ACCADEMIA SICOB
CORSO SICOB III EDIZIONE
MILANO 11-12 APRILE 2024

Assessment endocrino-metabolico

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CERT FOR BANGL
TAXI

Table 1 Hormonal alterations in obesity.

Hormone	Levels in obesity	Proposed pathophysiologic mechanism
TSH	N or ↑	↑ leptin and insulin ↑ peripheral T4 disposal
FT4	N or slightly ↓	↑ disposal
Cortisol (blood and urine, salivary)	N or ↑ Altered suppression tests	↑ CRH, ↑ adipose 11-HSD, ↓ CBG Hyperactivity of the HPA axis
ACTH	N or ↑	↑ CRH
Growth hormone	N or ↓	↓ GHRH, ↑GH-BP, ↑insulin, ↓ghrelin, ↑somatostatin
IGF-1	N or ↓	↑ GH sensitivity Increased intrahepatic triglyceride content
Prolactin	?	Discordant data
Testosterone (male)	↓	↓ SHBG ↑ aromatase ↓GnRH
Testosterone (female)	↑	Insulin resistance (PCOS) ↓ SHBG
LH/FSH	↓ in men ↑ LH in women	↑ oestrogens/androgens Insulin resistance
25-OH vitamin D	↓	Trapping in adipose tissue, ↓ sun exposure ↓ 25OH vitamin D binding protein ↓ liver synthesis
PTH	N or ↑	Secondary due to vitamin D deficiency
Insulin	↑	Insulin resistance
Renin	↑	↑ Sympathetic tone
Aldosterone	↑	↑ Adipokines, renin- angiotensin, leptin
GLP-1	↓	↑ FFA, microbiota
Leptin	↑	Increased adipose mass, Leptin resistance
Ghrelin	↓	Lack of ghrelin decrease after meals

11-HSD, 11β-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropic hormone; CBG, corticosteroid-binding globulin; CRH, corticotropin-releasing hormone; FFA, free fatty acids; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH-BP, growth hormone-binding protein; GHRH, growth hormone-releasing hormone; GLP, glucagon-like peptide; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal axis; IGF, insulin-like growth factor; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; PTH, parathyroid hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone.

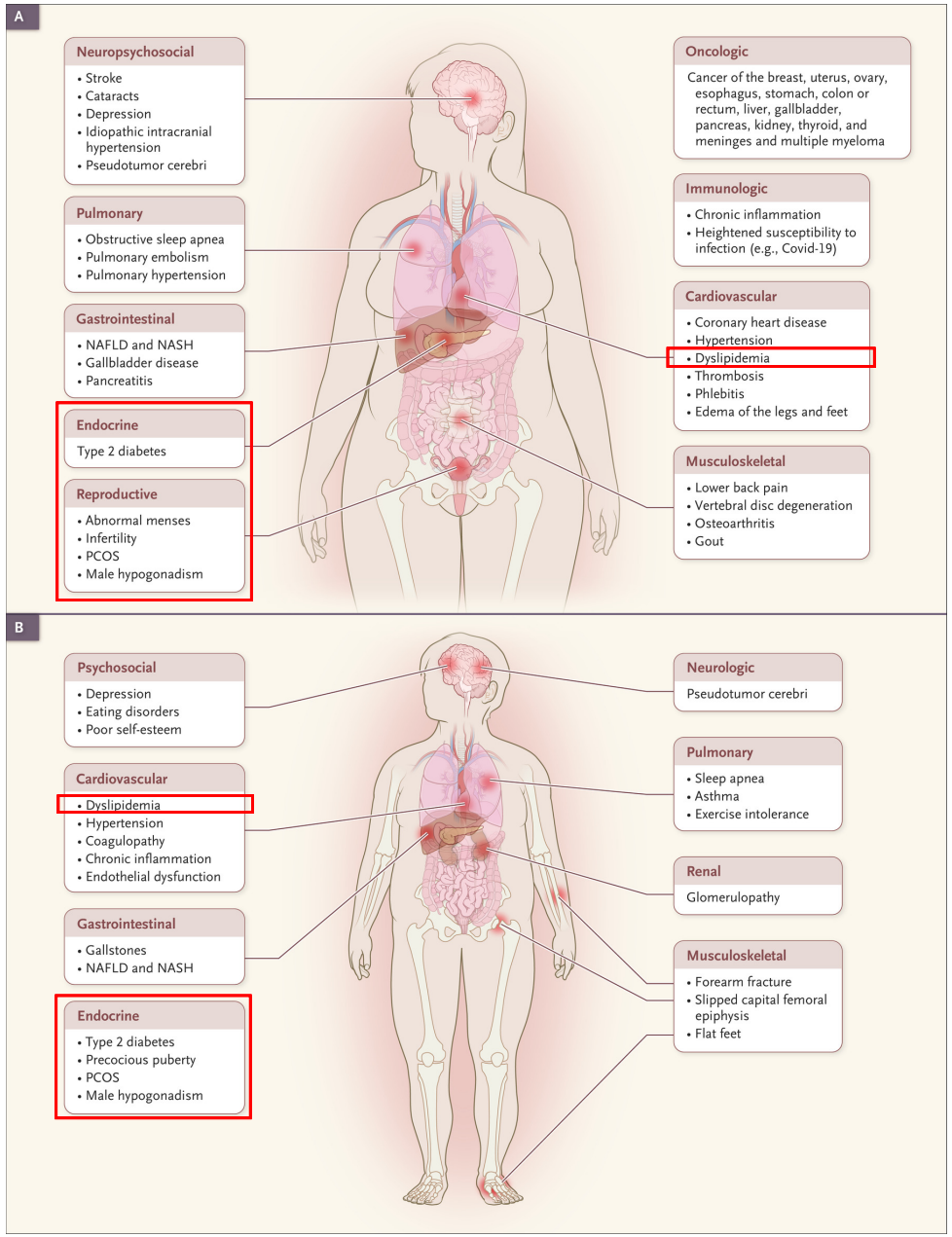
Table 2 Examples of endocrine diseases/disturbances causing or contributing to obesity.

Condition	Prevalence in obesity	When to think about it	First diagnostic procedure
Androgen deficiency (men)	Common	Severe obesity Symptoms and signs of hypogonadism	LH FSH testosterone
Androgen excess (women)	Common	Central obesity Irregular menses Hirsutism Acanthosis nigricans	LH FSH oestradiol testosterone
Cushing's disease or Cushing's syndrome	Rare	Central obesity Hypertension Type 2 diabetes	1 mg ODST
Drug-induced endocrine dysfunction (e.g. lithium, anti-depressants, antipsychotics, glucocorticoids...)	Common	Psychiatric disorders Glucocorticoid therapy	1 mg ODST to exclude Cushing syndrome (except in glucocorticoid use)
Ovarian failure (premature or menopause)	Premature uncommon Physiological (Menopause) Common	Secondary amenorrhea Vasomotor symptoms Vaginal mucosa atrophy	FSH, LH, oestradiol
GH deficiency	Rare	Hypothalamic or pituitary disease, pituitary or hypothalamic surgery or radiation therapy	Serum IGF-I, GH-stimulating tests
Hypopituitarism	Rare	Suspicion of hypothalamic obesity Surgery or radiotherapy in pituitary region	FT4 TSH LH FSH (testosterone or estradiol) GH IGF-1 PRL ACTH stimulation test GH stimulation test
Hypothalamic obesity associated with Genetic Syndromes	Extremely rare	Hypogonadism (hypogonadism or hypergonadotropic) or variable gonadal function. dysmorphic syndrome, mental and grow retardation	Leptin (leptin resistance) (7); genetic testing
Hypothalamic obesity acquired (hypothalamic lesions or, tumors)	Rare	Severe hyperphagia Possible multiple endocrine abnormalities	Brain CT or MRI
(Severe) hypothyroidism	Rare	Mixedematous features Concurrent autoimmune diseases	FT4 TSH
Insulinoma	Very rare	Hypoglycaemic symptoms	Blood glucose, insulin, C-peptide 72-h supervised fast
Leptin deficiency	Extremely rare	Severe childhood obesity	Leptin ↓
Leptin receptor deficiency or inactive leptin (8)	Extremely rare	Severe childhood obesity	Leptin ↑
MC4R mutation	rare	Severe childhood obesity	Leptin normal or ↑
Primary empty sella	Rare (increase intracranial pressure)	female, HTA, SAOS headache, menstrual disturbances	Prolactin, FSH LH, testosterone/ oestradiol, cortisol, IGF-1 MRI of pituitary
Abnormal processing of Propiomelanocortin (POMC) gene mutations	Extremely rare	Severe childhood obesity Red hair	ACTH ↓ (9)
Prohormone convertase 1/3 deficiency (PC-1/3) (PCSK1 gene mutation)	Extremely rare	Multiendocrine disorders, including diabetes insipidus, growth hormone deficiency, primary hypogonadism, adrenal insufficiency and hypothyroidism (10)	
Pseudohypoparathyroidism Type 1a (Albright hereditary osteodystrophy)	Rare	Short stature, short fourth metacarpal bones, obesity, s.c. calcifications, developmental delay	PTH ↑ calcium ↓ phosphate ↑

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; MC4R, melanocortin receptor 4; ODST, overnight dexamethasone suppression test; PCSK, proprotein convertase subtilisin/kexin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

Pasquali et al., Eur J Endocrinol. 2020 Jan;182(1):G1-G32

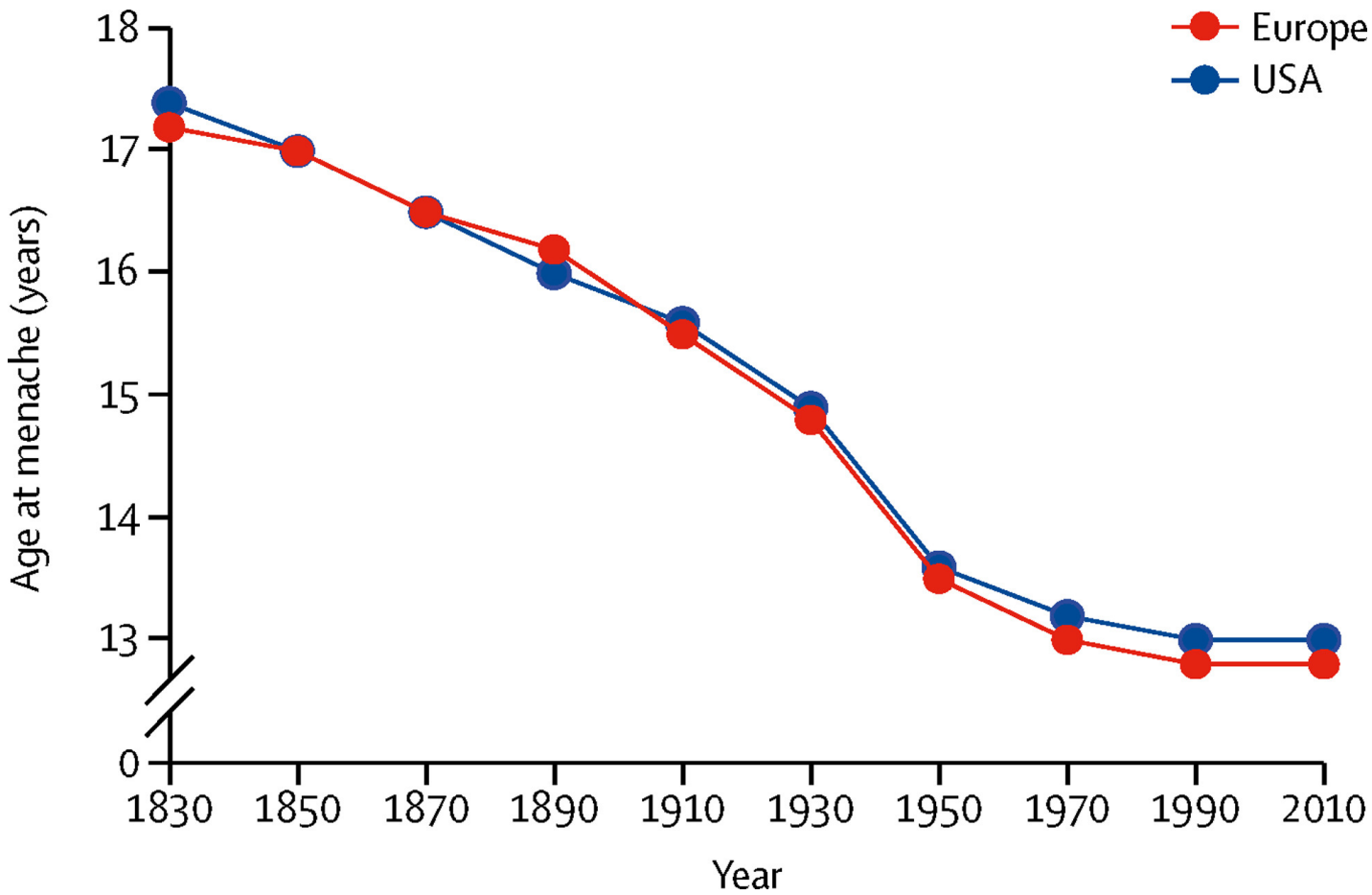
Complications of obesity and diseases associated with it in adults (Panel A) and children (Panel B)



