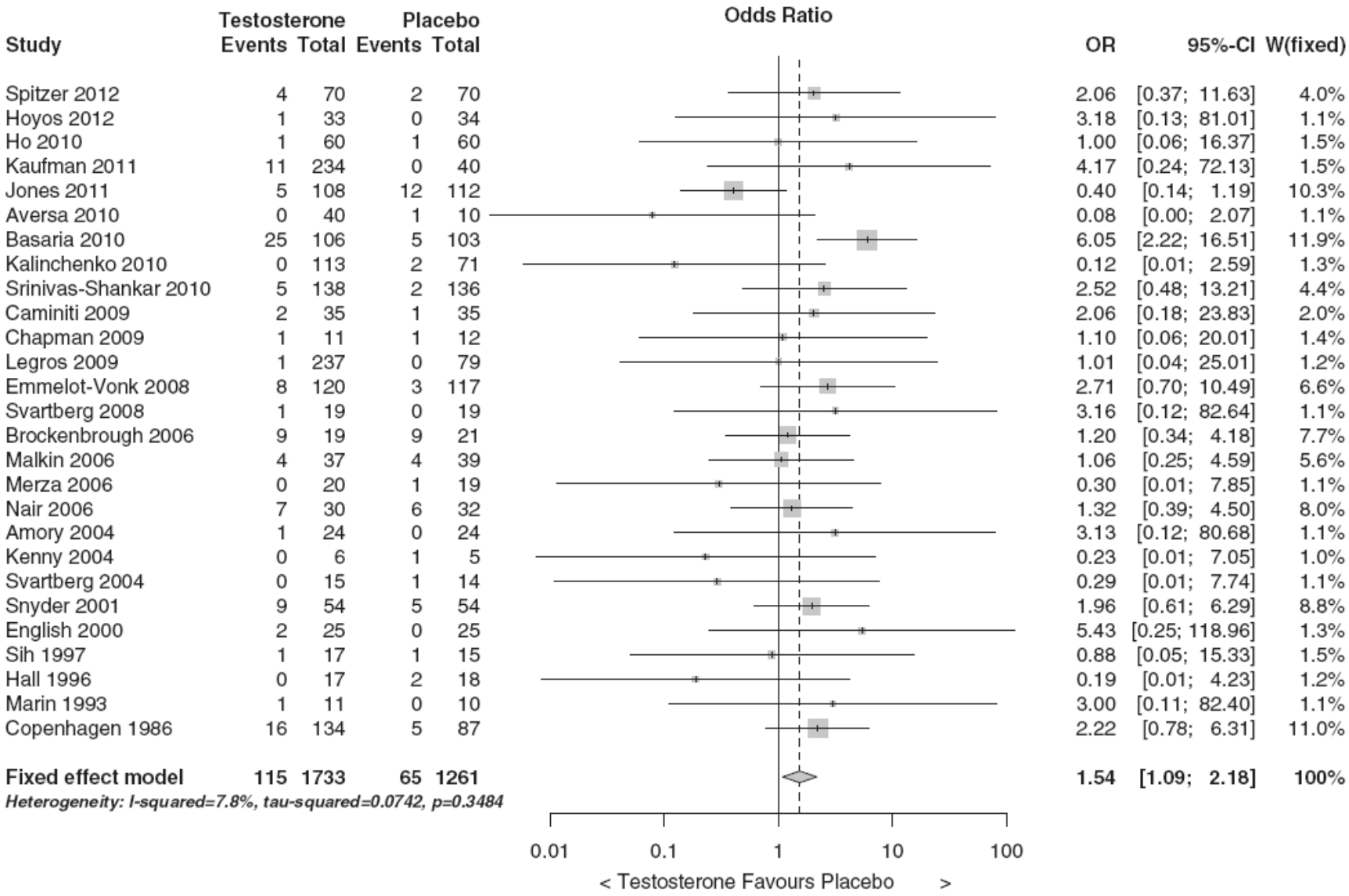
BMC Medicine

RESEARCH ARTICLE Open Access

Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials

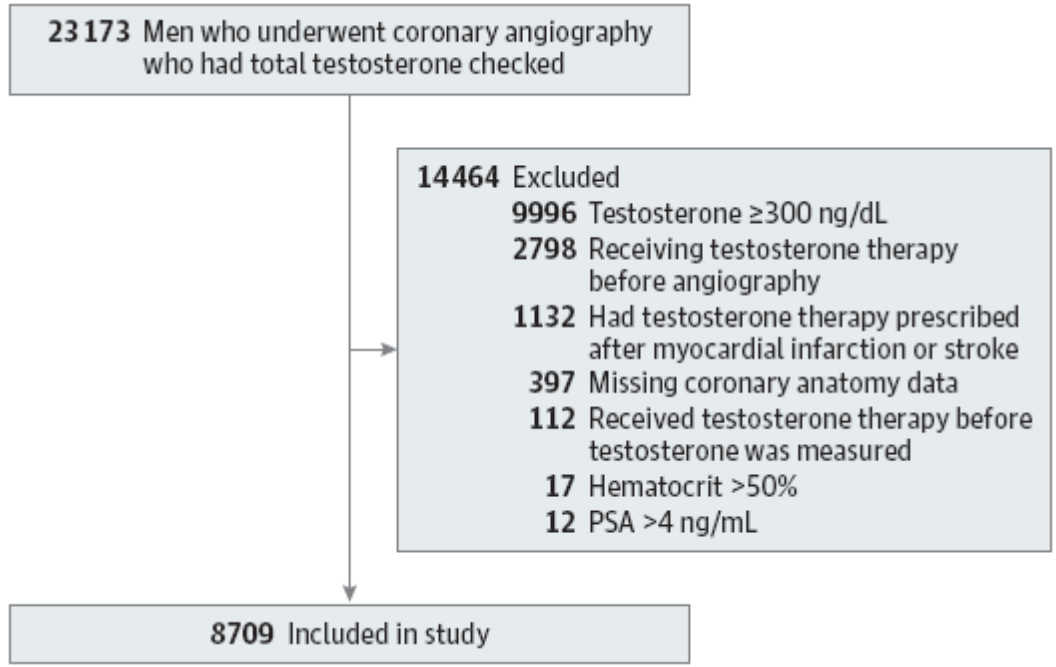
Lin Xu[1], Guy Freeman[1], Benjamin J Cowling[1] and C Mary Schooling[1,2*]



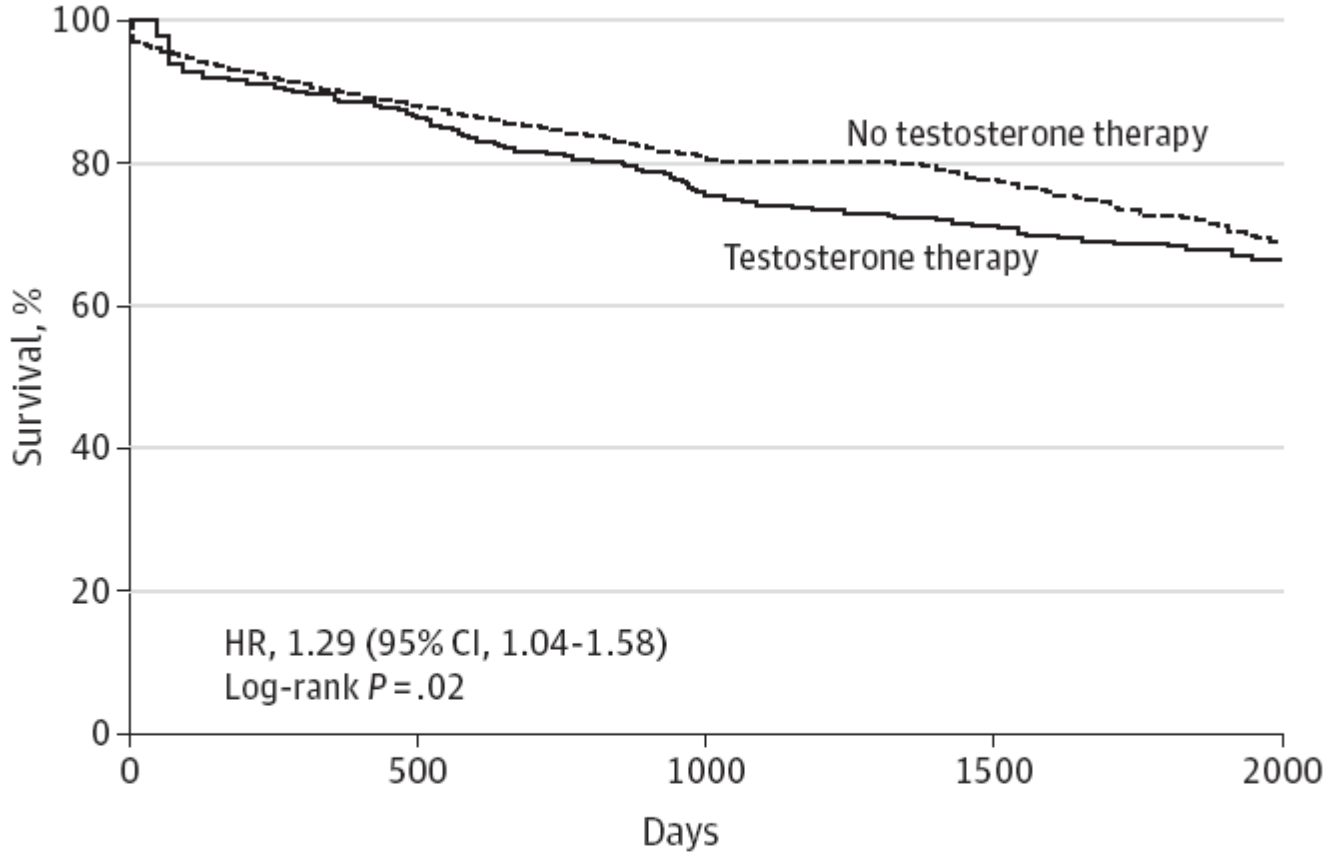

Odds Ratio
Study
Testosterone Events Total
Placebo Events Total
OR 95%-CI W(fixed)
Spitzer 2012 4 70 2 70 2.06 [0.37; 11.63] 4.0%
Hoyos 2012 1 33 0 34 3.18 [0.13; 81.01] 1.1%
Ho 2010 1 60 1 60 1.00 [0.06; 16.37] 1.5%
Kaufman 2011 11 234 0 40 4.17 [0.24; 72.13] 1.5%
Jones 2011 5 108 12 112 0.40 [0.14; 1.19] 10.3%
Aversa 2010 0 40 1 10 0.08 [0.00; 2.07] 1.1%
Basaria 2010 25 106 5 103 6.05 [2.22; 16.51] 11.9%
Kalinchenko 2010 0 113 2 71 0.12 [0.01; 2.59] 1.3%
Srinivas-Shankar 2010 5 138 2 136 2.52 [0.48; 13.21] 4.4%
Caminiti 2009 2 35 1 35 2.06 [0.18; 23.83] 2.0%
Chapman 2009 1 11 1 12 1.10 [0.06; 20.01] 1.4%
Legros 2009 1 237 0 79 1.01 [0.04; 25.01] 1.2%
Emmelot-Vonk 2008 8 120 3 117 2.71 [0.70; 10.49] 6.6%
Svartberg 2008 1 19 0 19 3.16 [0.12; 82.64] 1.1%
Brockenbrough 2006 9 19 9 21 1.20 [0.34; 4.18] 7.7%
Malkin 2006 4 37 4 39 1.06 [0.25; 4.59] 5.6%
Merza 2006 0 20 1 19 0.30 [0.01; 7.85] 1.1%
Nair 2006 7 30 6 32 1.32 [0.39; 4.50] 8.0%
Amory 2004 1 24 0 24 3.13 [0.12; 80.68] 1.1%
Kenny 2004 0 6 1 5 0.23 [0.01; 7.05] 1.0%
Svartberg 2004 0 15 1 14 0.29 [0.01; 7.74] 1.1%
Snyder 2001 9 54 5 54 1.96 [0.61; 6.29] 8.8%
English 2000 2 25 0 25 5.43 [0.25; 118.96] 1.3%
Sih 1997 1 17 1 15 0.88 [0.05; 15.33] 1.5%
Hall 1996 0 17 2 18 0.19 [0.01; 4.23] 1.2%
Marin 1993 1 11 0 10 3.00 [0.11; 82.40] 1.1%
Copenhagen 1986 16 134 5 87 2.22 [0.78; 6.31] 11.0%
Fixed effect model 115 1733 65 1261 1.54 [1.09; 2.18] 100%
Heterogeneity: I-squared=7.8%, tau-squared=0.0742, p=0.3484
0.01
0.1
1
10
100
< Testosterone Favours Placebo >
Xu et al., BMC Medicine 2013; 11:108

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



Vigen et al., JAMA 2013;310:1829



No. at risk

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

Vigen et al., JAMA 2013;310:1829

European Journal of Endocrinology (2011) 165 1–18 ISSN 0804-4643

CLINICAL STUDY

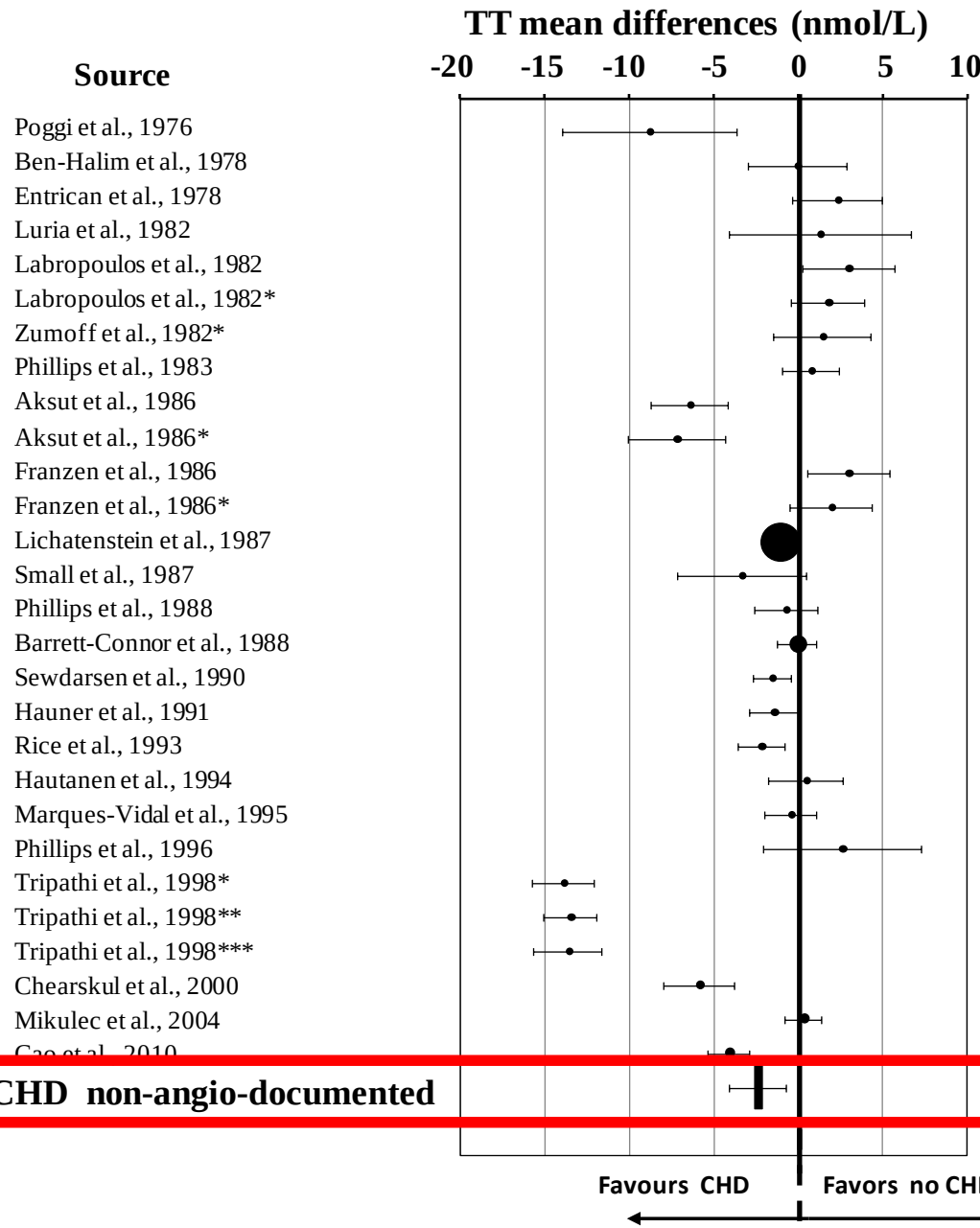
Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study

Giovanni Corona[1,2], Giulia Rastrelli[1], Matteo Monami[3], André Guay[4], Jaques Buvat[5], Alessandra Sforza[2], Gianni Forti[6], Edoardo Mannucci[3] and Mario Maggi[1]

[1]*Andrology and Sexual Medicine Unit, Department of Clinical Physiopathology, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy,* [2]*Endocrinology Unit, Medical Department, Azienda Usl Bologna Maggiore-Bellaria Hospital, Bologna, Italy,* [3]*Diabetes Section Geriatric Unit, Department of Critical Care, University of Florence, Florence, Italy,* [4]*Center For Sexual Function/Endocrinology, Lahey Clinic, Peabody, Massachusetts, USA,* [5]*Centre d'Etude et de Traitement de la Pathologie de l'Appareil Reproducteur et de la Psychosomatique, Lille, France and* [6]*Endocrinology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy*

(Correspondence should be addressed to M Maggi; Email: m.maggi@dfc.unifi.it)

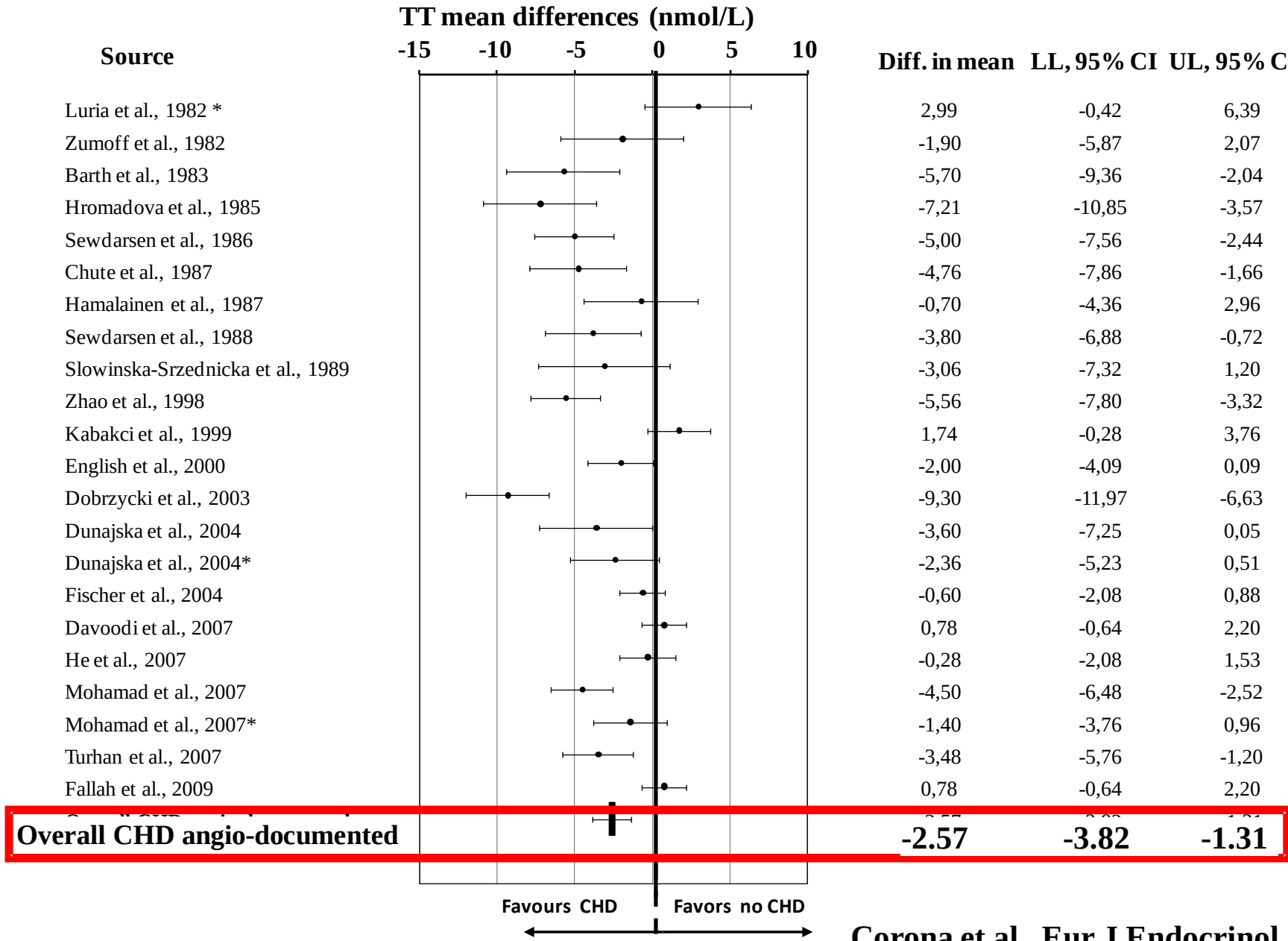
Weighted differences (with 95% confidence interval [CI]) of mean total testosterone between non-angiographically documented CHD and controls from cross-sectional studies



Source	Diff. in mean	LL, 95% CI	UL, 95% CI
Poggi et al., 1976	-8,75	-13,91	-3,59
Ben-Halim et al., 1978	0,00	-2,94	2,94
Entrican et al., 1978	2,35	-0,31	5,01
Luria et al., 1982	1,32	-4,06	6,70
Labropoulos et al., 1982	3,00	0,27	5,73
Labropoulos et al., 1982*	1,80	-0,38	3,98
Zumoff et al., 1982*	1,46	-1,43	4,35
Phillips et al., 1983	0,80	-0,86	2,46
Aksut et al., 1986	-6,36	-8,63	-4,10
Aksut et al., 1986*	-7,16	-10,03	-4,28
Franzen et al., 1986	3,00	0,57	5,43
Franzen et al., 1986*	2,00	-0,43	4,43
Lichatenstein et al., 1987	-1,10	-1,81	-0,39
Small et al., 1987	-3,30	-7,12	0,52
Phillips et al., 1988	-0,69	-2,57	1,18
Barrett-Connor et al., 1988	-0,04	-1,18	1,10
Sewdarsen et al., 1990	-1,51	-2,64	-0,38
Hauner et al., 1991	-1,40	-2,85	0,05
Rice et al., 1993	-2,15	-3,53	-0,76
Hautanen et al., 1994	0,50	-1,71	2,71
Marques-Vidal et al., 1995	-0,40	-1,95	1,15
Phillips et al., 1996	2,64	-2,01	7,29
Tripathi et al., 1998*	-13,85	-15,68	-12,02
Tripathi et al., 1998**	-13,43	-14,97	-11,89
Tripathi et al., 1998***	-13,56	-15,59	-11,53
Chearskul et al., 2000	-5,81	-7,92	-3,70
Mikulec et al., 2004	0,31	-0,77	1,39
Cao et al., 2010	-4,06	-5,30	-2,82
Overall CHD non-angio-documented	**-2.33**	**-3.99**	**-0.68**

Corona et al., Eur J Endocrinol. 2011;165:1

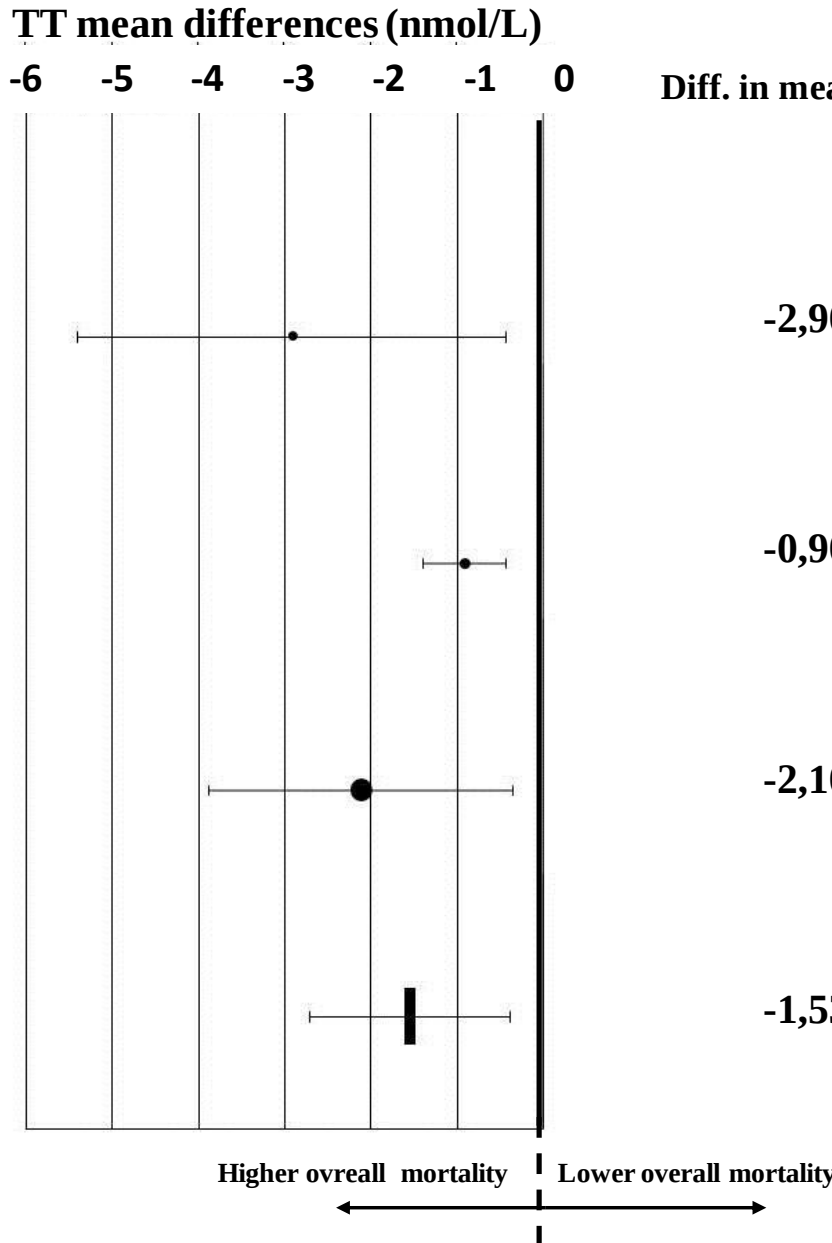
Weighted differences (with 95% confidence interval [CI]) of mean total testosterone between angiographically documented CHD and controls from cross-sectional studies



Source	Diff. in mean	LL, 95% CI	UL, 95% CI
Luria et al., 1982 *	2,99	-0,42	6,39
Zumoff et al., 1982	-1,90	-5,87	2,07
Barth et al., 1983	-5,70	-9,36	-2,04
Hromadova et al., 1985	-7,21	-10,85	-3,57
Sewdarsen et al., 1986	-5,00	-7,56	-2,44
Chute et al., 1987	-4,76	-7,86	-1,66
Hamalainen et al., 1987	-0,70	-4,36	2,96
Sewdarsen et al., 1988	-3,80	-6,88	-0,72
Slowinska-Srzednicka et al., 1989	-3,06	-7,32	1,20
Zhao et al., 1998	-5,56	-7,80	-3,32
Kabakci et al., 1999	1,74	-0,28	3,76
English et al., 2000	-2,00	-4,09	0,09
Dobrzycki et al., 2003	-9,30	-11,97	-6,63
Dunajska et al., 2004	-3,60	-7,25	0,05
Dunajska et al., 2004*	-2,36	-5,23	0,51
Fischer et al., 2004	-0,60	-2,08	0,88
Davoodi et al., 2007	0,78	-0,64	2,20
He et al., 2007	-0,28	-2,08	1,53
Mohamad et al., 2007	-4,50	-6,48	-2,52
Mohamad et al., 2007*	-1,40	-3,76	0,96
Turhan et al., 2007	-3,48	-5,76	-1,20
Fallah et al., 2009	0,78	-0,64	2,20
Overall CHD angio-documented	**-2.57**	**-3.82**	**-1.31**

Corona et al., Eur J Endocrinol. 2011;165:1

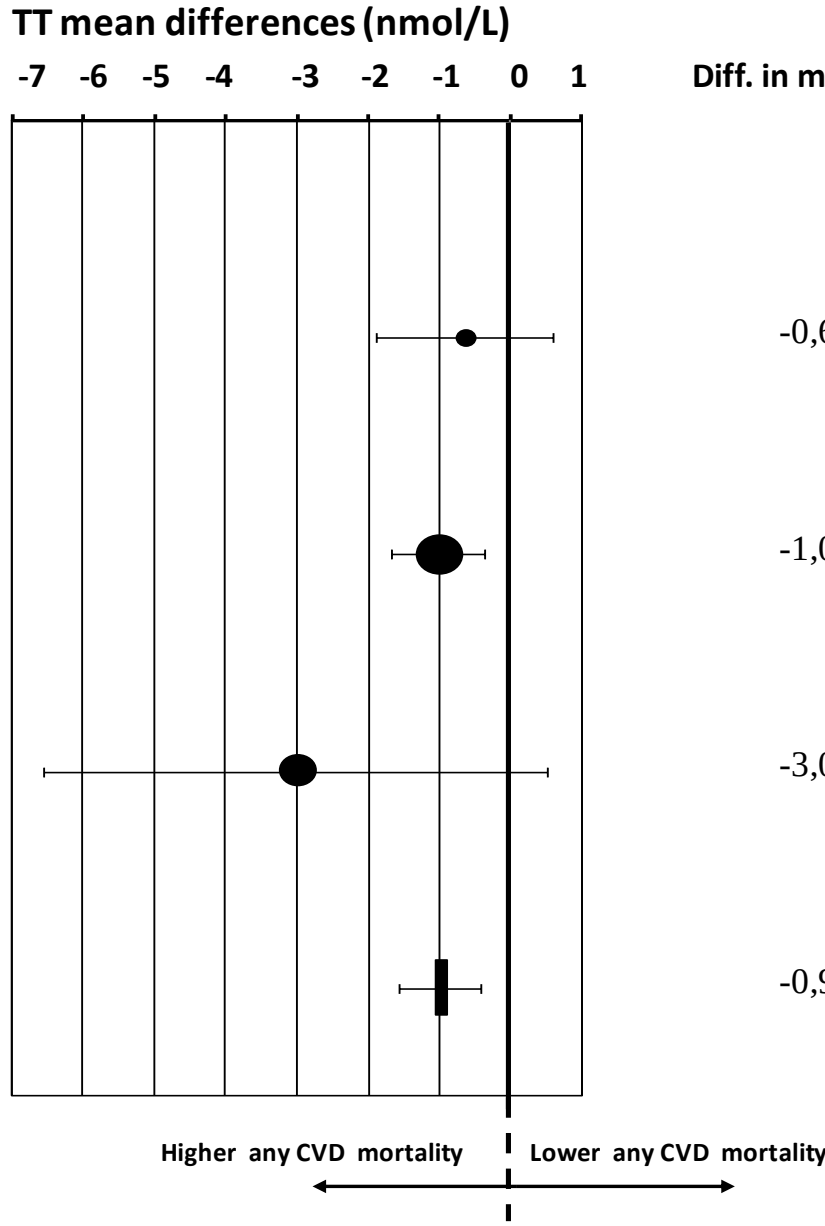
Baseline weighted differences (with 95% confidence interval) of mean total testosterone (TT) between patients with incident overall mortality and controls