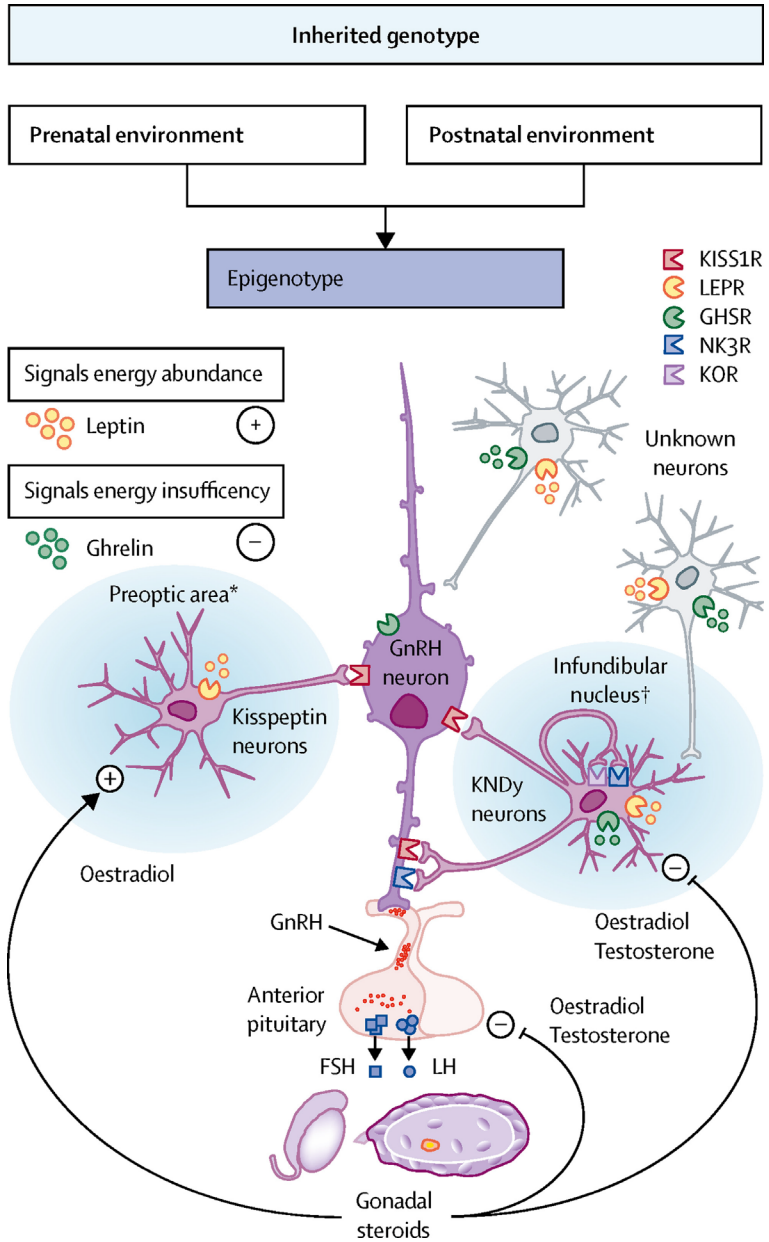
Cypess AM. N Engl J Med. 2022 Feb 24;386(8):768-779.

PUBERTA’ PRECOCE

Age at menarche in the USA and Europe in the past 180 years

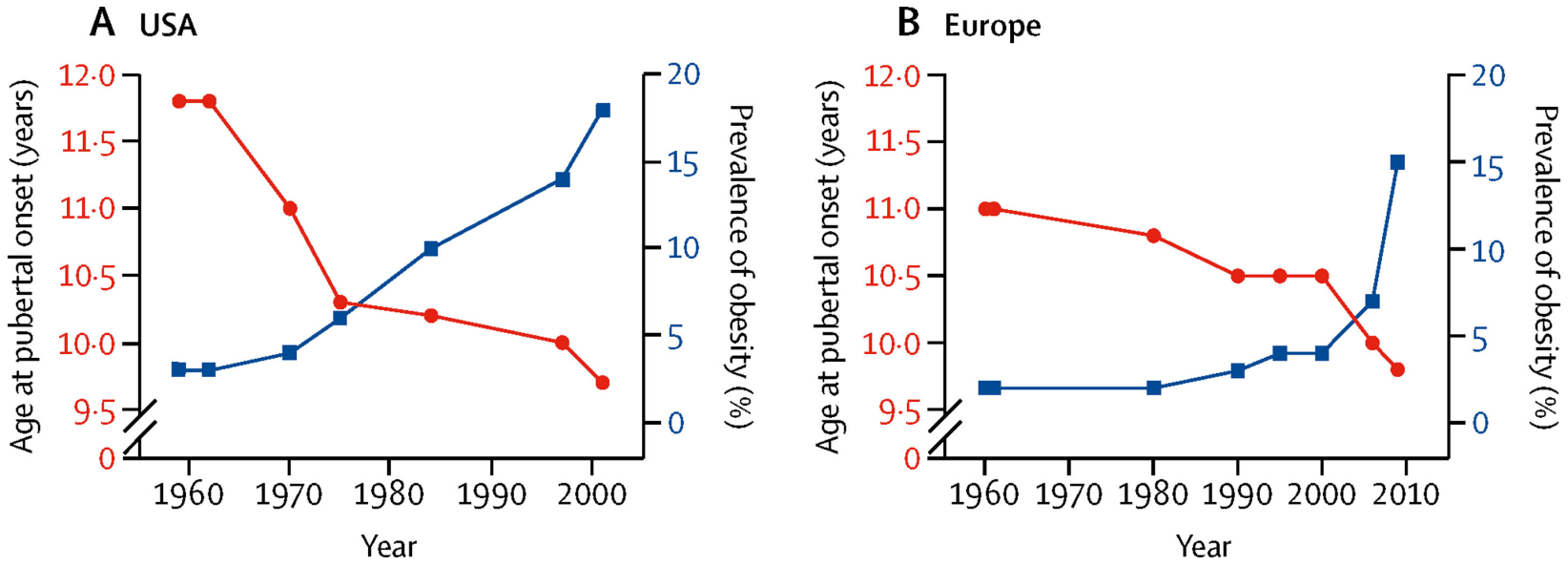


The regulation of puberty onset

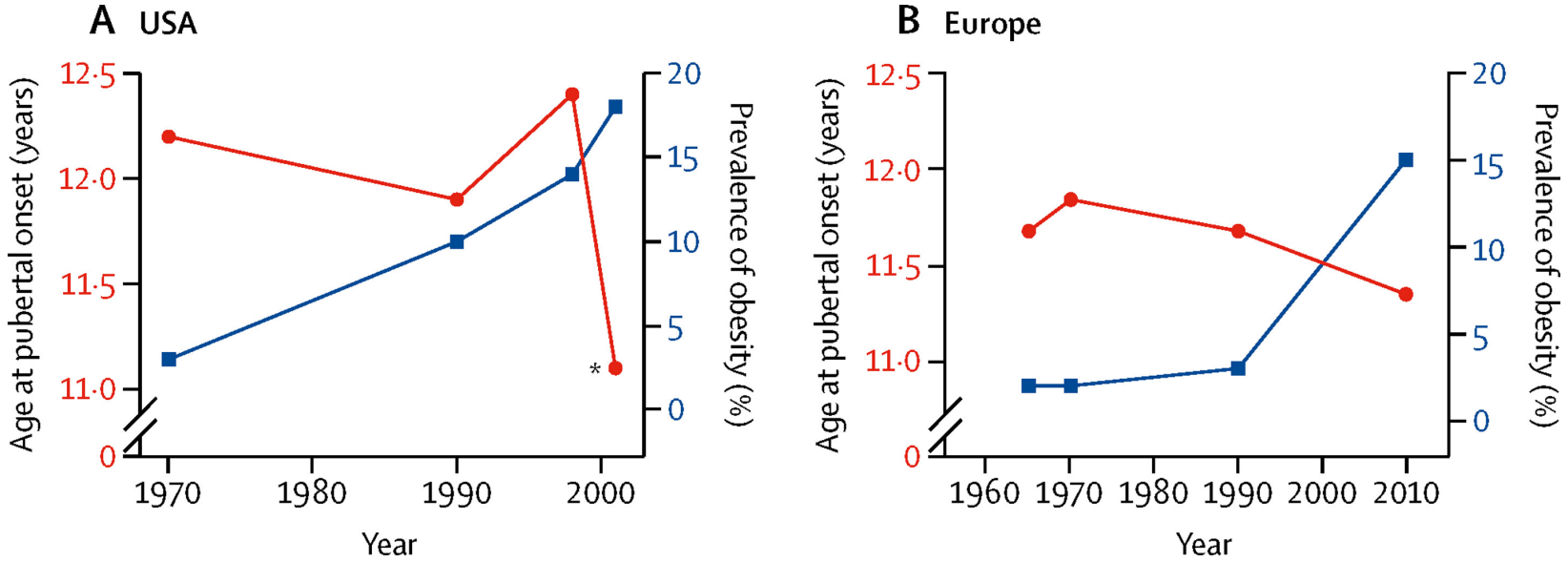


Reinehr T, Roth CL. Lancet Child Adolesc Health. 2019 Jan;3(1):44-54.

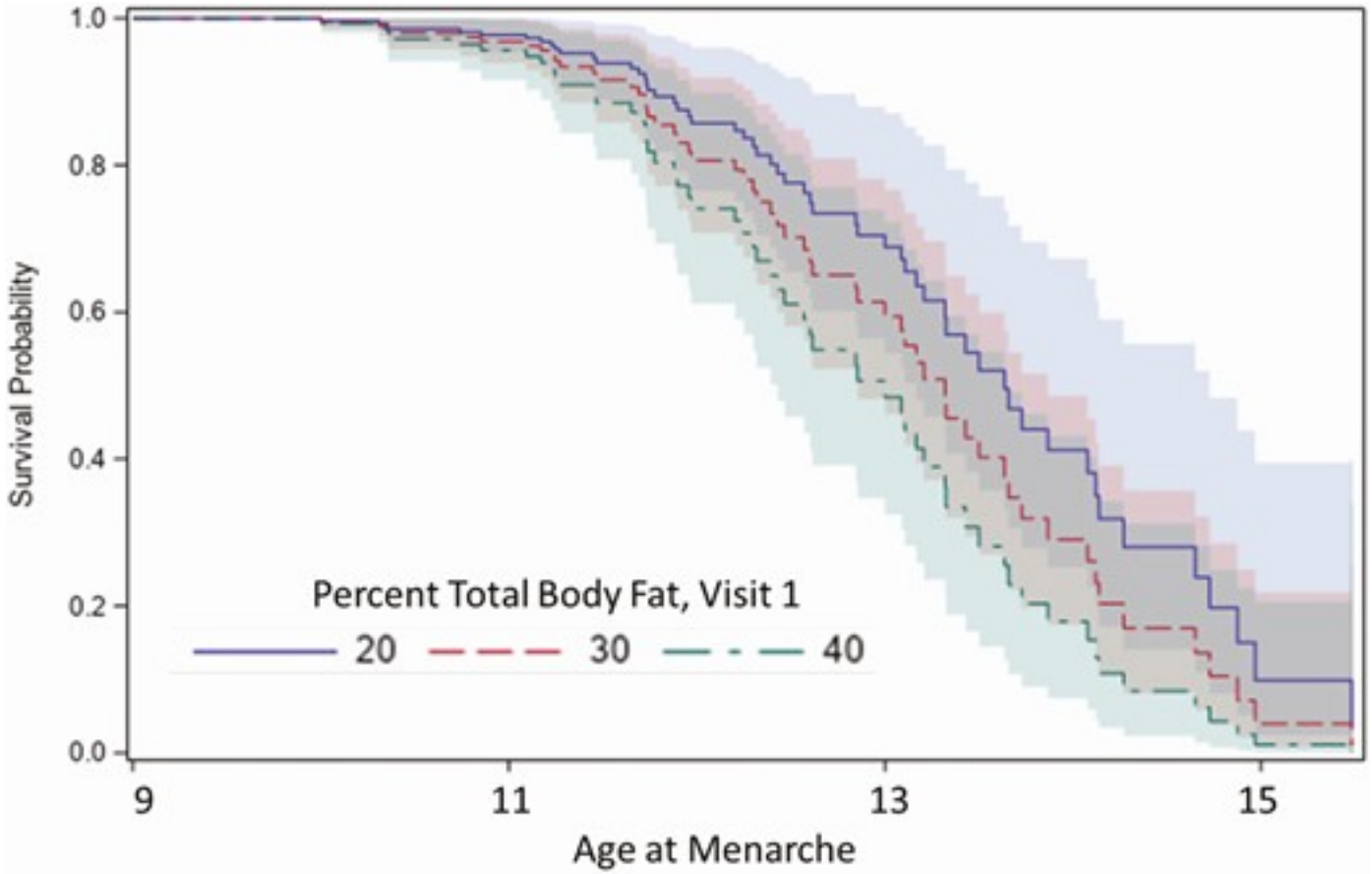
Prevalence of obesity in childhood and age at pubertal onset in girls in the USA (A) and Europe (B) in the past few decades



Prevalence of obesity in childhood and age at pubertal onset in boys in the USA (A) and Europe (B) in the past few decades



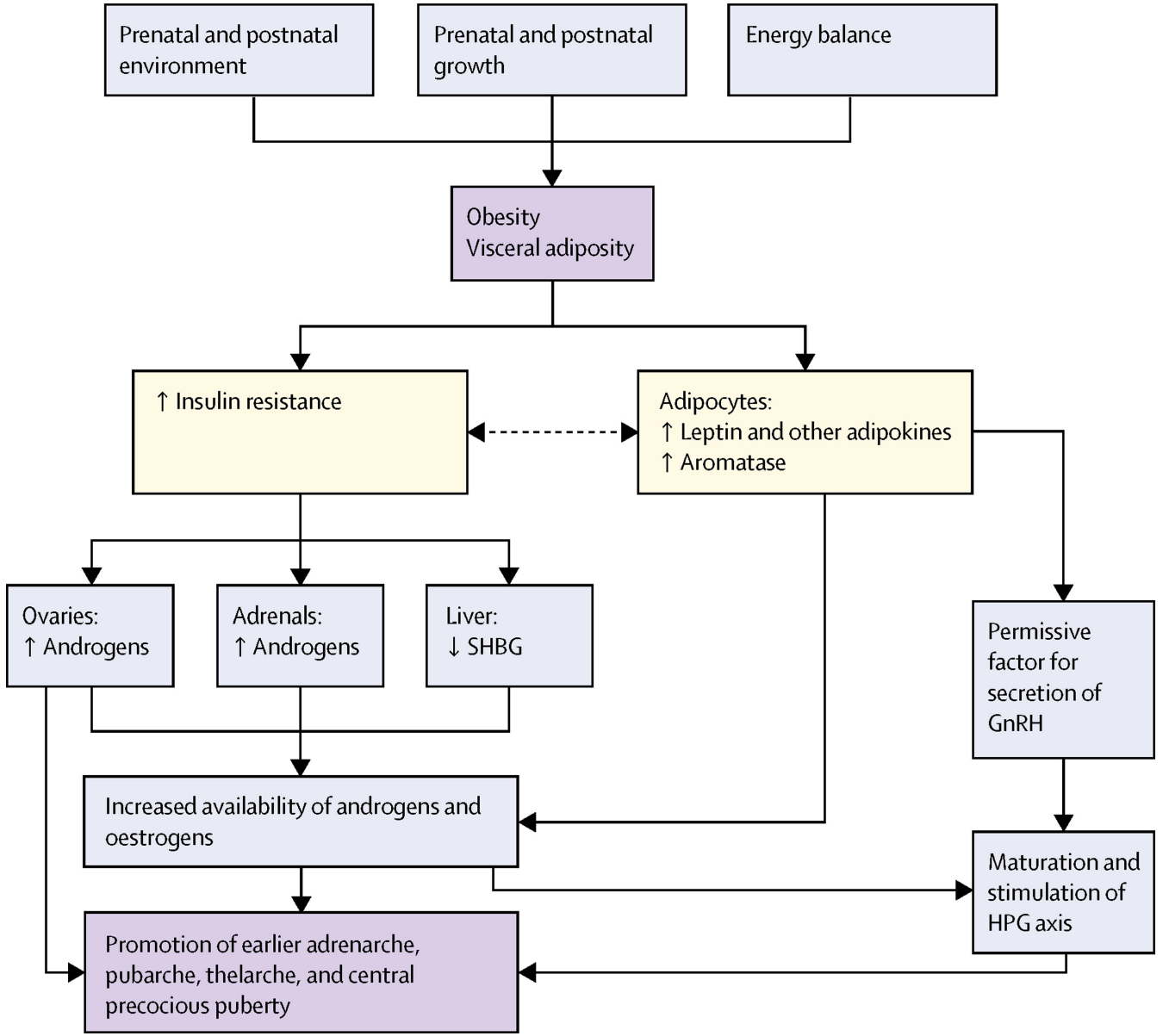
Reinehr T, Roth CL. Lancet Child Adolesc Health. 2019 Jan;3(1):44-54.



Survival curves of age at menarche in girls with percentage total body fat (TBF) of 20%, 30%, or 40% demonstrating that menarche occurred earlier in girls with higher TBF. Shaded areas indicate the 95% CI.2

The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 6, June 2021, Pages 1668–1683

Hypotheses linking obesity, insulin resistance, and adipokine secretion to timing of pubertal development

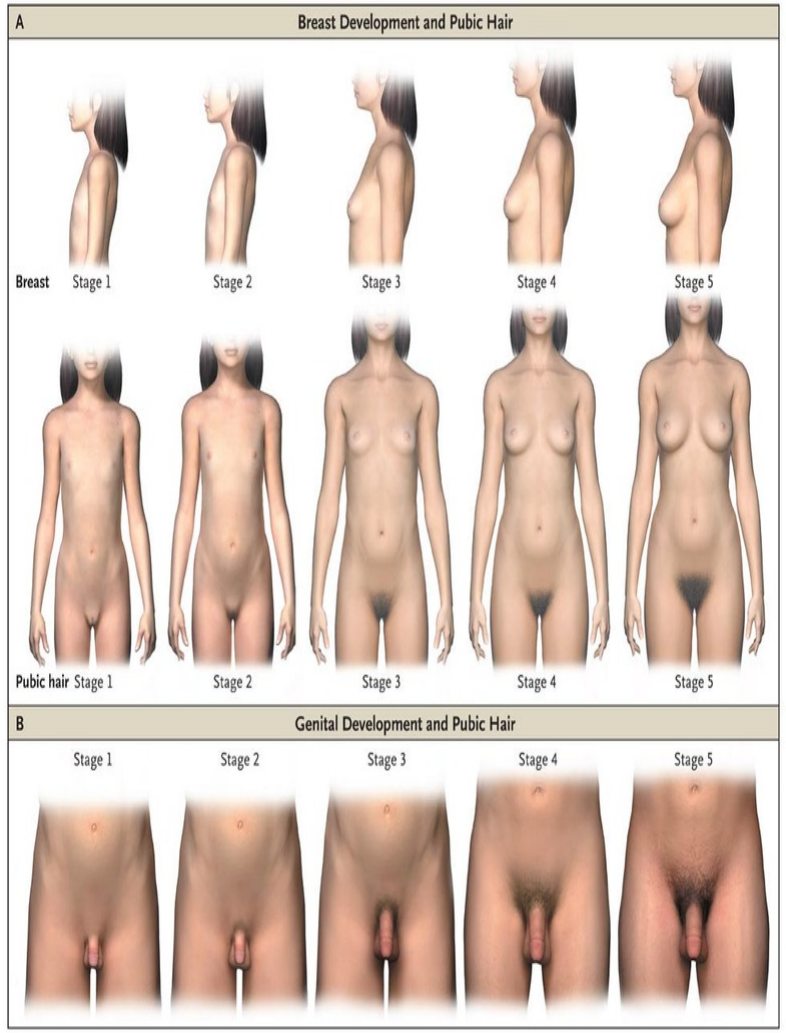


Reinehr T, Roth CL. Lancet Child Adolesc Health. 2019 Jan;3(1):44-54.

Key messages

- Obesity is associated with earlier onset of thelarche in girls
- Boys who are overweight seem to mature earlier, and boys who are obese seem to mature later, than boys at a healthy weight
- Leptin and its interaction with the kisspeptin system could explain the link between obesity and puberty
- The change of puberty onset in obesity could be attributed to an earlier activation of the hypothalamic-pituitary-gonadal axis, but further evidence is required
- The underlying mechanisms explaining the link are unclear, and peripheral actions of adipose tissue could also be involved in the relationship between puberty and obesity

Pubertal Rating According to Tanner Stages.



N Engl J Med 2008; 358:2366-2377

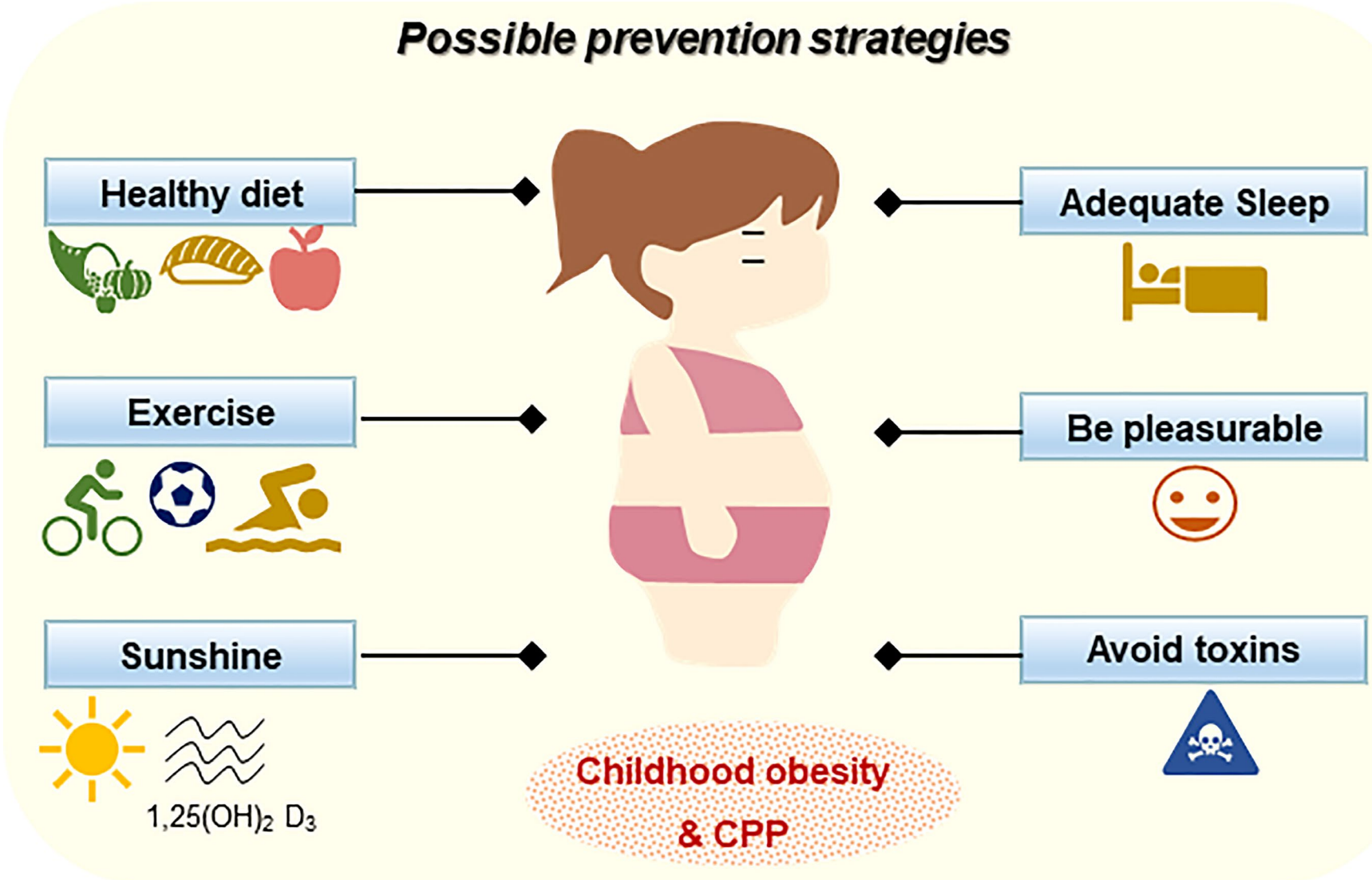
Precocious puberty is the appearance of any sign of secondary sex characteristics in **girls younger than 7½ or 8 and in boys younger than age 9**. In the United States, most children with early puberty have a variation of normal puberty, and no medical problem is present. Many children who go through puberty early or late have other family members who also went through puberty early or late, and differences in timing may be familial. However, **girls younger than age 6-7 or any boys are at higher risk of having an endocrine problem that causes precocious puberty and requires treatment**.