Source	Diff. in mean	LL, 95% CI	UL, 95% CI
Letonen et al., 1996	-2,90	-5,39	-0,41
Khaw et al., 2007	-0,90	-1,38	-0,42
Corona et al., 2010	-2,10	-3,87	-0,33
OVERALL	-1,53	-2,69	-0,37

Corona et al., Eur J Endocrinol. 2011;165:1

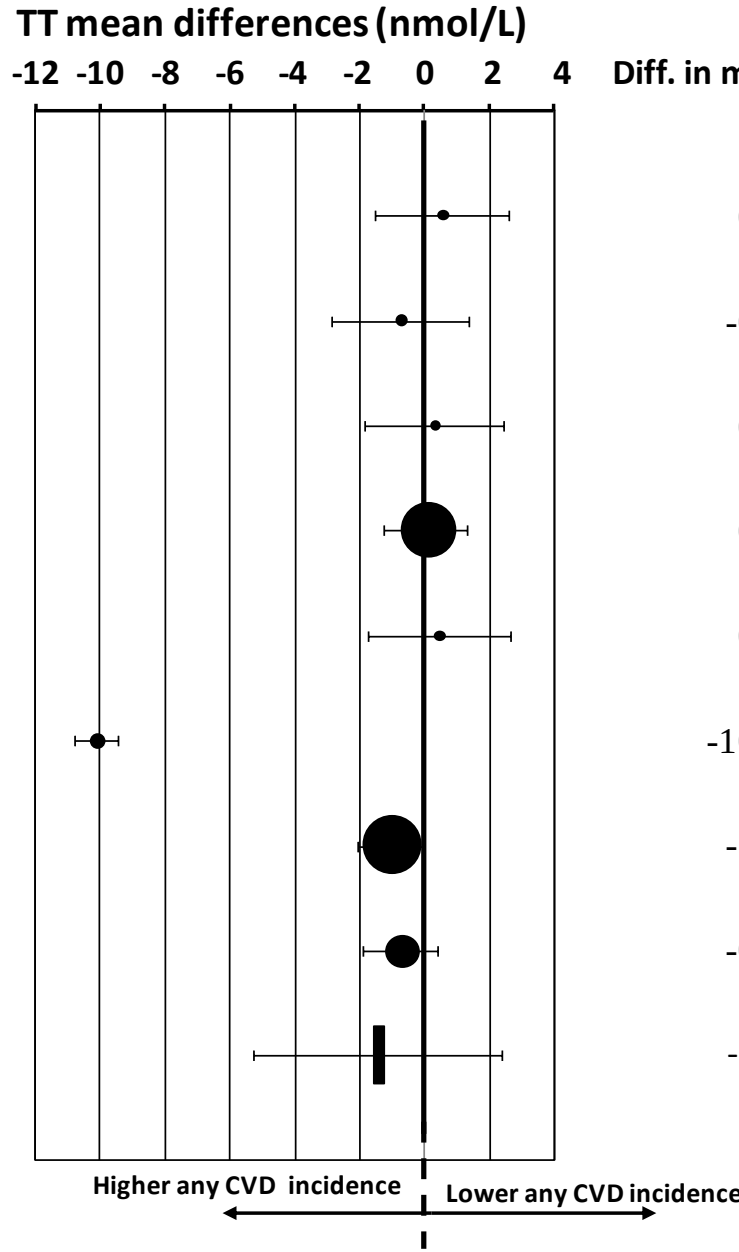
Baseline weighted differences (with 95% confidence interval) of mean total testosterone (TT) between patients with incident CV mortality and controls



Source	Diff. in mean	LL, 95% CI	UL, 95% CI
Barrett-Connor et al., 1988	-0,61	-1,86	0,64
Khaw et al., 2007	-1,00	-1,66	-0,34
Corona et al., 2010	-3,00	-6,53	0,53
OVERALL	-0,97	-1,55	-0,40

Corona et al., Eur J Endocrinol. 2011;165:1

Baseline weighted differences (with 95% confidence interval) of mean total testosterone (TT) between patients with incident MACE and controls



Source	Diff. in mean	LL, 95% CI	UL, 95% CI
Cauley et al., 1987	0,60	-1,47	2,67
Phillips et al., 1988	-0,69	-2,83	1,44
Contoreggi et al., 1990	0,35	-1,79	2,49
Yarnell et al., 1993	0,10	-1,19	1,39
Hautanen et al 1994	0,50	-1,71	2,71
Mikulec et al., 2004	-10,10	-10,77	-9,44
Yeap et al., 2009	-1,00	-2,02	0,02
Corona et al., 2010	-0,70	-1,85	0,45
Overall	-1,40	-5,23	2,44

Corona et al., Eur J Endocrinol. 2011;165:1

J Clin Endocrin Metab. First published ahead of print August 3, 2011 as doi:10.1210/jc.2011-1137

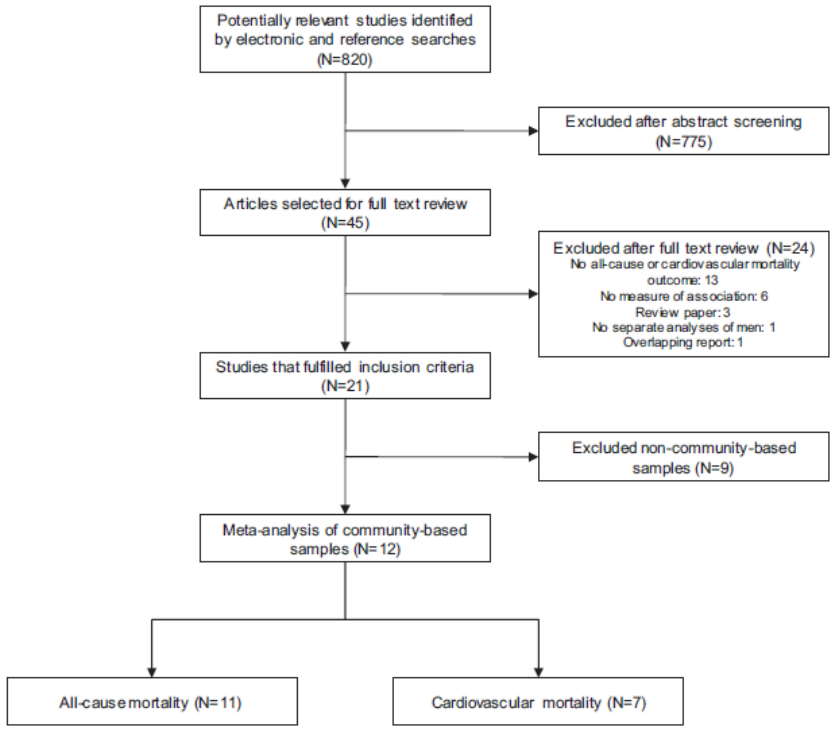
SPECIAL FEATURE

Clinical Review

Clinical Review: Endogenous Testosterone and Mortality in Men: A Systematic Review and Meta-Analysis

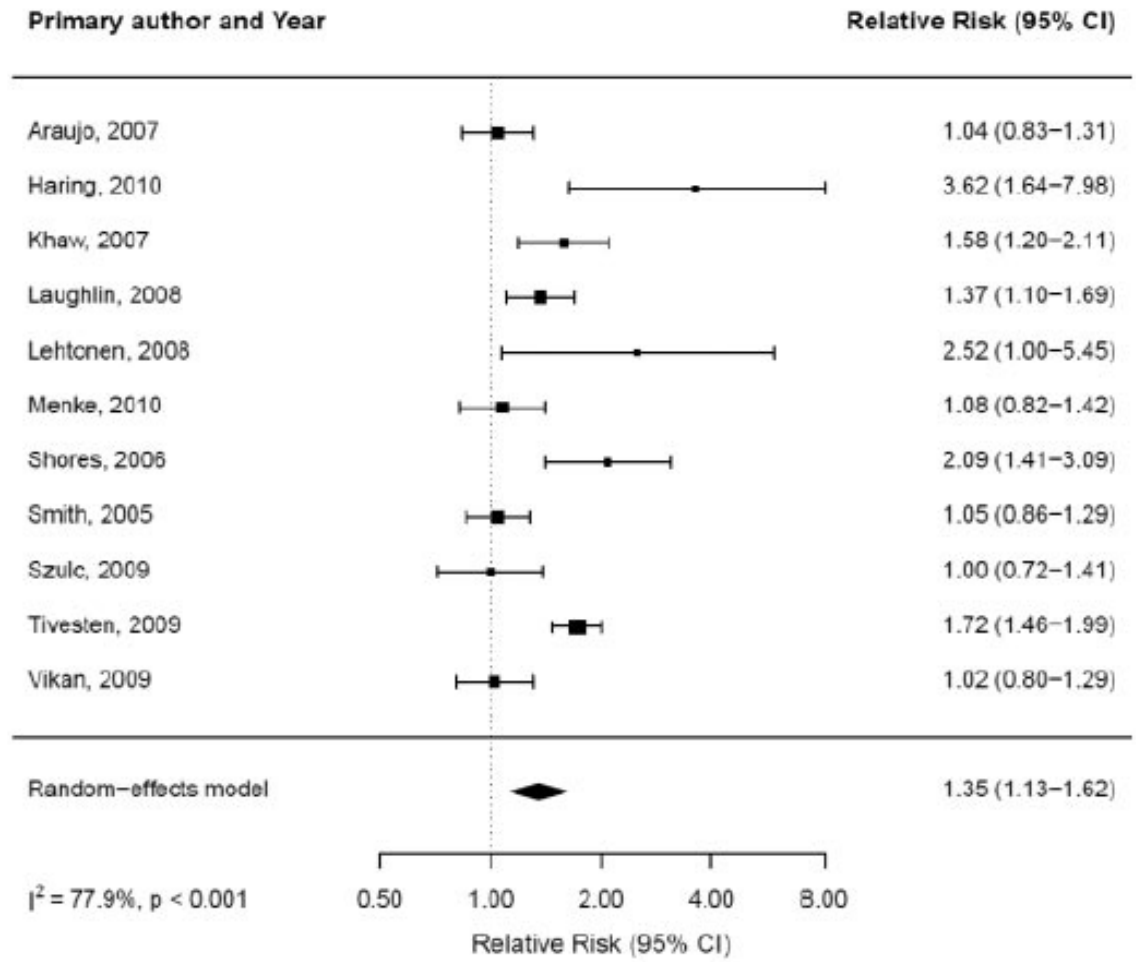
Andre B. Araujo, Julia M. Dixon, Elizabeth A. Suarez, M. Hassan Murad, Lin T. Guey, and Gary A. Wittert

Department of Epidemiology (A.B.A., J.M.D., E.A.S., L.T.G.), New England Research Institutes, Inc., Watertown, Massachusetts 02472; Division of Preventative Medicine (M.H.M.), Mayo Clinic, Rochester, Minnesota 55905; and Department of Medicine (G.A.W.), University of Adelaide, Adelaide, South



Araujo et al., J Clin Endocrinol Metab. 2011;96:3007-19

All-Cause Mortality



Araujo et al., J Clin Endocrinol Metab. 2011;96:3007-19

Table 2 Meta-analysis of relationship between testosterone and cardiovascular disease in healthy men.

Studies	No	RR (95% CI)	p Value*
Total testosterone	18	0.89 (0.83 to 0.96)	0.00
Age of study population <70 years	7	1.01 (0.95 to 1.08)	0.41
Including men >70 years	11	0.84 (0.76 to 0.92)	0.00
Year of publication before 1 January 2007	6	0.97 (0.94 to 1.00)	0.08
After 1 January 2007	5	0.77 (0.72 to 0.82)	0.81
Free testosterone	7	0.88 (0.78 to 1.00)	0.00
Age of study population <70 years	3	0.99 (0.90 to 1.09)	0.11
Including men >70 years	4	0.84 (0.71 to 1.00)	0.00
Year of publication before 1 January 2007	2	0.95 (0.91 to 1.00)	0.63
After 1 January 2007	2	0.77 (0.72 to 0.82)	0.65
Bioavailable testosterone (men>70 years)	3	0.74 (0.62 to 0.88)	0.71

Estimated summary RRs are provided for a change of 1 SD of testosterone level (high vs low), with the help of random-effects model RRs (95% CI).
*p Value of heterogeneity.