Two main types of precocious puberty are abnormal:

Central Precocious Puberty (CPP): occurs when the hypothalamus releases GnRH and activates puberty early. In most girls with CPP, there is no underlying medical problem. In boys, the condition is less common and is more likely to have a link to a medical problem. Such problems include a tumor, brain trauma (such as a blow to the head, brain surgery, or radiation treatment to the head), or inflammation (such as meningitis).

Peripheral Precocious puberty (PPP): rarer than CPP. It results from early production of sex hormones due to problems with the ovaries, testicles, or adrenal glands. Another cause can be external exposure to sex hormones (such as coming into contact with an adult using estrogen or testosterone cream).

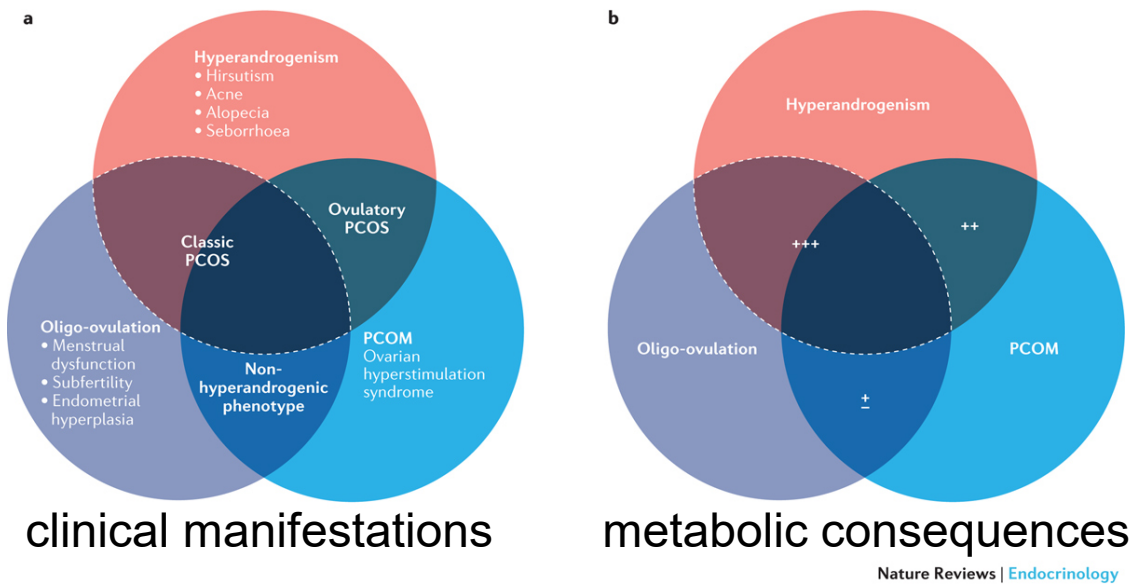
https://www.endocrine.org/patient-engagement/endocrine-library/precocious-puberty


Possible prevention strategies
Healthy diet
Exercise
Sunshine
1,25(OH)2 D3
Adequate Sleep
Be pleasurable
Avoid toxins
Childhood obesity
& CPP

Polycystic ovary syndrome (PCOS)

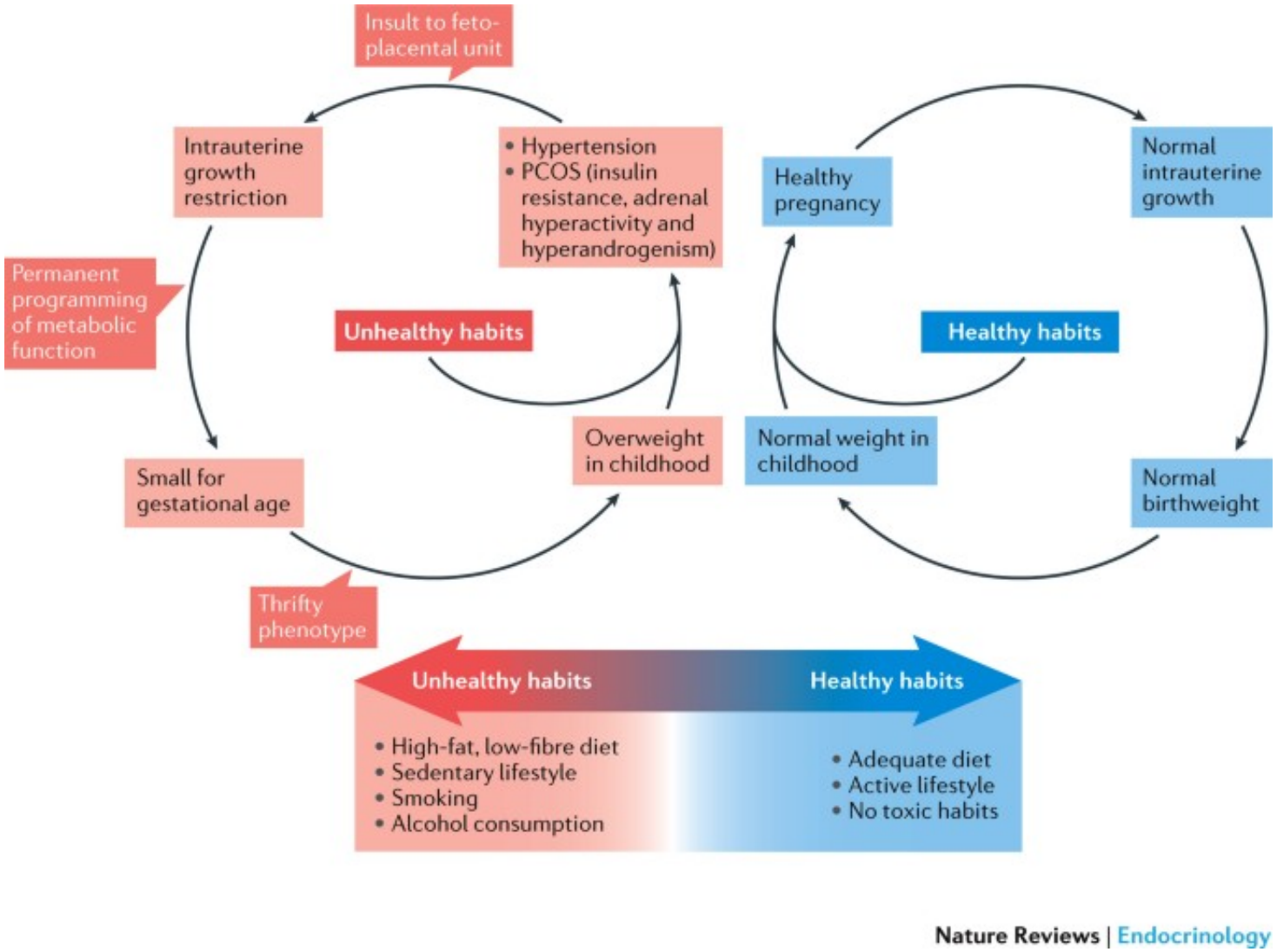
- Polycystic ovary syndrome (PCOS) is defined by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses.
- Heterogeneity, from aetiology to clinical presentation and long-term prognosis, is intrinsic to PCOS.
- Mounting evidence suggests that PCOS might be a complex multigenic disorder with strong epigenetic and environmental influences, including diet and other lifestyle issues.
- The diagnosis of PCOS is uncomplicated, requiring only the careful application of a few well-standardized diagnostic methods.
- Treatment should be symptom-oriented, long term and dynamic and adapted to the changing circumstances, personal needs and expectations of the individual patient.
- Therapeutic approaches should target hyperandrogenism, the consequences of ovarian dysfunction and/or the associated metabolic disorders.

The heterogeneous nature of PCOS



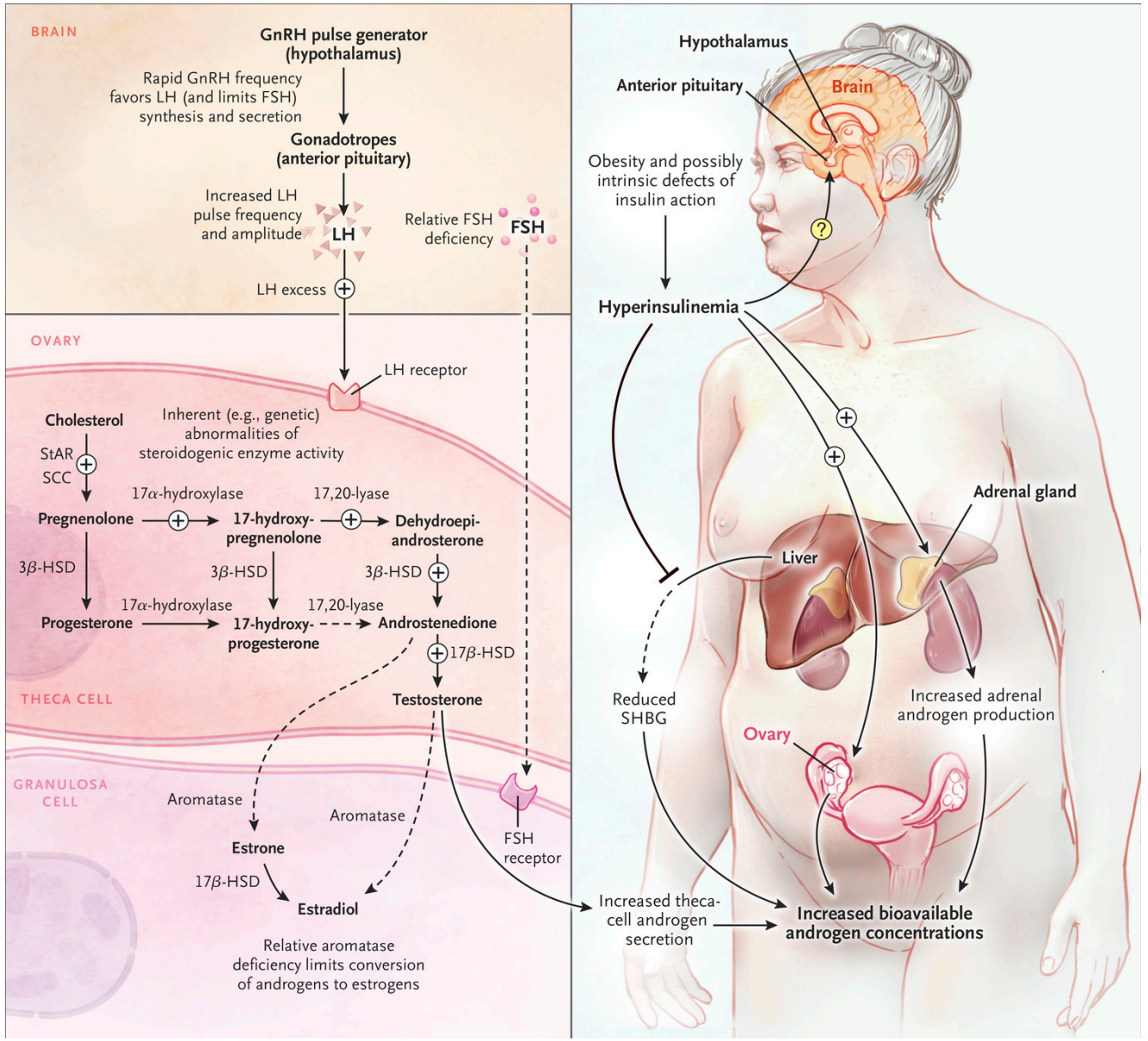
Escobar-Morreale, H. F. (2018) Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2018.24

Environmental factors influencing PCOS



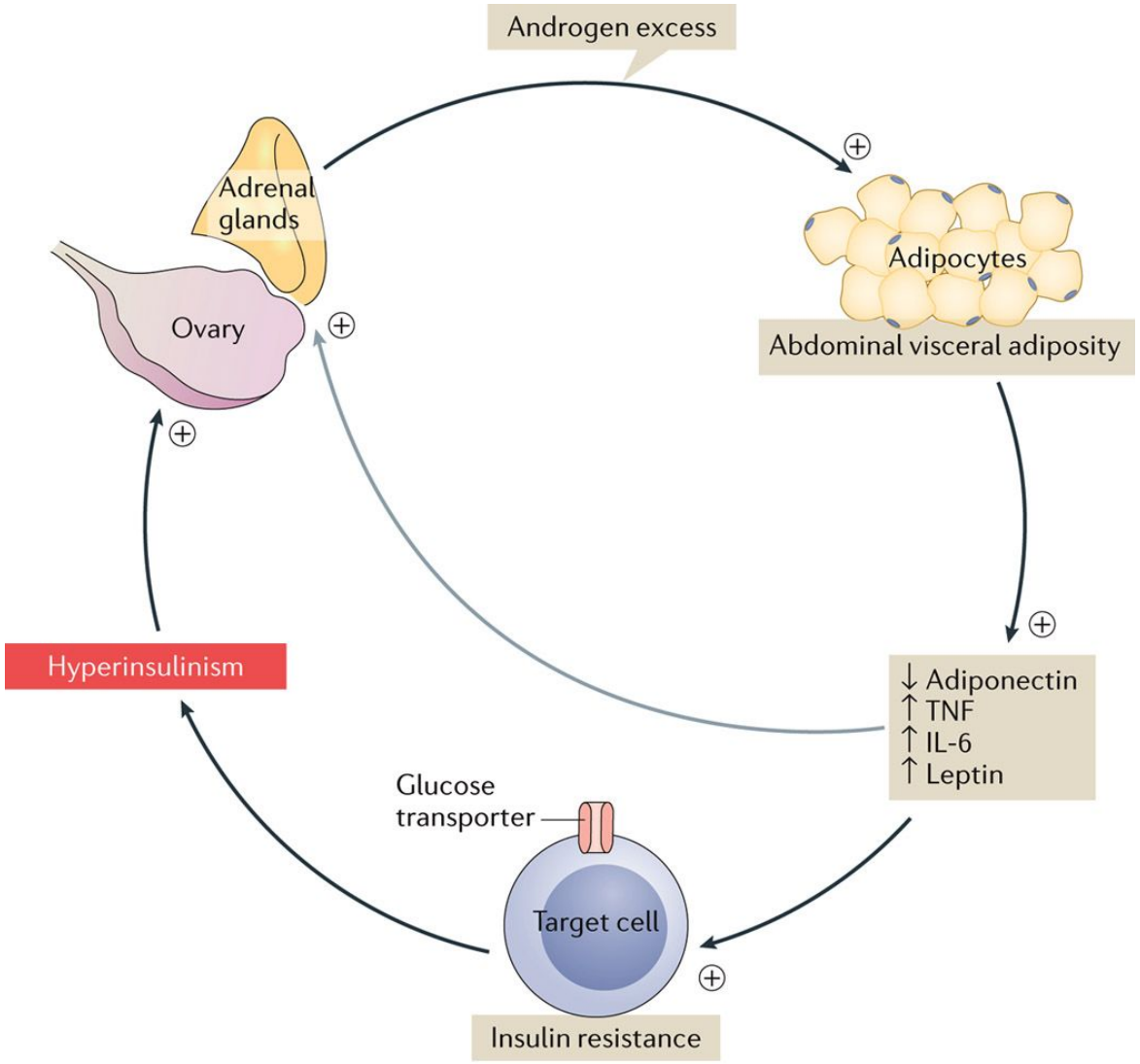
Nature Reviews | Endocrinology

Basic Pathophysiology of Hyperandrogenemia in the Polycystic Ovary Syndrome



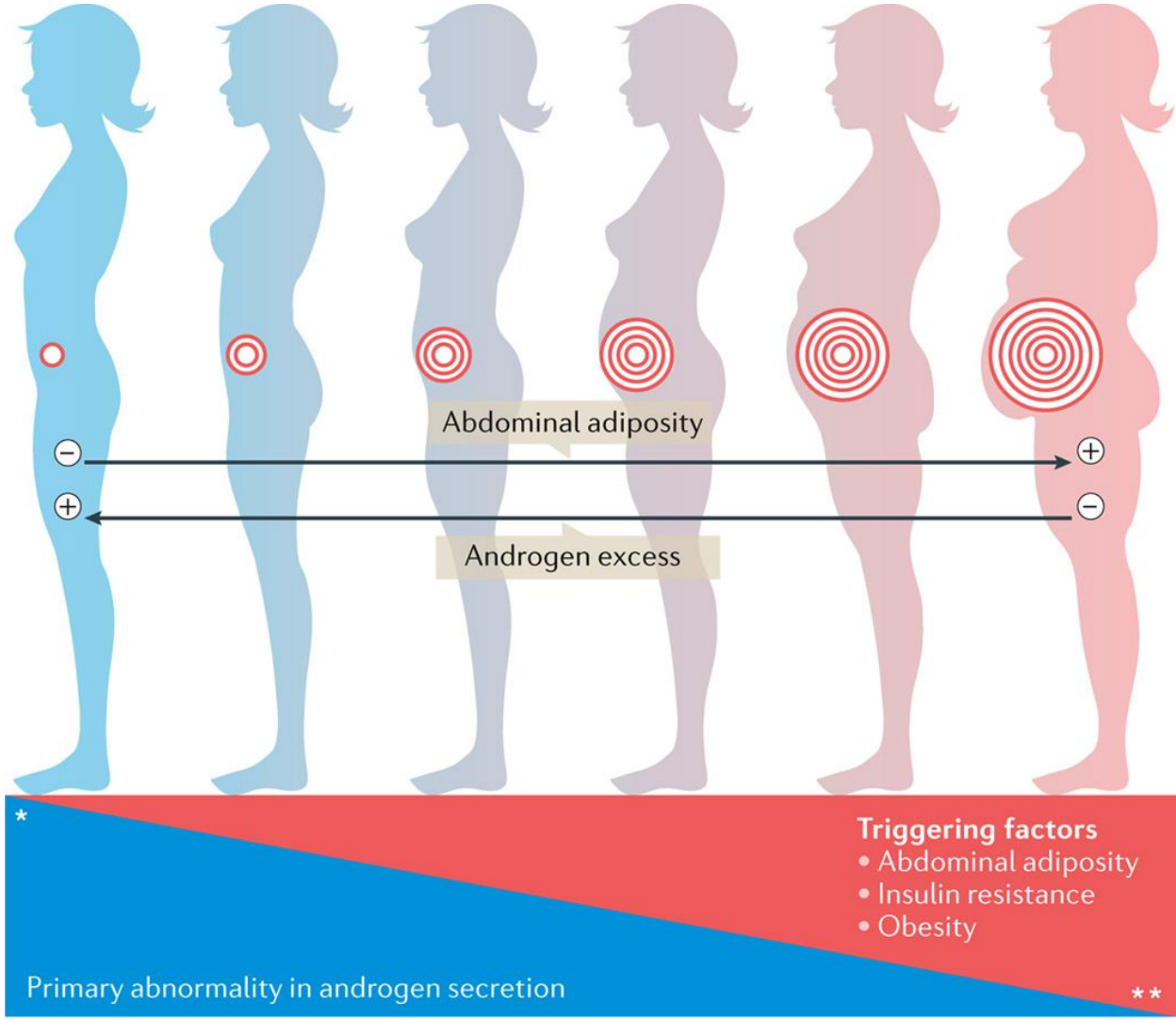
McCartney CR, Marshall JC. N Engl J Med. 2016 Jul 7;375(1):54-64

Abdominal adiposity and PCOS



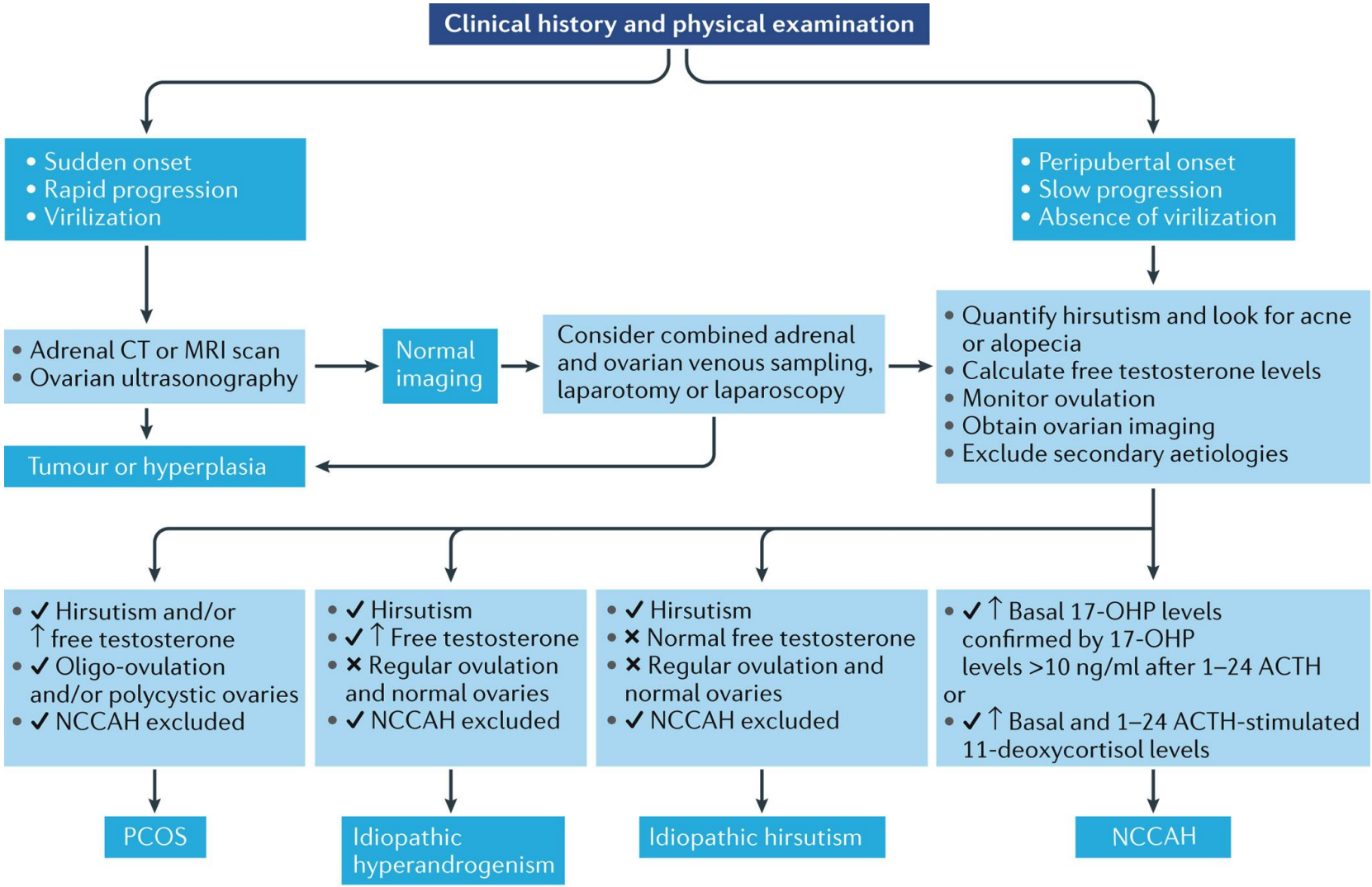
Nature Reviews | Endocrinology

Pathophysiological heterogeneity in patients with PCOS.