Ruige et al., Heart. 2011;97:570

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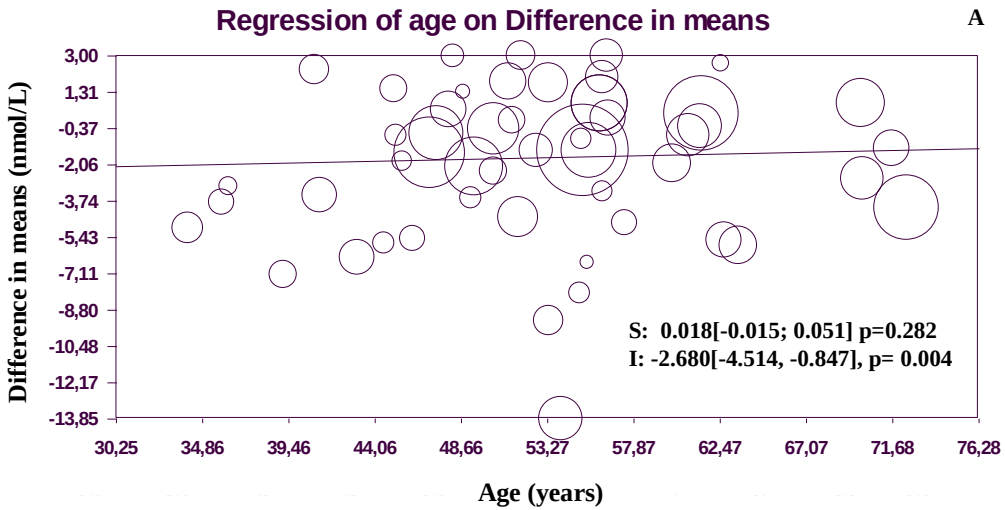
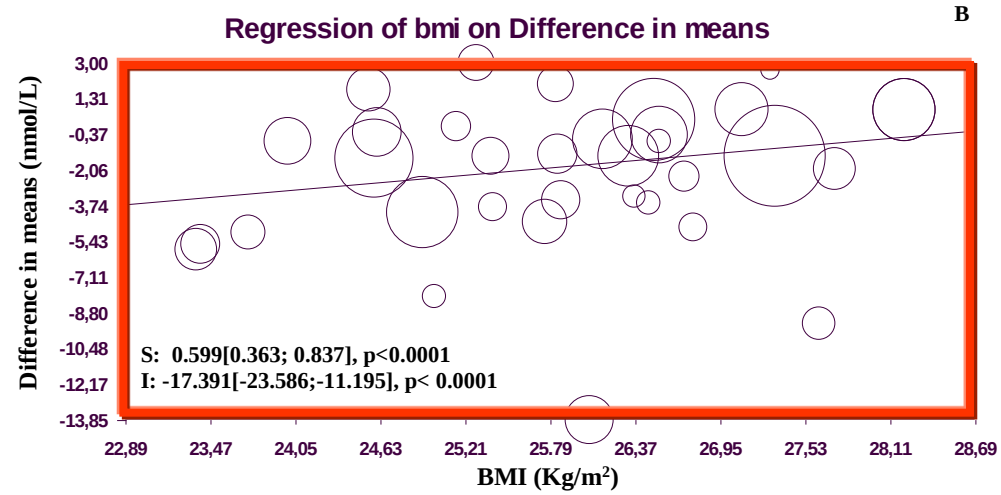
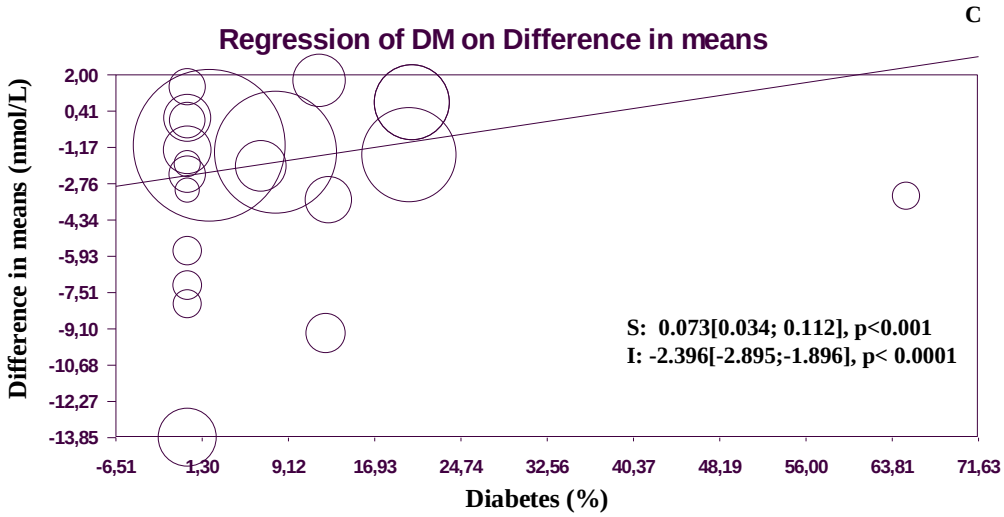
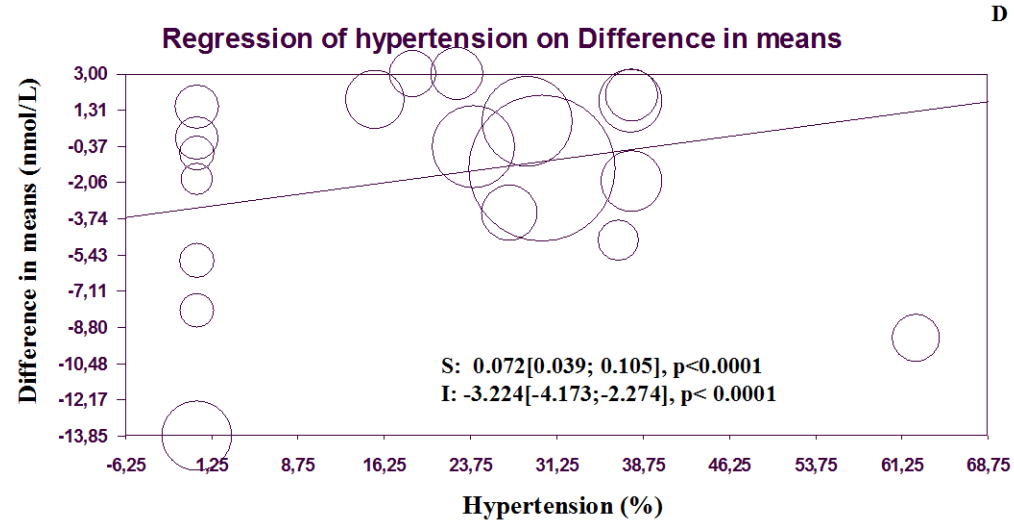
Ruige et al., Heart. 2011;97:570

Associated morbidities reduce Testosterone differences



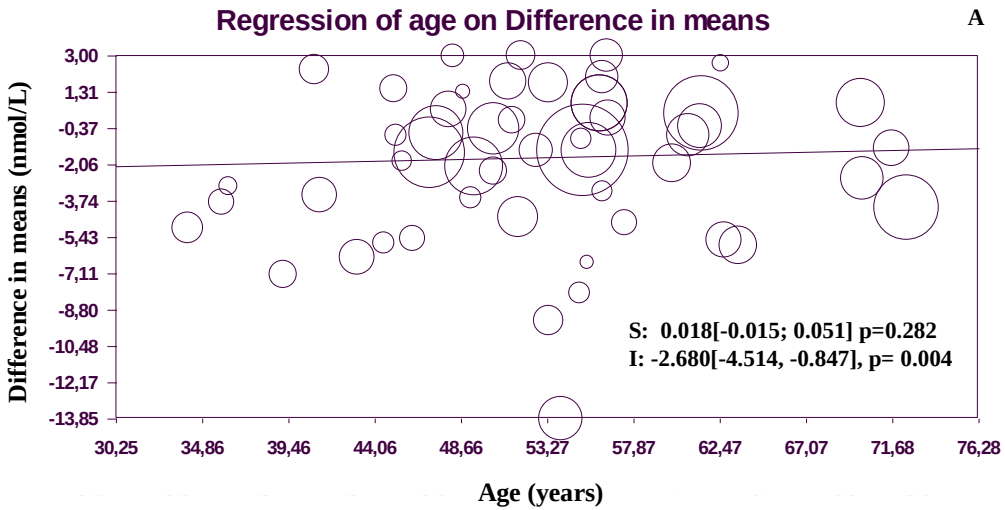


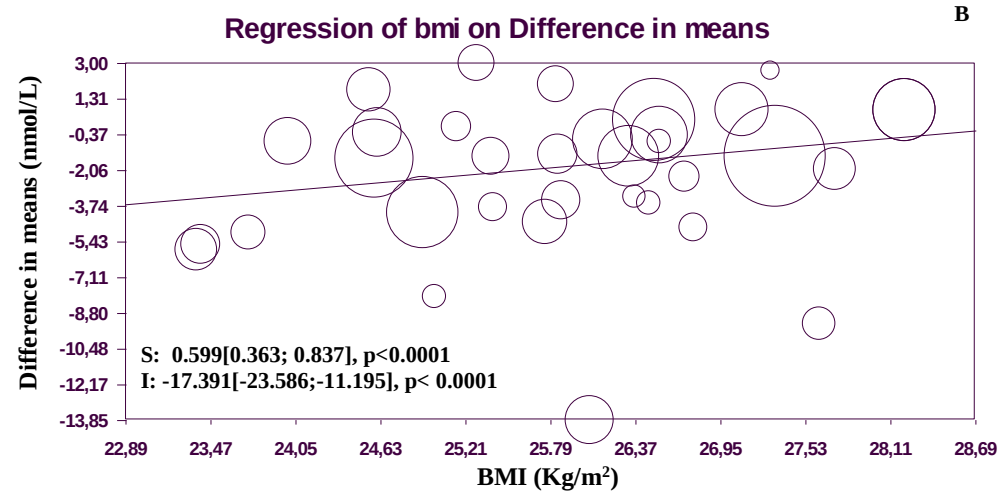


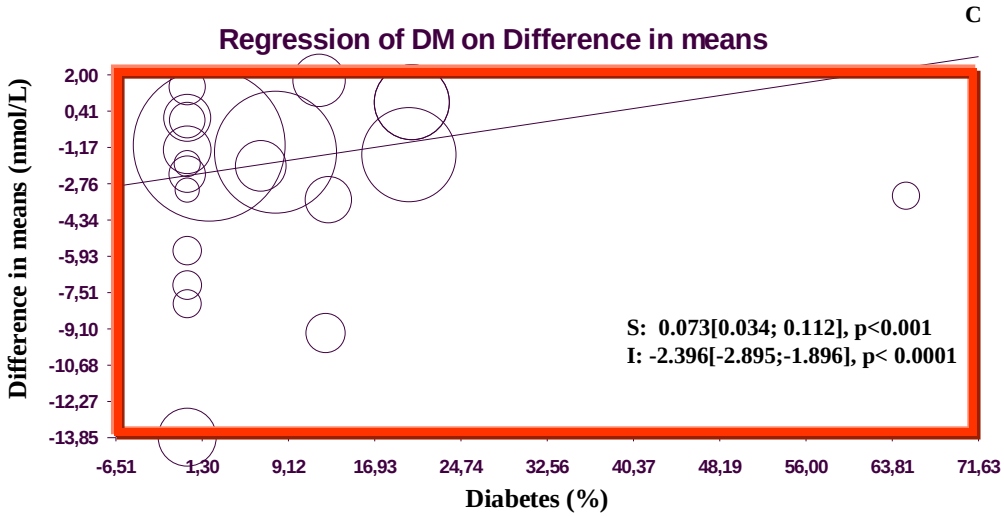


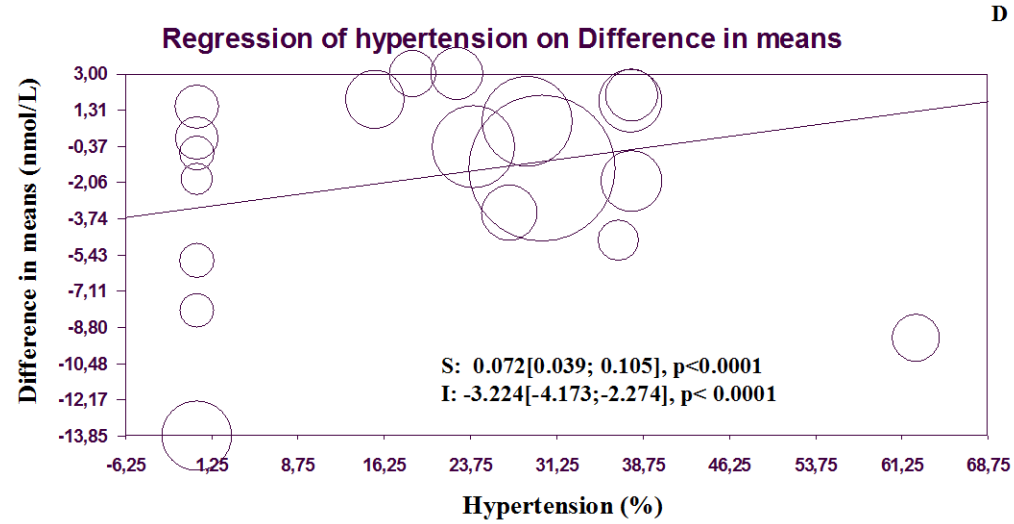
Corona et al., Eur J Endocrinol. 2011;165:1