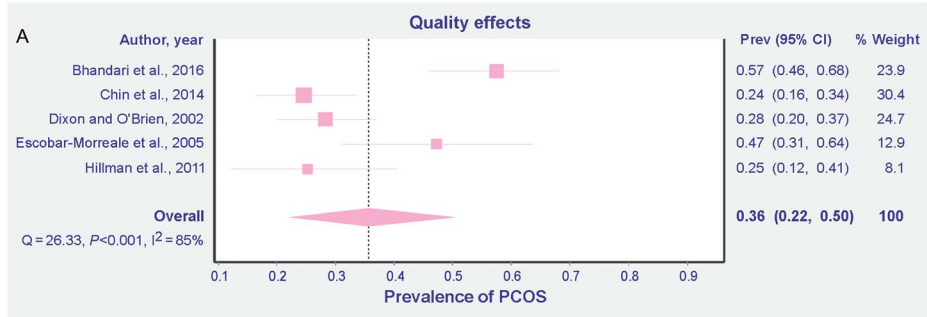
Nature Reviews | Endocrinology

Algorithm for the aetiological diagnosis of women thought to have PCOS

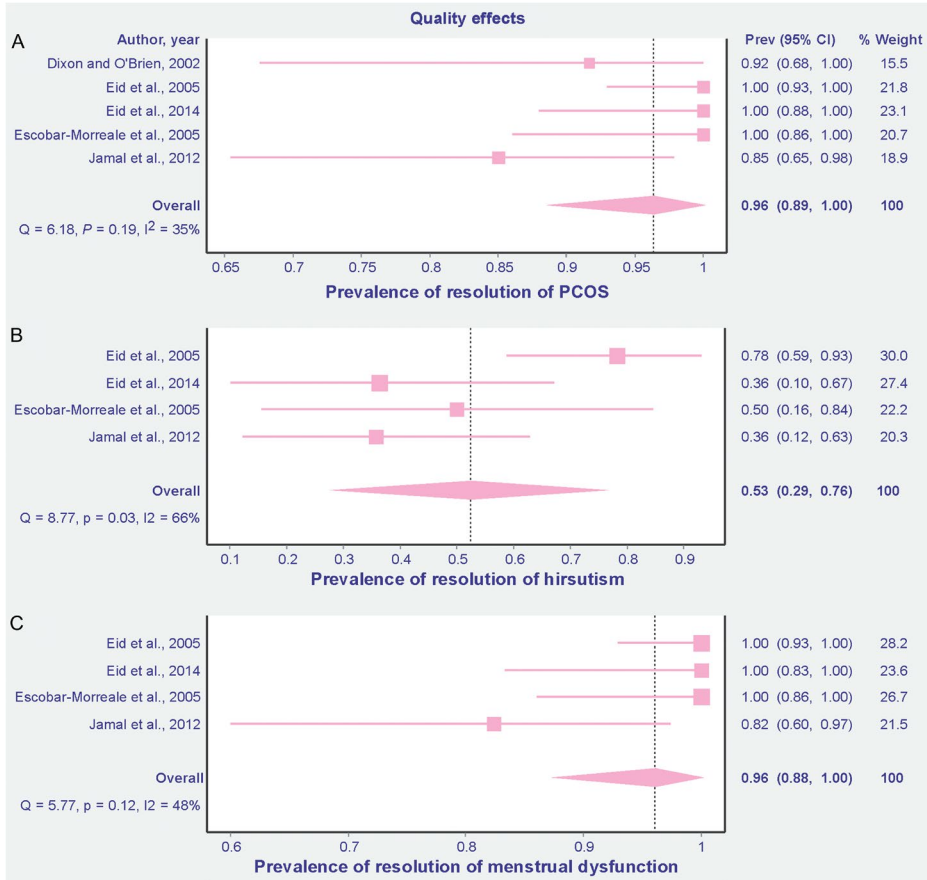


NCCAH: non-classic congenital adrenal hyperplasia

Meta-analysis of the prevalence of PCOS in severely obese patients submitted to bariatric surgery.



Meta-analysis of the prevalence of resolution of PCOS in severely obese patients after weight loss following bariatric surgery.



Human Reproduction Update, Volume 23, Issue 4, 2017

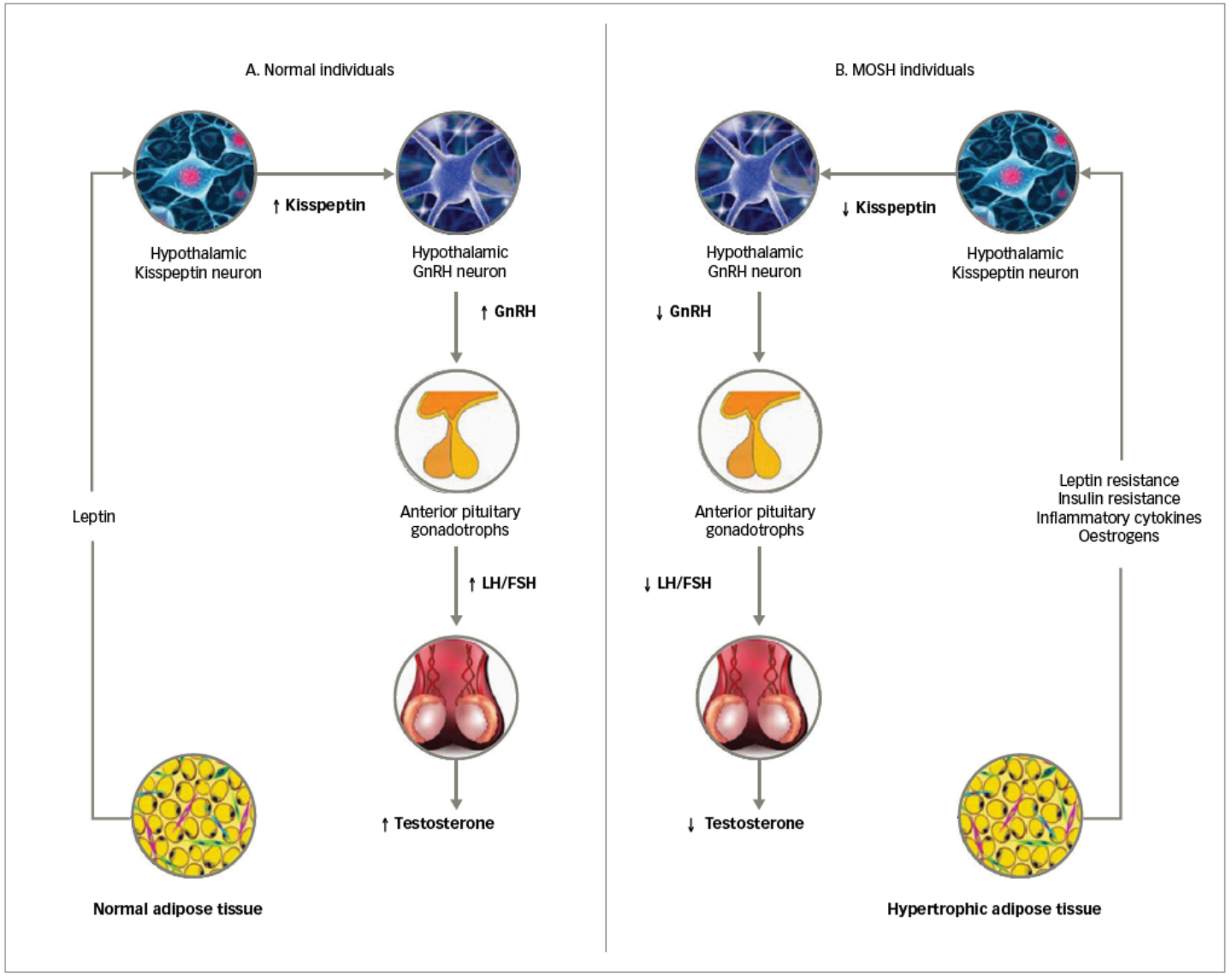
MALE HYPOGONADISM

Male Obesity-related Secondary Hypogonadism

Obesity and hypogonadism – bidirectional relationship

- In population-based studies, obesity is the single most important factor resulting in testosterone deficiency.
- Similarly, testosterone deficiency can cause increased adipogenesis and visceral obesity as evidenced by rapid weight gain observed in men following androgen deprivation therapy or surgical castration.
- Testosterone deficiency is associated with visceral fat dysfunction, subsequent chronic inflammation, insulin resistance and low sex hormone binding globulin (SHBG) levels.
- Weight loss achieved pharmacologically with liraglutide or with bariatric surgery improved testosterone and gonadotrophin levels, and were able to reverse the hypogonadotrophic hypogonadism caused by obesity.

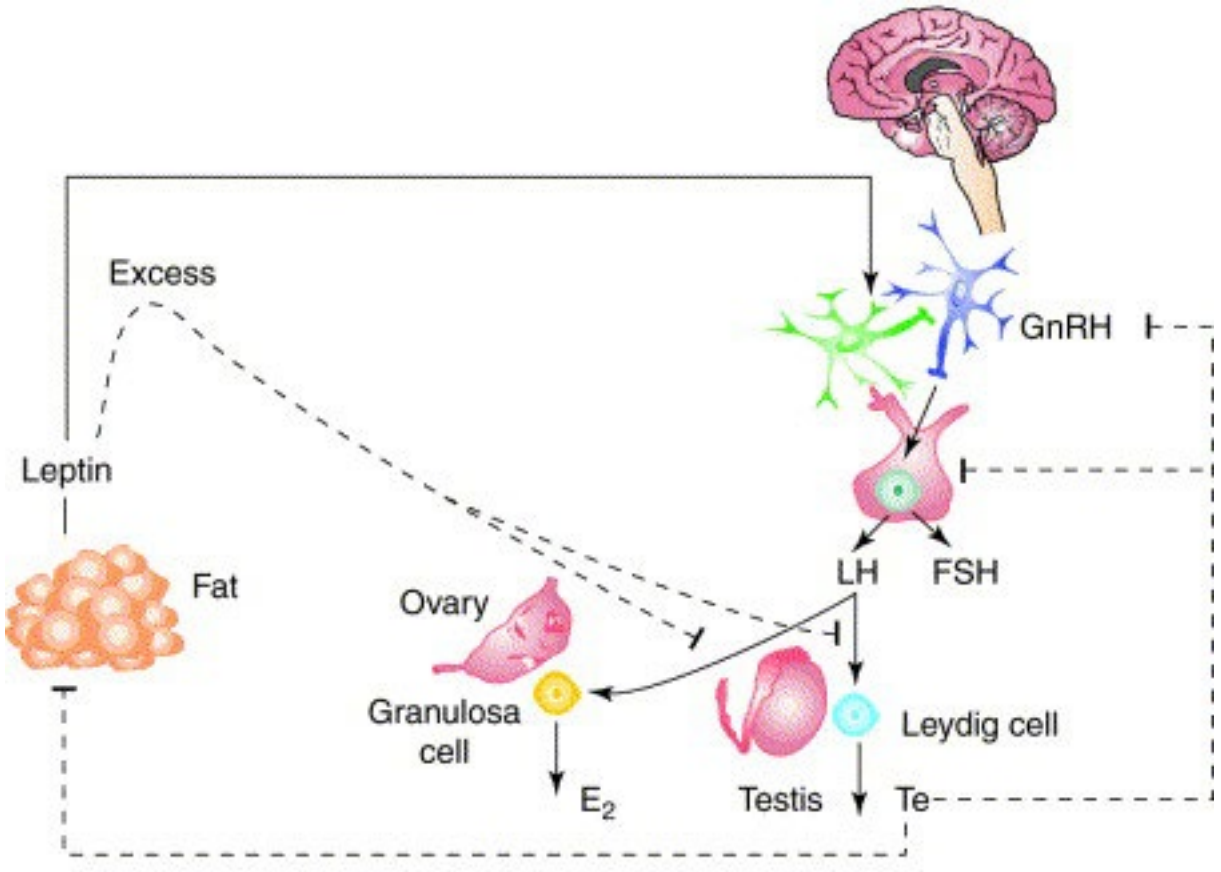
Figure 1: The central regulation of testosterone production in normal individuals and individuals with male obesity-related secondary hypogonadism



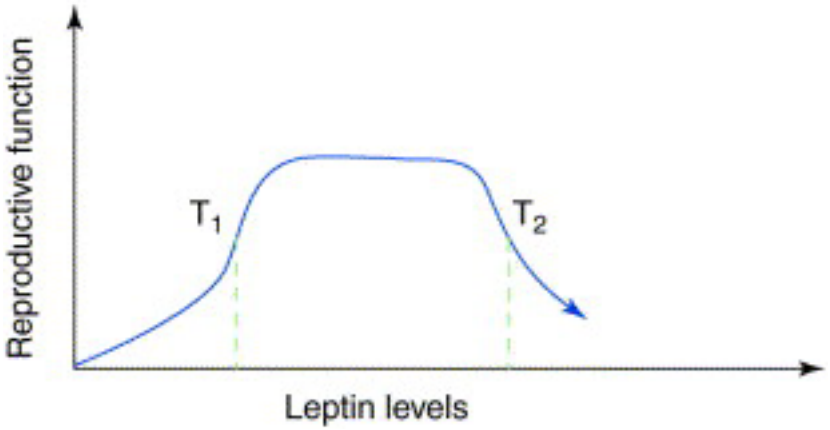
FSH = follicle stimulating hormone; GnRH = gonadotropin releasing hormone; LH = luteinising hormone; MOSH = male obesity-related secondary hypogonadism.

European Endocrinology. 2019;15(2):83–90

Leptin in reproduction

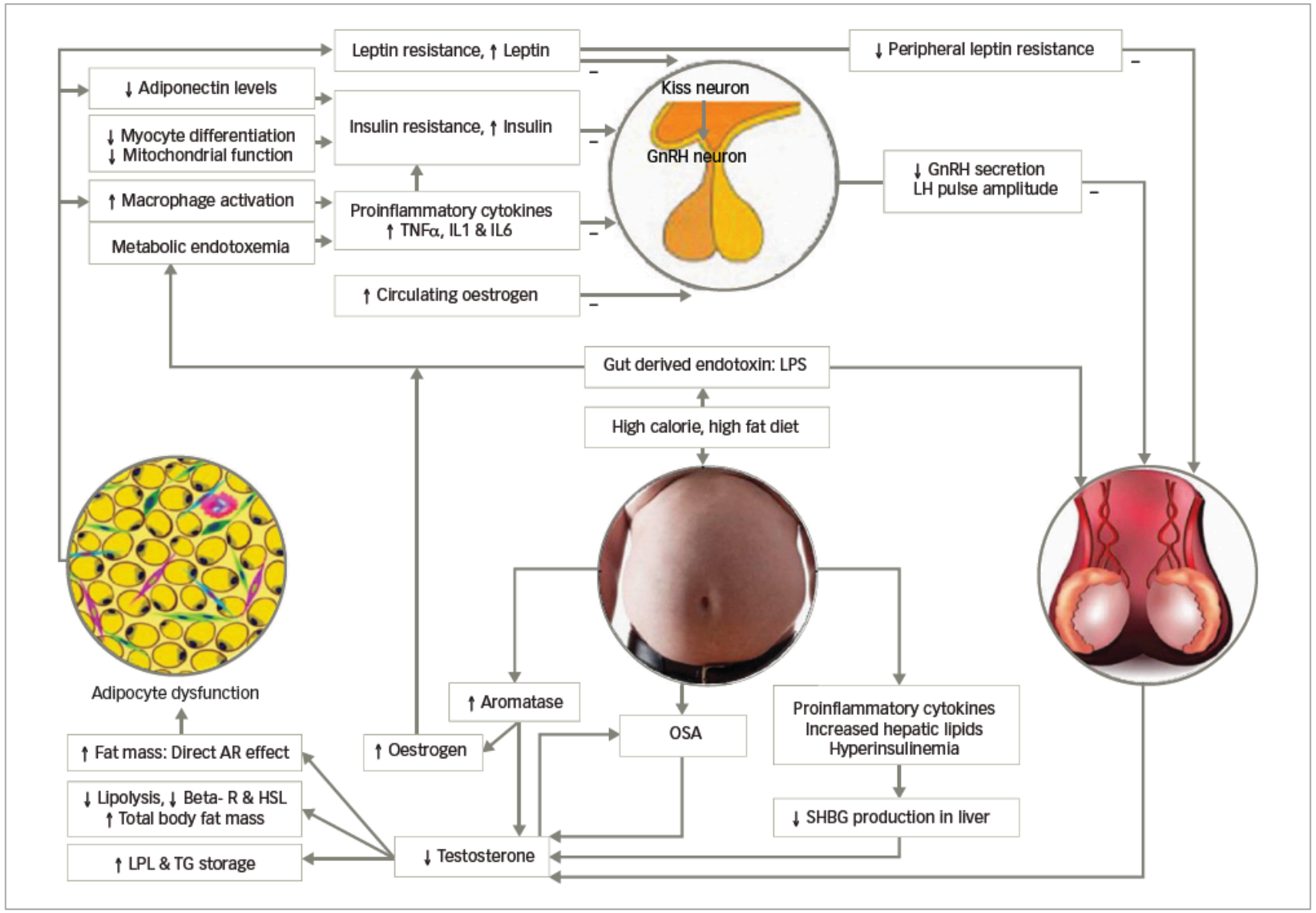


Proposed dual action of leptin on reproductive function. Leptin concentrations above a minimal threshold (T_1) are necessary in the hypothalamus to activate the hypothalamus–pituitary–gonadal (HPG) axis, to trigger puberty and to maintain reproductive function. Leptin excess above a certain threshold (T_2), such as is found in obesity, might impair testicular and ovarian steroidogenesis and have deleterious effects on reproduction.



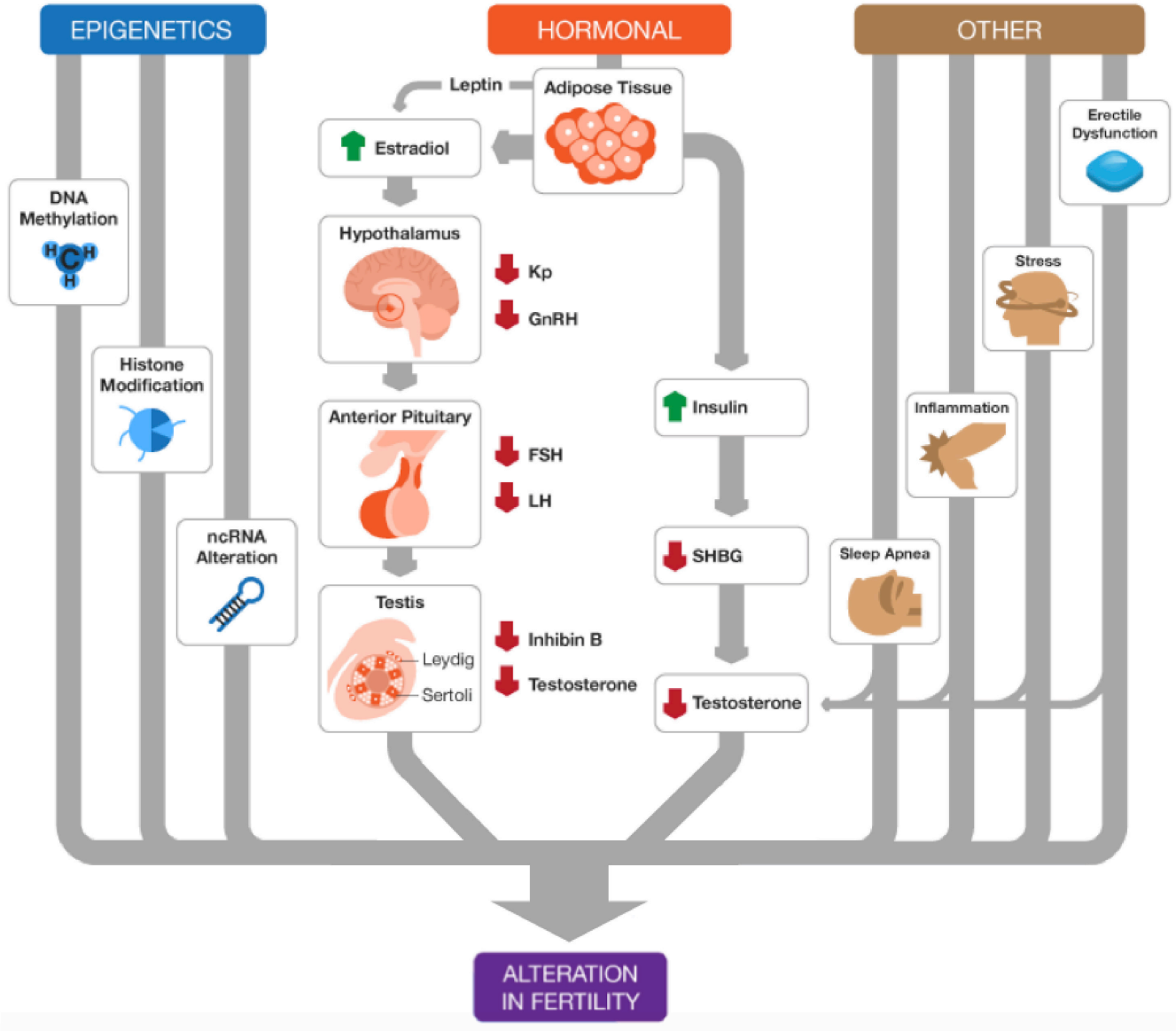
Trends in Endocrinology & Metabolism Volume 12, Issue 2, 1 March 2001, Pages 65-72

Figure 2: The pathophysiological aspects of male obesity-related secondary hypogonadism



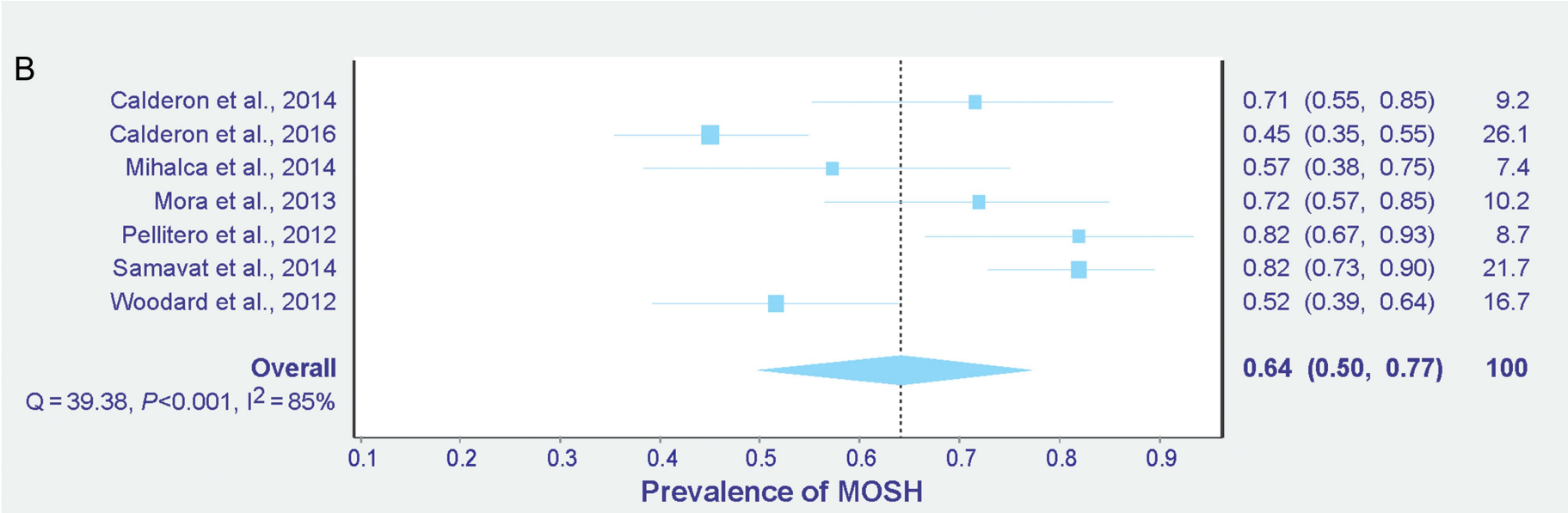
AR = androgen receptor; Beta-R = beta adrenoreceptor; GnRH = gonadotropin releasing hormone; HSL = hormone sensitive lipase; IL = interleukin; LH = luteinising hormone; LPL = lipoprotein lipase; LPS = lipopolysaccharide; OSA = obstructive sleep apnoea; SHBG = sex hormone binding globulin; TG = triglyceride; TNF = tumor necrosis factor.