Associated morbidities reduce Testosterone differences



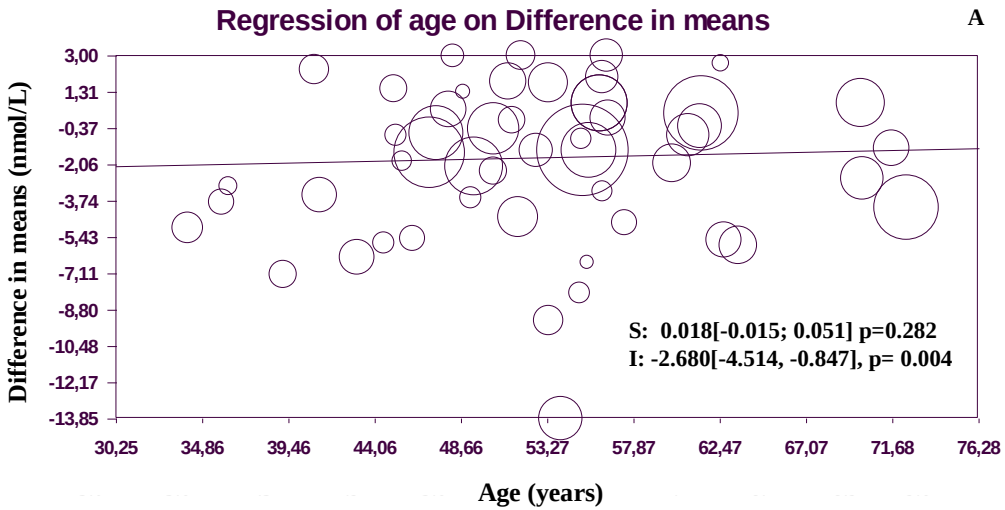


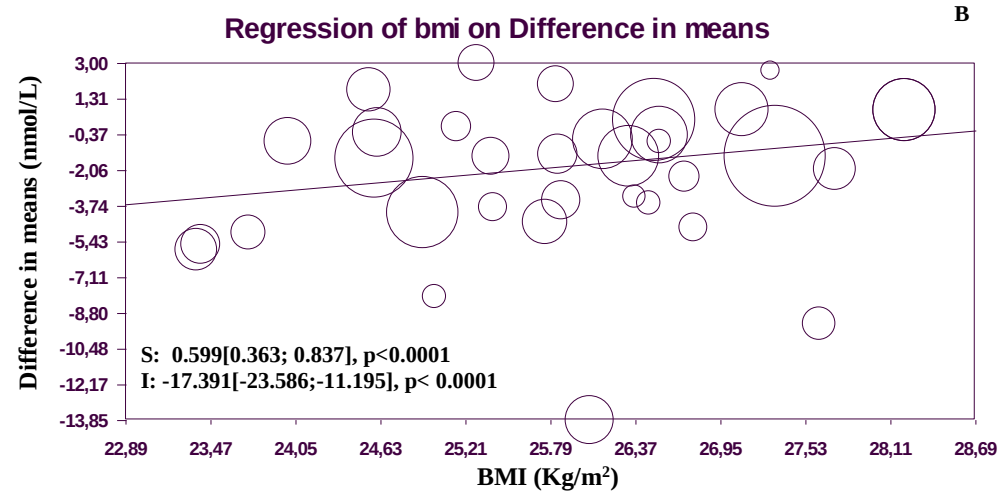


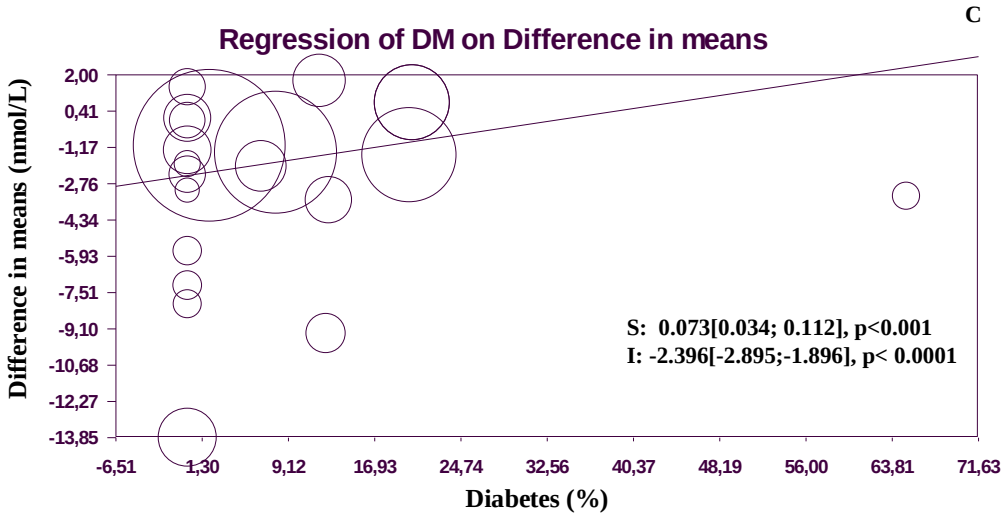


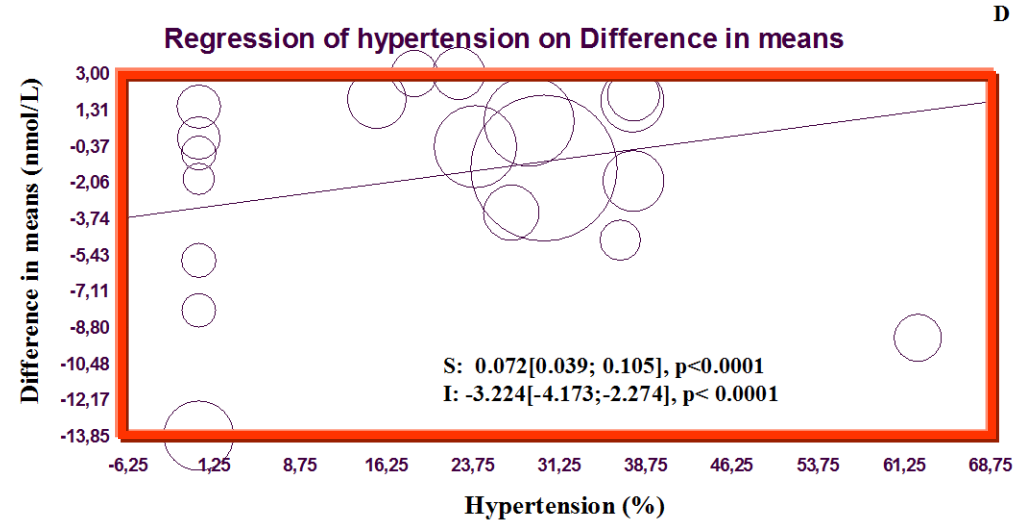
Corona et al., Eur J Endocrinol. 2011;165:1

Associated morbidities reduce Testosterone differences



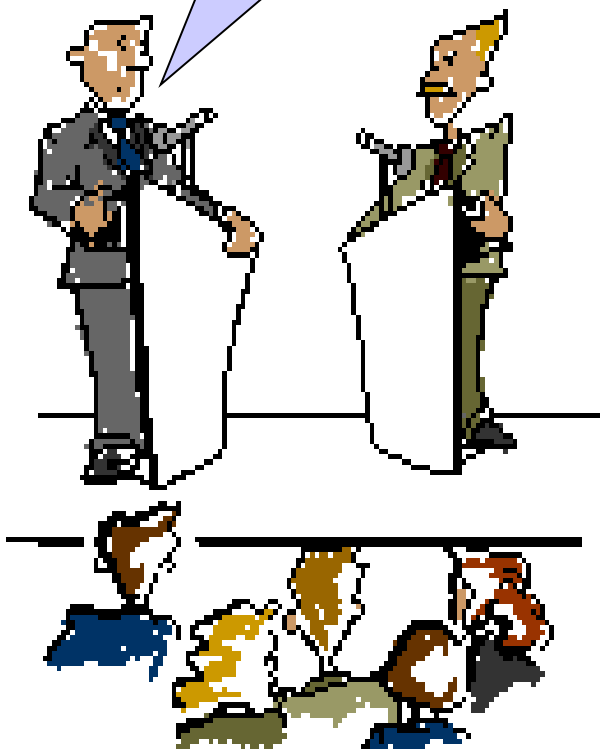






Corona et al., Eur J Endocrinol. 2011;165:1

L’ipogonadismo può rappresentare un meccanismo di adattamento (low T syndrome) nel paziente malato…



Corona et al., J Sex Med. 2011;8:2098

ORIGINAL ARTICLE

Endocrine Care

Low Free Testosterone Predicts Frailty in Older Men: The Health in Men Study

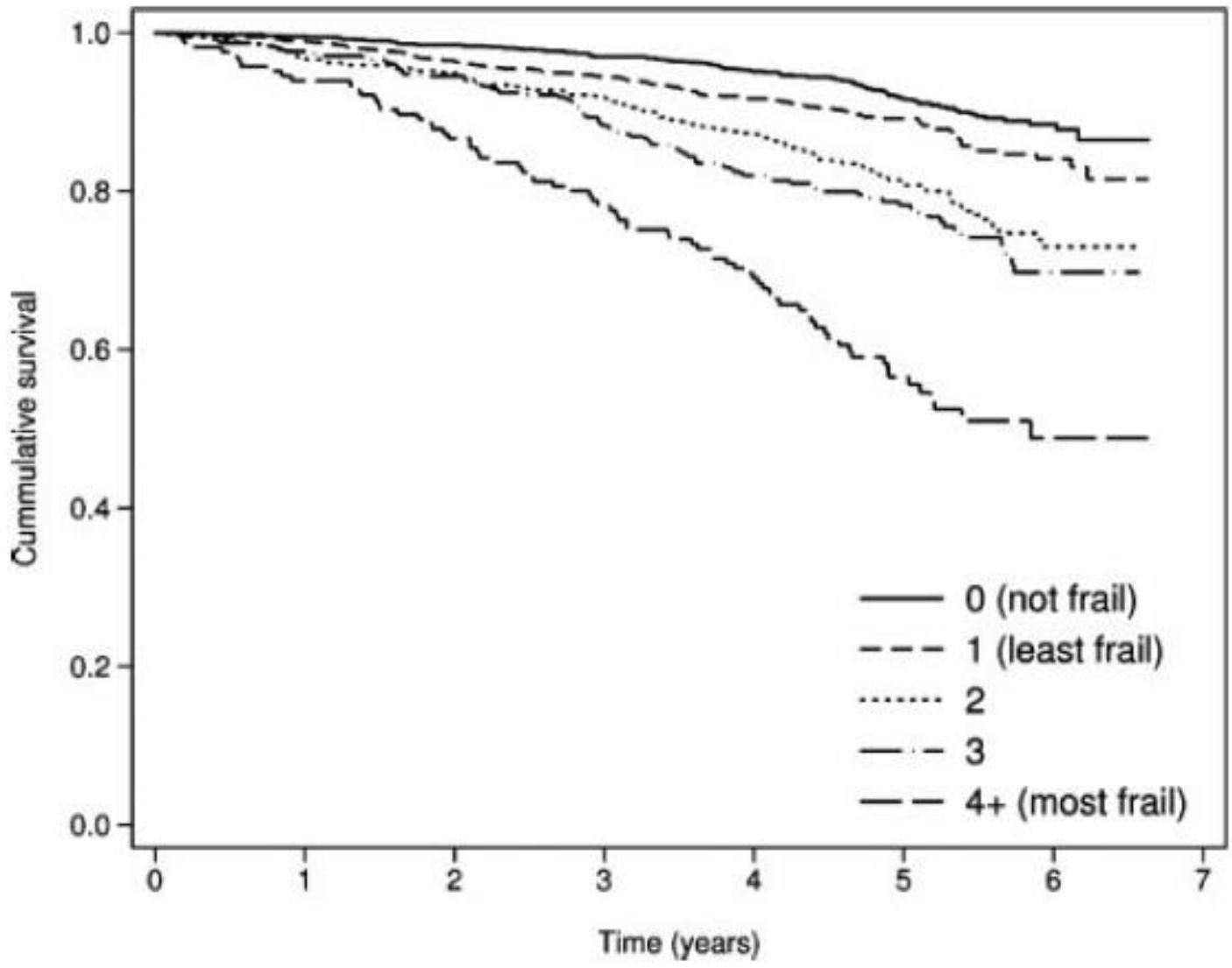
Zoë Hyde, Leon Flicker, Osvaldo P. Almeida, Graeme J. Hankey, Kieran A. McCaul, S. A. Paul Chubb, and Bu B. Yeap

Western Australian Centre for Health and Ageing (Z.H., L.F., O.P.A., K.A.M.), Centre for Medical Research, Western Australian Institute for Medical Research, and Schools of Medicine and Pharmacology (Z.H., L.F., G.J.H., K.A.M., S.A.P.C., B.B.Y.) and Psychiatry and Clinical Neurosciences (O.P.A.), University of Western Australia Perth WA 6009, Australia; Department of Psychiatry (O.P.A.) and Stroke Unit (G.J.H.), Royal Perth Hospital, Perth WA 6001, Australia; and PathWest (S.A.P.C.), Department of Biochemistry, and Department of Endocrinology and Diabetes (B.B.Y.), Fremantle Hospital, Fremantle WA 6160, Australia

Community-dwelling men involving
3116 subjects aged 70-88 years evaluated 2001-2004
1586 subjects aged 76-93 years evaluated 2008-2009

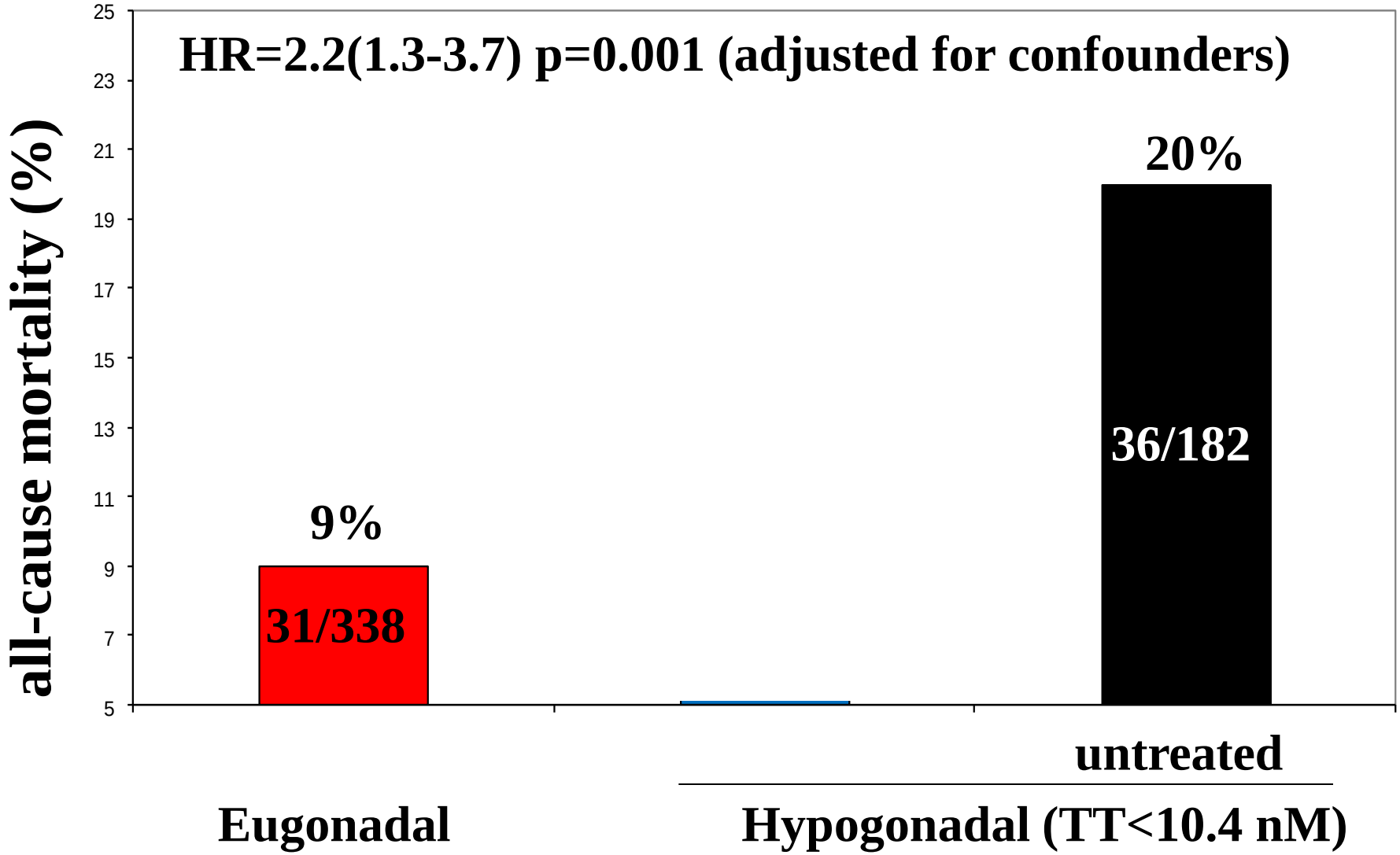
Hyde., J Clin Endocrinol and Metab. 2010;95:1

Frailty predicts mortality



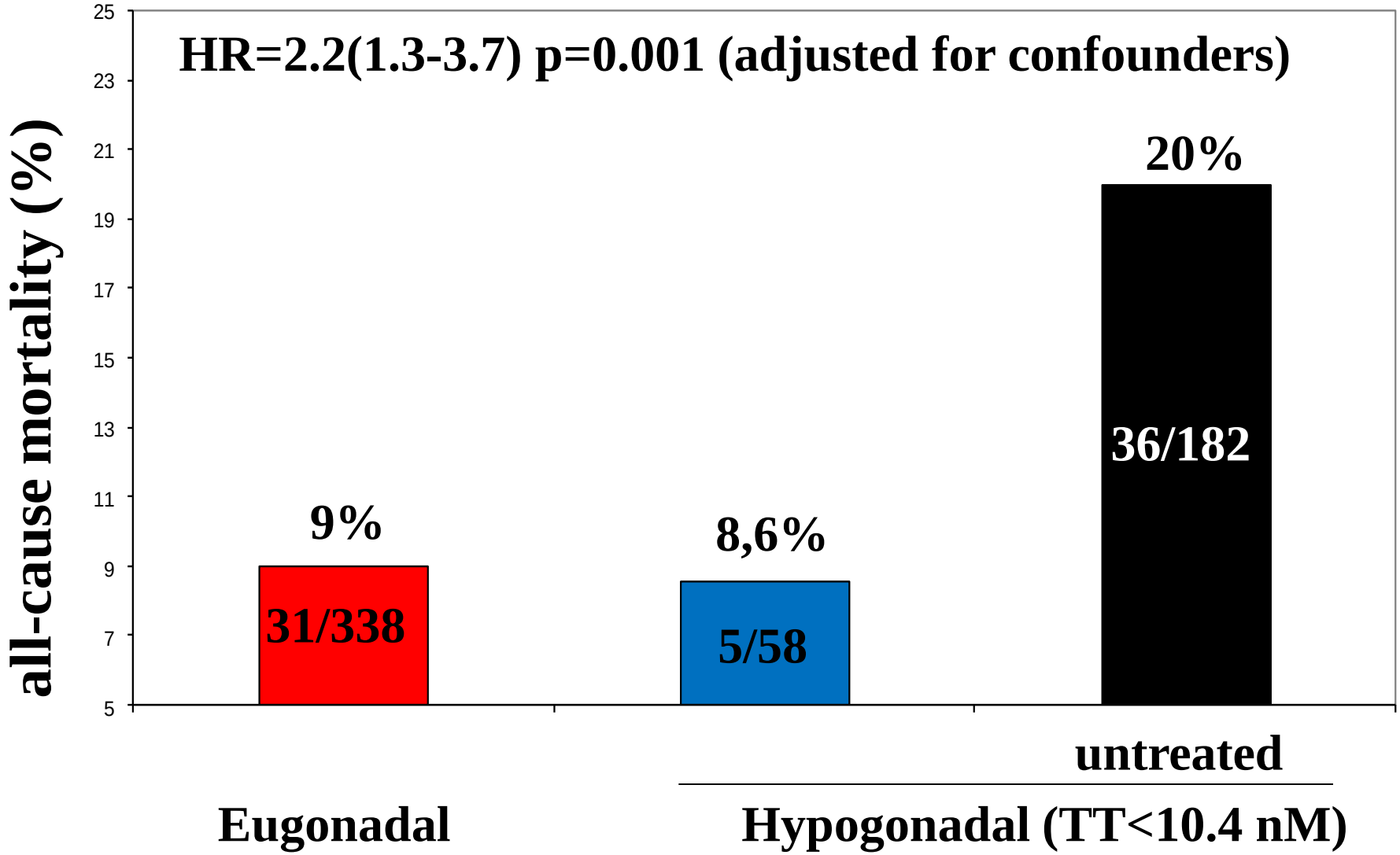
Hyde., J Clin Endocrinol and Metab. 2010;95:1

A 5.8±1.3 year follow-up study: effect of baseline TT and TRT on all-cause mortality in 580 T2DM men



Muraleedharan et al., Eur J Endocrinol 2013;169:725

A 5.8±1.3 year follow-up study: effect of baseline TT and TRT on all-cause mortality in 580 T2DM men



Muraleedharan et al., Eur J Endocrinol 2013;169:725

A 5 year follow-up study: effect of TRT on all-cause mortality in 1031 hypogonadal men (TT<8.7 nM)

Testosterone Treatment and Mortality in Men with Low Testosterone Levels

Molly M. Shores, Nicholas L. Smith, Christopher W. Forsberg, Bradley D. Anawalt, and Alvin M. Matsumoto

Veterans Affairs (VA) Puget Sound Health Care System (M.M.S., N.L.S., C.W.F., A.M.M.), Seattle, Washington 98108; VA Epidemiologic Research and Information Center, (N.L.S., C.W.F.) and VA Geriatric Research, Education, and Clinic Center (A.M.M.), Seattle, Washington 98108; Departments of Psychiatry and Behavioral Sciences (M.M.S.), Epidemiology (N.L.S.), and Medicine (B.D.A., A.M.M.), University of Washington, Seattle, Washington 98105; and Group Health Research Institute (N.L.S.), Group Health Cooperative, Seattle, Washington 98101

Muraleedharan et al., J Clin Endocrinol and Metab 2012;97:2050

Overall mortality: effect of TRT

- **treated: 10.3%**
- **untreated: 20.7%**

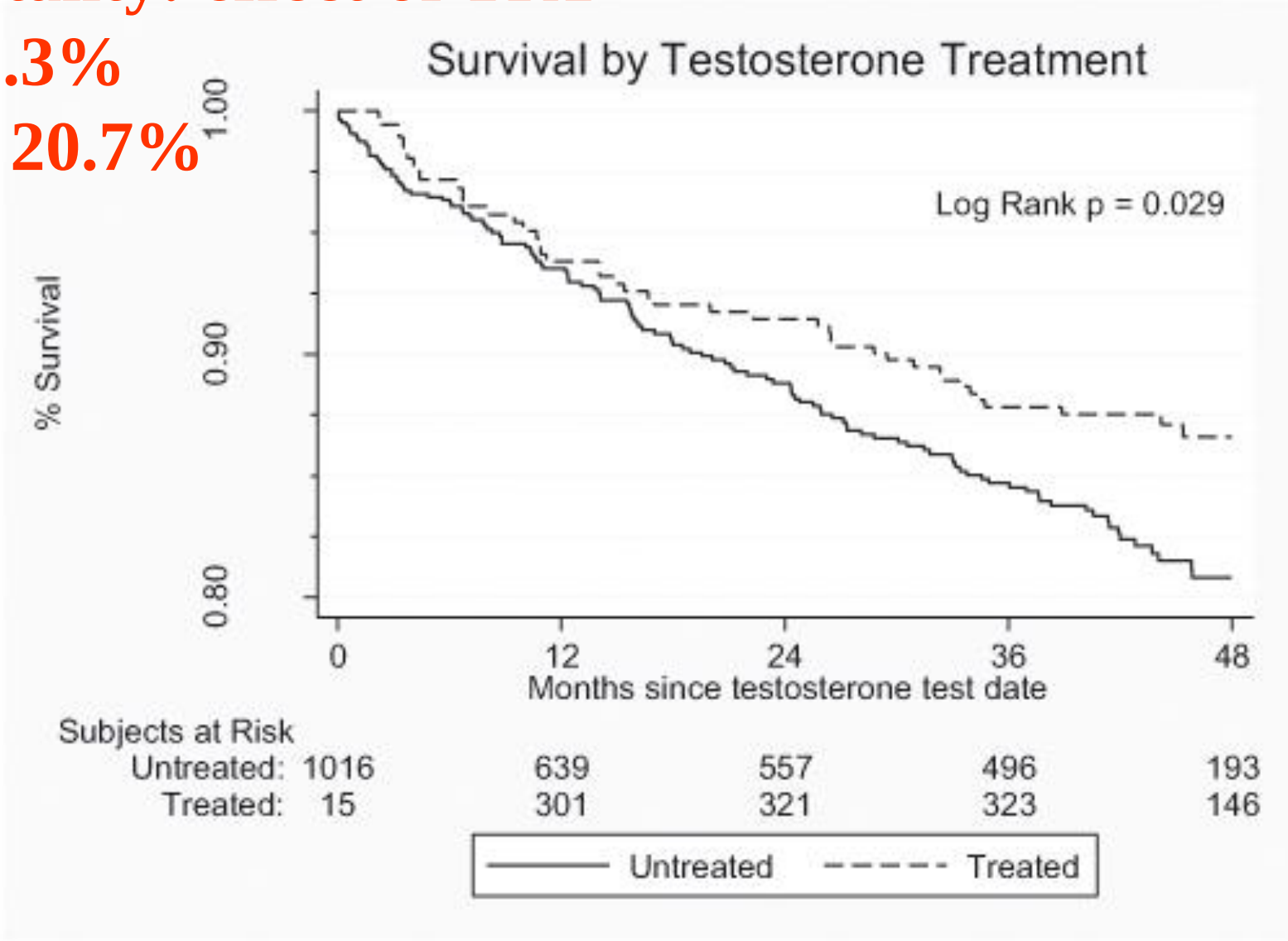


Fig. 1. Unadjusted Kaplan-Meier survival curves illustrate that testosterone-treated men had a longer survival time than untreated men ($P = 0.029$).

A 5 year follow-up study: effect of TRT on all-cause mortality in 1031 hypogonadal men (TT<8.7 nM)

Testosterone Treatment and Mortality in Men with Low Testosterone Levels

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TABLE 2. Mortality in testosterone-treated and -untreated men

Testosterone exposure	Person-years	Deaths	Mortality per 100 person-years	Fully adjusted HR (95% CI)[a]	Sensitivity HR (95% CI)[b]	Propensity score HR (95% CI)[c]
Untreated (n = 633)	2290	131	5.73	1.00 (reference)	1.00 (reference)	1.00 (reference)
Treated (n = 398)	1190	41	3.44	0.61 (0.42–0.88); $P = 0.008$	0.47 (0.29–0.76); $P = 0.003$	0.64 (0.44–0.95); $P = 0.026$
Total (n = 1031)	3480	172	4.95			

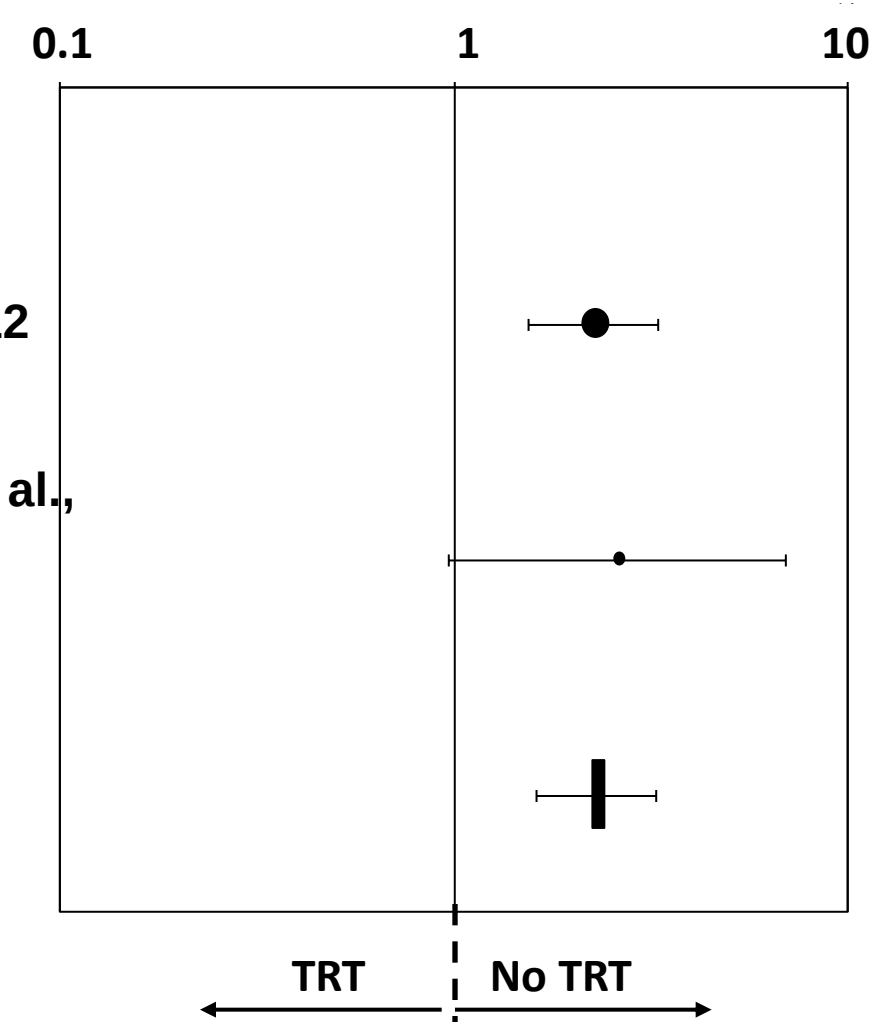
[a] Adjusted for age, site, medical morbidity, baseline testosterone level, BMI, prevalent coronary heart disease, prevalent diabetes mellitus, and hospitalization in the year prior to testosterone measurement.

[b] Sensitivity analysis excluding men who died within the first year (n = 62).

[c] Adjusted for propensity scores by quintiles.

Muraleedharan et al., J Clin Endocrinol and Metab 2012;97:2050

Odd ratio for overall mortality in hypogonadal subjects with or w/o TRT



Source	OR	LL, 95% CI	UL, 95% CI	P
Shores et al., 2012	2,272	1,560	3,310	<0.0001
Muraleedharan et al., 2013	2,614	0,974	7,012	0.056
OVERALL	**2,313**	**1,628**	**3,287**	**<0.0001**

No TRT doubles the risk of overall mortality in low T

Corona et al., World J Mens Health 2013;2: 103

Best Practice & Research Clinical Endocrinology & Metabolism 27 (2013) 557–579

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7

Diagnosis and treatment of late-onset hypogonadism: Systematic review and meta-analysis of TRT outcomes

G. Corona, MD, PhD, Endocrinologist [a, b], G. Rastrelli, MD, PhD, Endocrinologist [a], M. Maggi, MD, PhD, Endocrinologist [a, *]

[a] *Sexual Medicine and Andrology Unit Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy*

[b] *Endocrinology Unit, Maggiore-Bellaria Hospital, Medical Department, Azienda-Usl Bologna, Bologna, Italy*

EFFECTS OF TRT ON DM & MetS PATIENT RESULTS FROM META-ANALYSIS EVALUATION

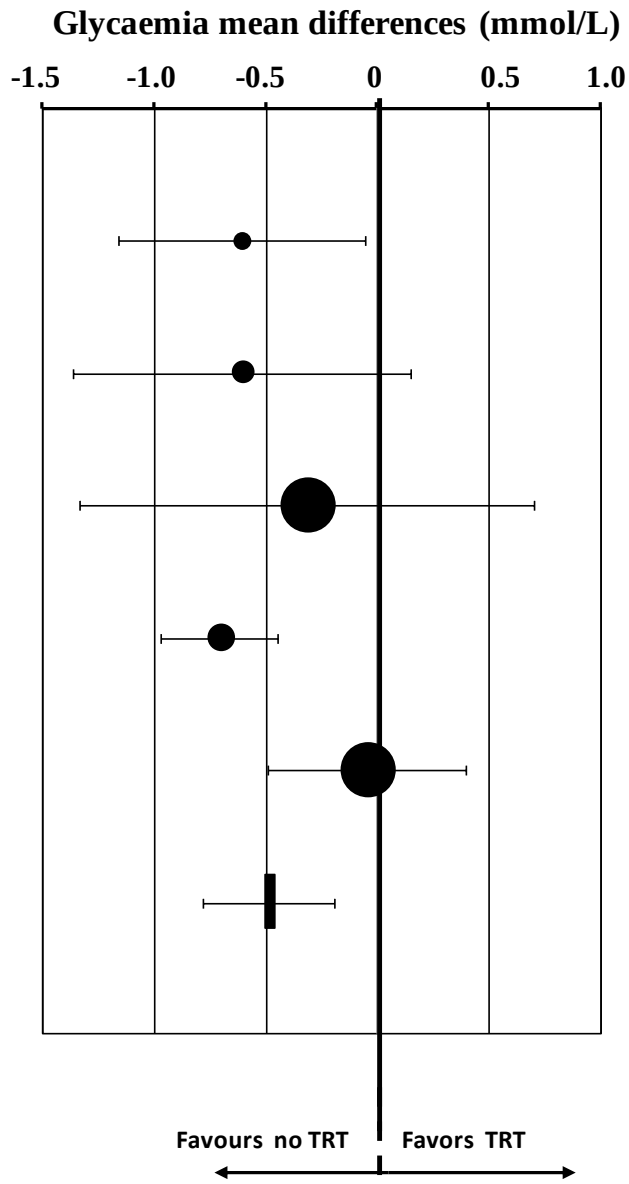
Patients with metabolic syndrome and or type 2 diabetes

Study (Ref.)	Boyanov et al 2003	Kapoor et al., 2006	La Vignera et al., 2008	Heufelder et al., 2009	Aversa et al., 2010	Gopal et al., 2010	Jones et al. 2011	Aversa et al., 2011	Tishova et al., 2011
Location	Sofia, Bulgaria	Sheffield, UK	Catania, Italy	Munich, Germany	Rome, Italy	Mumbai, India	Multicenter	Rome, Italy	Moscow, Russia
# patients (ID/C)	24/24	12/12	7/5	16/16	32/10	11/11	103/102	40/10	105/65
Hypogonadism cut off	TT <15 nM	TT <12 nM	TT <8 nM	TT <12 nM	TT <11 nM	cFT <225 pM	TT < 11 nM	TT <11 nM	TT < 12 nM
Trial duration (weeks)	12	12	52	52	52	12	52	104	30
Drugs	O-TU	i.m T	T gel 1%	T gel 1%	TU	i.m T	T gel 2%	TU	TU
Dose	120 mg daily	200 mg/ 2weeks	50 mg/ daily	50 mg/ daily	1000 mg/ 12 weeks	200 mg/ 2weeks	60mg/ Daily	1000 mg/ 12 weeks	1000 mg/ 12 weeks
Comparator	No TRT group	Placebo	No TRT group	No TRT group	Placebo	Placebo	Placebo	Placebo	Placebo
Metabolic characteristics	T2DM	T2DM	NCEP-ATPIII-MetS	T2DM with IDF-MetS	IDF-MetS	T2DM	IDF-MetS with or without T2DM	IDF-MetS	IDF-MetS

MetS n=483 patients; mean follow up 37 weeks

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

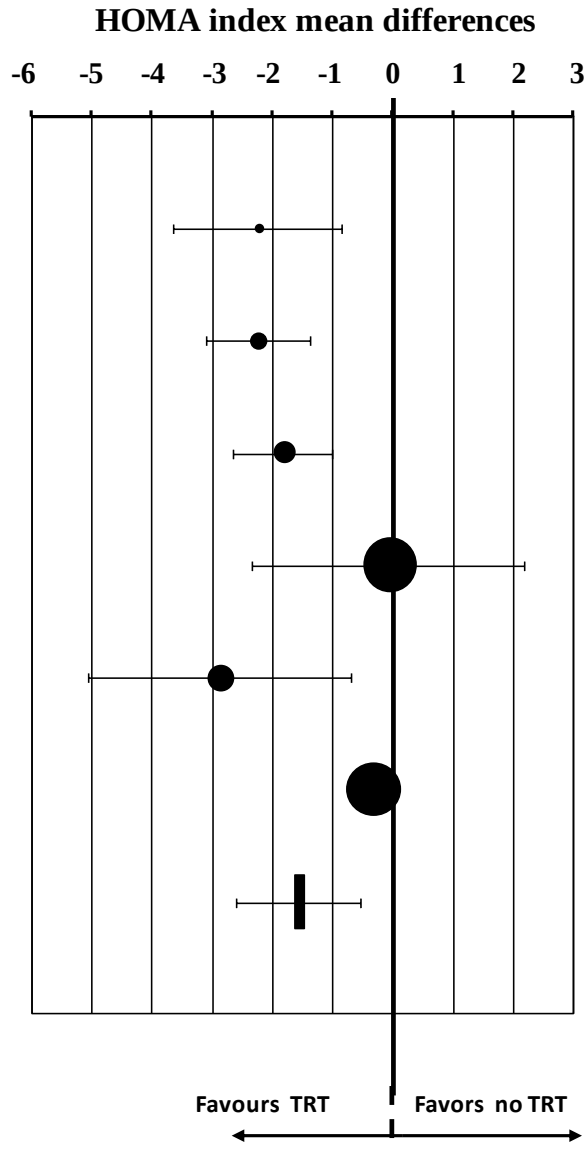
Effects of TRT on metabolic parameter in patients with MetS



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
Heufelder et al., 2009	-0,60	-1,15	-0,05	0,03
Aversa et al., 2010	-0,60	-1,35	0,15	0,12
Jones et al., 2011	-0,31	-1,33	0,71	0,55
Aversa et al., 2011	-0,70	-0,96	-0,44	0,00
Tishova et al., 2011	-0,04	-0,49	0,41	0,86
Overall	-0,48	-0,78	-0,19	0,00

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

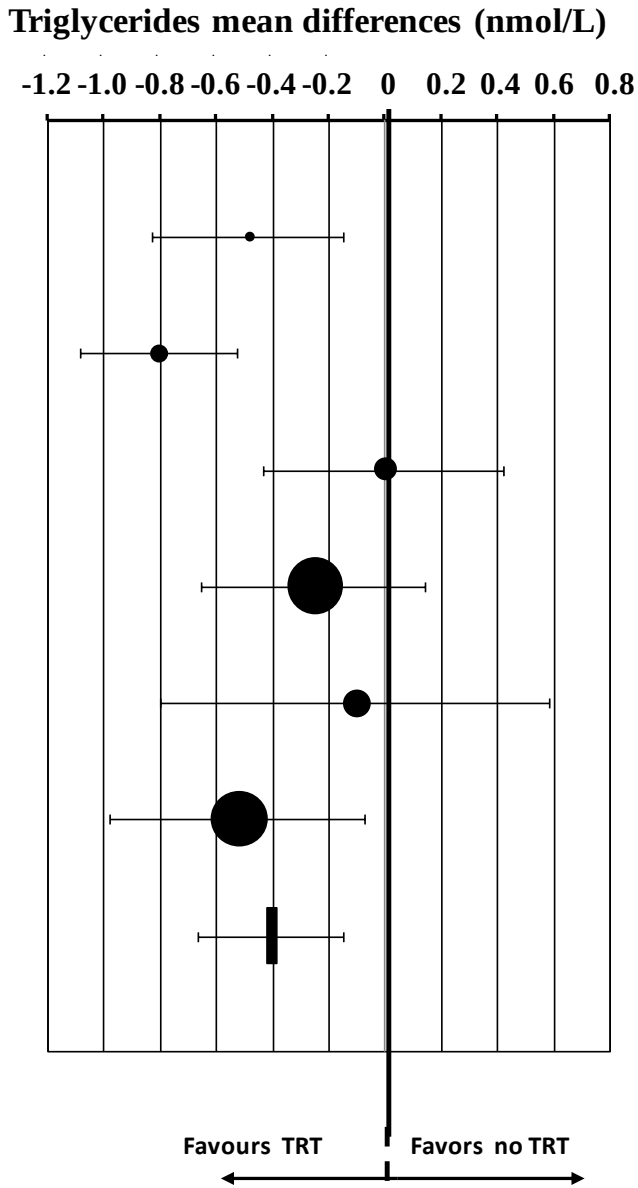
Effects of TRT on metabolic parameter in patients with MetS



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
La Vignera et al., 2009	-2,22	-3,62	-0,81	0,00
Heufelder et al., 2009	-2,22	-3,08	-1,35	0,00
Aversa et al., 2010	-1,80	-2,62	-0,98	0,00
Jones et al., 2011	-0,05	-2,31	2,21	0,97
Aversa et al., 2011	-2,85	-5,04	-0,66	0,01
Tishova et al., 2011	-0,32	-0,53	-0,11	0,00
Overall	-1,54	-2,59	-0,50	0,00

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

Effects of TRT on metabolic parameter in patients with MetS



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
La Vignera et al., 2009	-0,48	-0,82	-0,14	0,01
Heufelder et al., 2009	-0,80	-1,08	-0,52	0,00
Aversa et al., 2010	0,00	-0,43	0,43	1,00
Jones et al., 2011	-0,25	-0,65	0,15	0,22
Aversa et al., 2011	-0,10	-0,79	0,59	0,78
Tishova et al., 2011	-0,52	-0,98	-0,06	0,03
Overall	-0,40	-0,66	-0,14	0,00

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

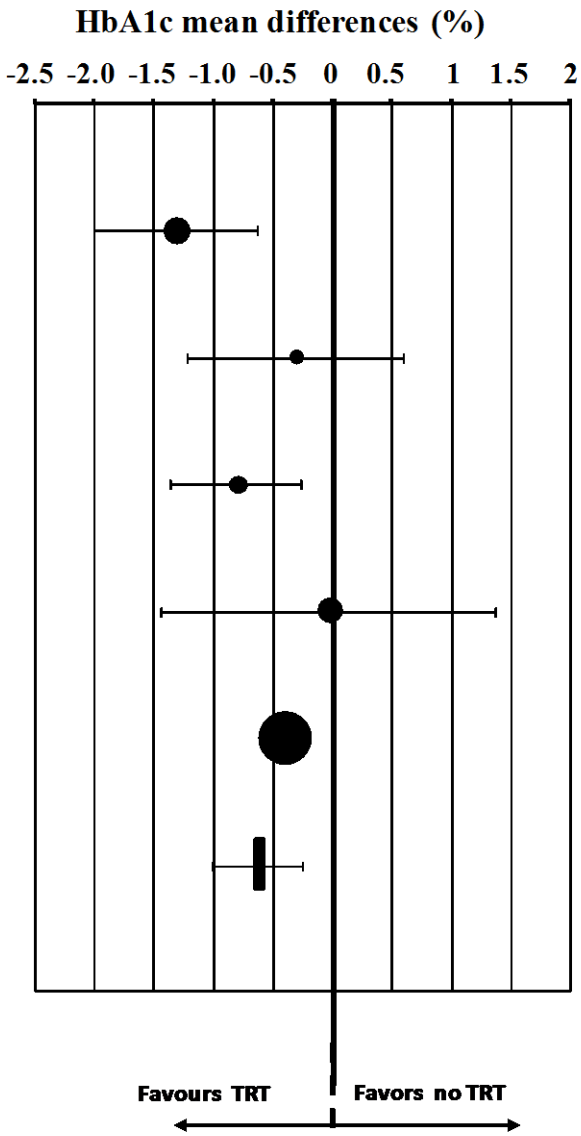
Patients with metabolic syndrome and or type 2 diabetes

Study (Ref.)	Boyanov et al 2003	Kapoor et al., 2006	La Vignera et al., 2008	Heufelder et al., 2009	Aversa et al., 2010	Gopal et al., 2010	Jones et al., 2011	Aversa et al., 2011	Tishova et al., 2011
Location	Sofia, Bulgaria	Sheffield, UK	Catania, Italy	Munich, Germany	Rome, Italy	Mumbai, India	Multicenter	Rome, Italy	Moscow, Russia
# patients (ID/C)	24/24	12/12	7/5	16/16	32/10	11/11	103/102	40/10	105/65
Hypogonadism cut off	TT <15 nM	TT <12 nM	TT <8 nM	TT <12 nM	TT <11 nM	cFT <225 pM	TT < 11 nM	TT <11 nM	TT < 12 nM
Trial duration (weeks)	12	12	52	52	52	12	52	104	30
Drugs	O-TU	i.m T	T gel 1%	T gel 1%	TU	i.m T	T gel 2%	TU	TU
Dose	120 mg daily	200 mg/ 2weeks	50 mg/ daily	50 mg/ daily	1000 mg/ 12 weeks	200 mg/ 2weeks	60mg/ Daily	1000 mg/ 12 weeks	1000 mg/ 12 weeks
Comparator	No TRT group	Placebo	No TRT group	No TRT group	Placebo	Placebo	Placebo	Placebo	Placebo
Metabolic characteristics	T2DM	T2DM	NCEP-ATPIII-MetS	T2DM with IDF-MetS	IDF-MetS	T2DM	IDF-MetS with or without T2DM	IDF-MetS	IDF-MetS

Type 2 diabetes n=263 patients; mean follow up 28 weeks

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

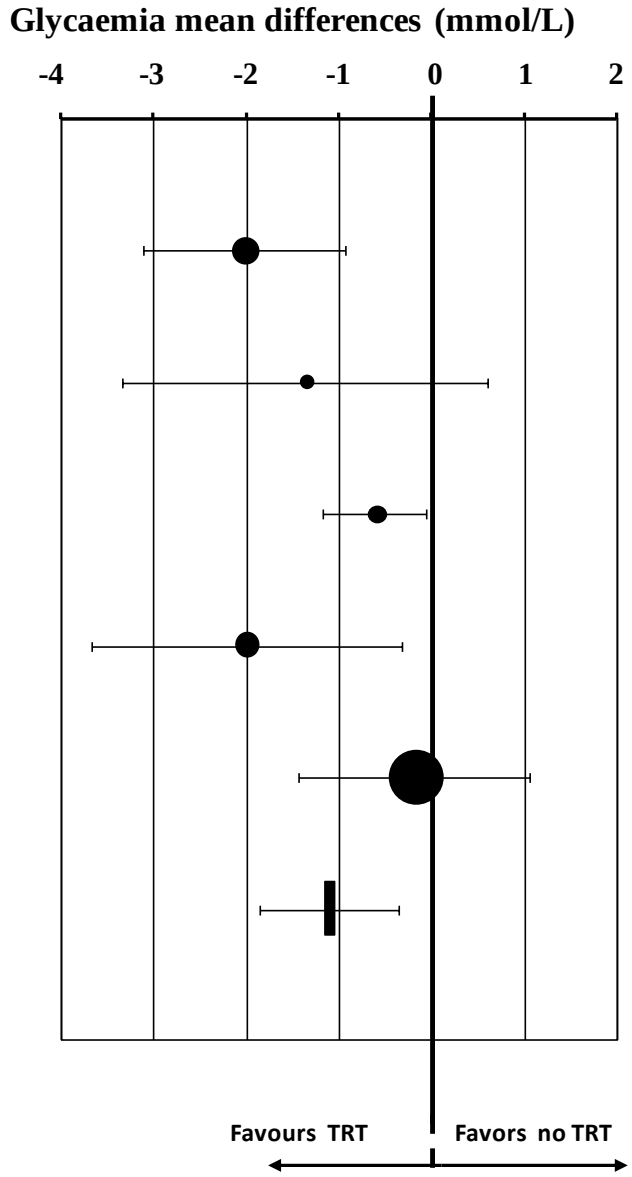
Effects of TRT on metabolic parameter in patients with T2DM



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
Boyanov et al., 2003	-1,30	-1,99	-0,61	0,00
Kapoor et al., 2006	-0,30	-1,21	0,61	0,52
Heufelder et al., 2009	-0,80	-1,35	-0,25	0,00
Gopal et al., 2010	-0,02	-1,43	1,39	0,98
Jones et al., 2011	-0,40	-0,55	-0,25	0,00
Overall	-0,62	-1,00	-0,24	0,00

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

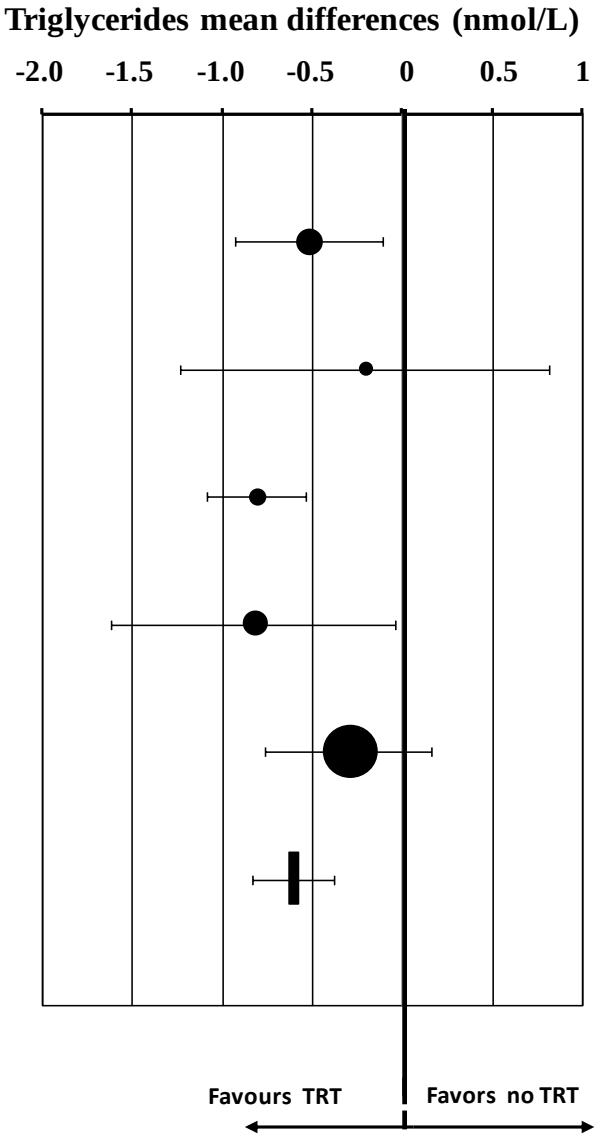
Effects of TRT on metabolic parameter in patients with T2DM



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
Boyanov et al., 2003	-2,00	-3,09	-0,91	0,00
Kapoor et al., 2006	-1,35	-3,33	0,63	0,18
Heufelder et al., 2009	-0,60	-1,15	-0,05	0,03
Gopal et al., 2010	-1,98	-3,66	-0,30	0,02
Jones et al., 2011	-0,17	-1,42	1,08	0,79
Overall	-1,09	-1,84	-0,35	0,00

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557

Effects of TRT on metabolic parameter in patients with T2DM



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	p
Boyanov et al., 2003	-0,51	-0,92	-0,10	0,02
Kapoor et al., 2006	-0,20	-1,23	0,83	0,70
Heufelder et al., 2009	-0,80	-1,08	-0,52	0,00
Gopal et al., 2010	-0,82	-1,61	-0,03	0,04
Jones et al., 2011	-0,29	-0,75	0,17	0,22
Overall	-0,60	-0,83	-0,37	0,00

Corona et al., Best Pract Clin Endocrinol & Metab 2013;27;557


E per il GH?

ORIGINAL ARTICLE

Endocrine Care

Long-Term Mortality after Recombinant Growth Hormone Treatment for Isolated Growth Hormone Deficiency or Childhood Short Stature: Preliminary Report of the French SAGhE Study

Jean-Claude Carel, Emmanuel Ecosse, Fabienne Landier,
Djamila Meguellati-Hakkas, Florentia Kaguelidou, Grégoire Rey, and Joël Coste

Increased in treated subjects:

- All-cause mortality 1.33 [1.08–1.64].
- Use of GH doses greater than 50 mcg/kg/d mortality rates 2.94[1.22–7.07]
- Bone tumor-related mortality 5.00[1.01–14.63].
- CVD mortality 3.07[1.40–5.83]
- Subarachnoid or intracerebral hemorrhage 6.66[1.79–17.05].

Carel et al., J Clin Endocrinol & Metab 2012;97;416

Pituitary
DOI 10.1007/s11102-013-0529-6

Adult mortality or morbidity is not increased in childhood-onset growth hormone deficient patients who received pediatric GH treatment: an analysis of the Hypopituitary Control and Complications Study (HypoCCS)

Daojun Mo · Dana Sue Hardin · Eva Marie Erfurth · Shlomo Melmed

The Hypopituitary Control and Complications Study (HypoCCS), a global post-marketing surveillance study conducted by Eli Lilly and Company, monitored clinical outcomes of adult GH-deficient (GHD) patients

Mo et al., Pituitary 2013, 12 Oct [Epub ahead of print]

Crude mortality rate and SMRs by country for COGHD group

Country	N	Follow-up years	Crude mortality (100,000 person-years) (95 % CI)	Observed deaths	Expected deaths	SMR (95 % CI)
Czech Republic	27	141.4	707.2 (17.9–3,940.4)	1	0.299	3.35 (0.08–18.64)
France	125	372.2	806.0 (166.2–2,355.6)	3	0.927	3.24 (0.67–9.46)
Germany	113	505.22	197.9 (5.0–1,102.8)	1	1.12	0.89 (0.02–4.97)
Netherlands	66	474.74	210.6 (5.3–1,173.6)	1	0.779	1.28 (0.03–7.15)
United Kingdom	40	160.81	1,865.5 (384.7–5,451.9)	3	0.278	10.81 (2.23–31.58)
United States	359	1,134.8	88.1 (2.2–491.0)	1	1.931	0.52 (0.01–2.89)
Overall	1,204	4,462.4	224.0 (107.5–412.1)	10	8.751	1.14 (0.55–2.10)

Crude incident cancer rate and SIR by country for COGHD group

Country	N	Follow-up years	Crude incidence (100,000 person-years) (95 % CI)	Observed cancer cases	Expected cancer cases	SMR (95 % CI)
United Kingdom	31	127.2	786.3 (19.9–4,381.0)	1	0.119	8.37 (0.21–46.6)
Overall	1,056	3,965.4	25.2 (0.6–140.5)	1	3.718	0.27 (0.01–1.50)

Mo et al., Pituitary 2013, 12 Oct [Epub ahead of print]

Crude incident cancer rate and SIR by country for COGHD group

Country	N	Follow-up years	Stroke type	Number of cases	Crude incidence rate (per 100,000 person-years) (95 % CI)
France	121	361.3	Unspecific	1	276.8 (7.0–1,542.0)
Germany	112	502.1	Unspecific	1	199.25 (5.0–1,109.6)
Japan	90	136.6	Ischemia	1	732.2 (18.5–4,079.8)
United Kingdom	40	160.8	Ischemia	1	621.9 (15.7–3,464.7)
United States	356	1,130.9	Hemorrhage	1	88.4 (2.2–492.7)
			Ischemia	3	265.3 (54.7–775.3)
Overall	1,189	4,413.1	Hemorrhage	1	22.7 (0.6–126.3)
			Ischemia	5	113.3 (36.8–264.4)
			Unspecific	2	45.3 (5.5–163.7)
			Overall	8	181.3 (78.3–357.2)

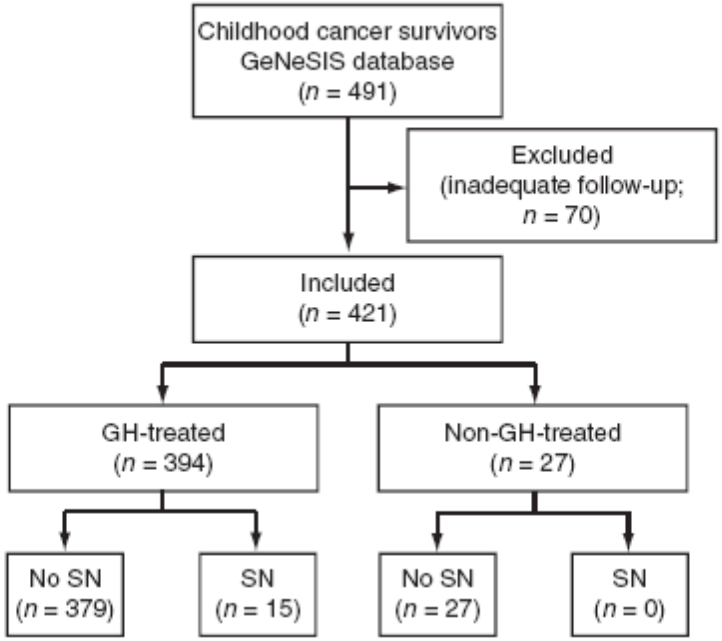
Mo et al., Pituitary 2013, 12 Oct [Epub ahead of print]

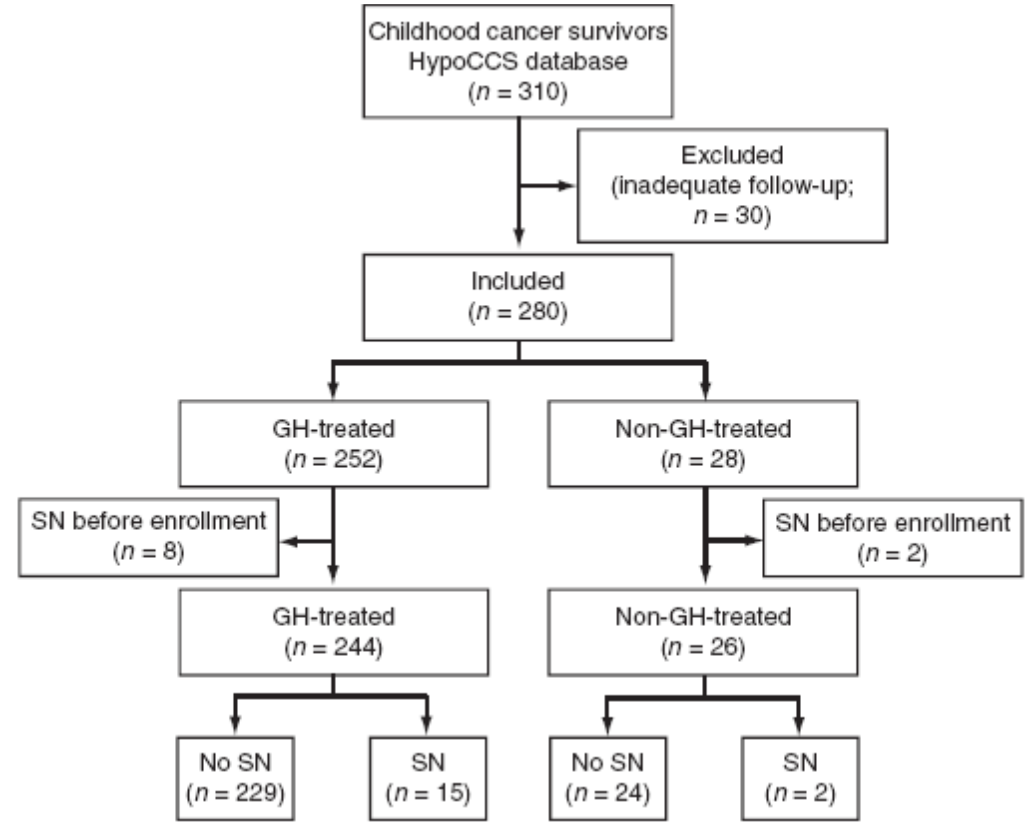
European Journal of Endocrinology (2013) **168** 565–573 ISSN 0804-4643

CLINICAL STUDY

Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS

Whitney W Woodmansee, Alan G Zimmermann[1], Christopher J Child[2], Qi Rong[1], Eva Marie Erfurth[3], Paolo Beck-Peccoz[4], Werner F Blum[5], Leslie L Robison[6] on behalf of the GeNeSIS and HypoCCS International Advisory Boards





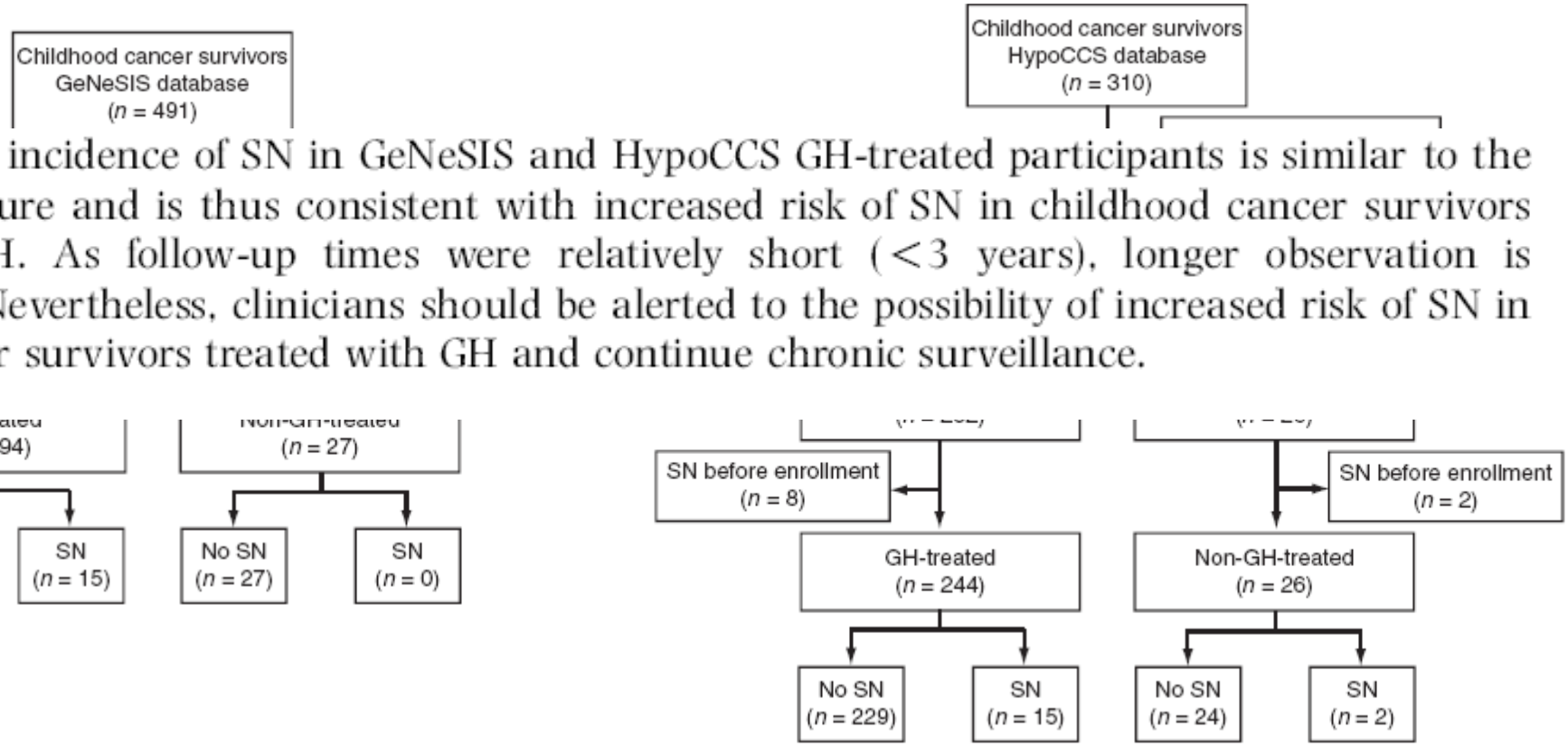
Woodmansee et al., Eur J Endocrinol 2013, 168:565

European Journal of Endocrinology (2013) **168** 565–573 ISSN 0804-4643

CLINICAL STUDY

Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS

Whitney W Woodmansee, Alan G Zimmermann[1], Christopher J Child[2], Qi Rong[1], Eva Marie Erfurth[3], Paolo Beck-Peccoz[4], Werner F Blum[5], Leslie L Robison[6] on behalf of the GeNeSIS and HypoCCS International Advisory Boards



Conclusions: The incidence of SN in GeNeSIS and HypoCCS GH-treated participants is similar to the published literature and is thus consistent with increased risk of SN in childhood cancer survivors treated with GH. As follow-up times were relatively short (<3 years), longer observation is recommended. Nevertheless, clinicians should be alerted to the possibility of increased risk of SN in childhood cancer survivors treated with GH and continue chronic surveillance.

Woodmansee et al., Eur J Endocrinol 2013, 168:565