Obesity and Male Infertility: Potential Mechanisms

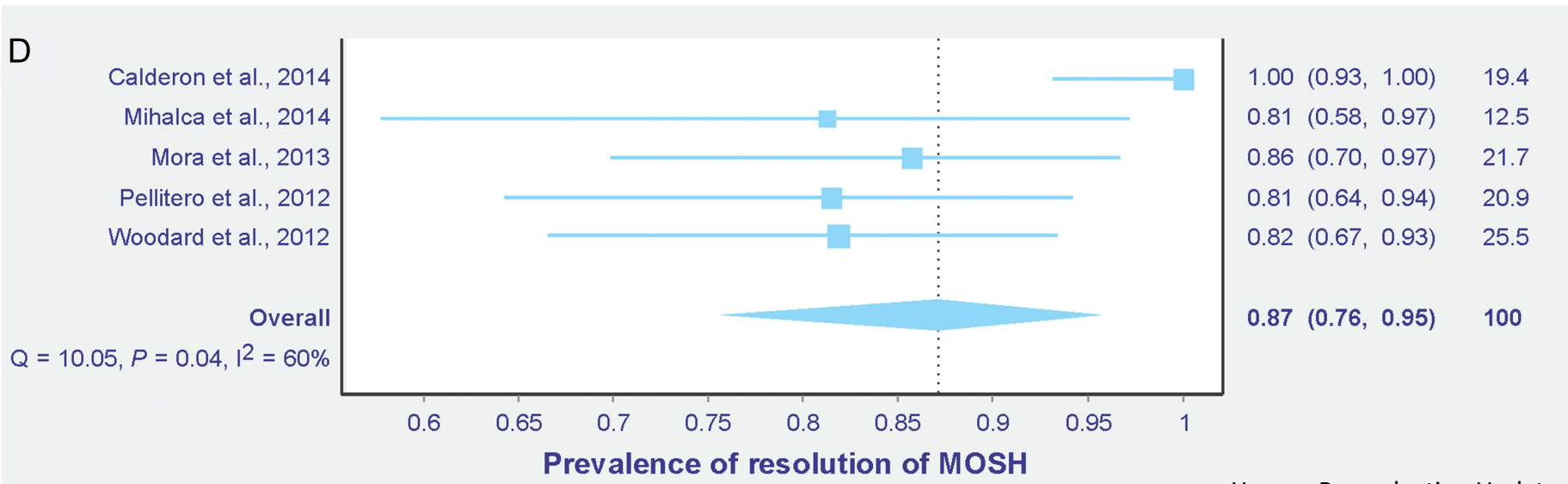


Craig et al., Obesity, male infertility, and the sperm epigenome. Fertil Steril. 2017 Apr;107(4):848-859

Meta-analysis of the prevalence of male obesity associated secondary hypogonadism (MOSH) in severely obese patients submitted to bariatric surgery.



Meta-analysis of the prevalence of resolution of MOSH in severely obese patients after the weight loss following bariatric surgery.



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DOI: 10.1111/and.14099

ORIGINAL ARTICLE

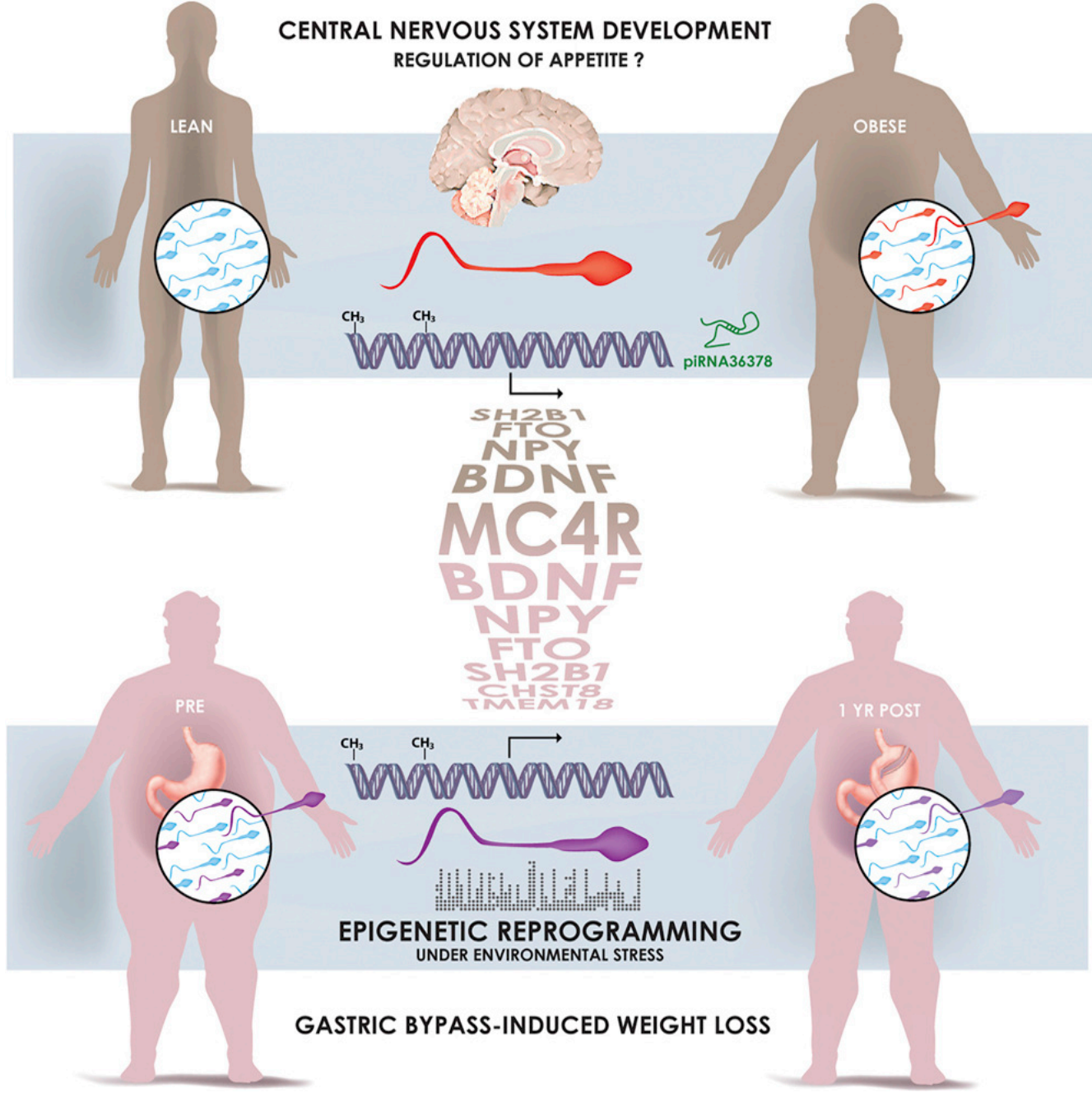
First International Journal of Andrology ANDROLOGIA WILEY

Does obesity based on body mass index affect semen quality?—A meta-analysis and systematic review from the general population rather than the infertile population

SuiYan Wang[1] | Jun Sun[1] | JunYi Wang[2] | ZhiGuang Ping[2] | Li Liu[1]

TABLE 4 Analysis of obesity and male sperm quality

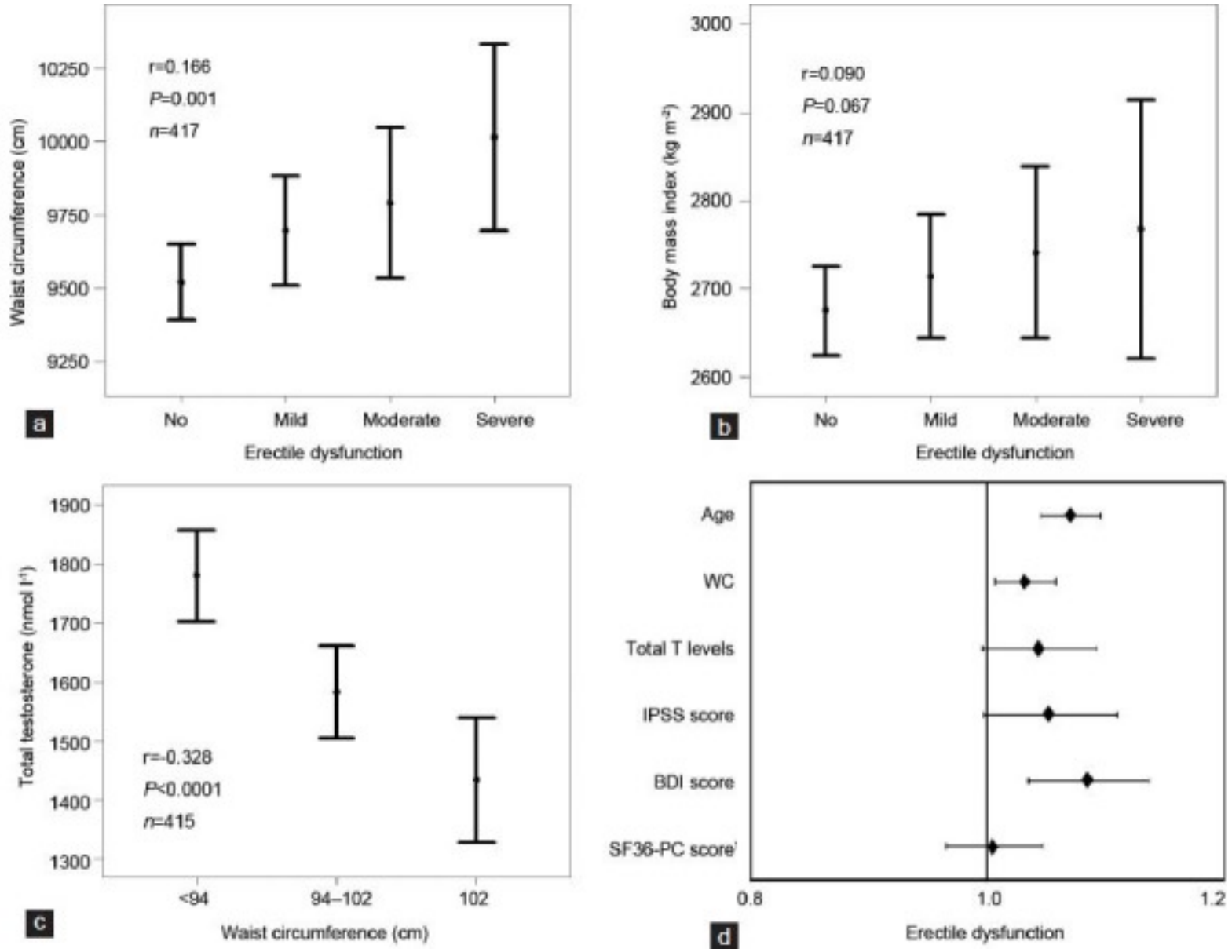
Index	Number of articles	SMD (95% CI)	*p* value
Semen volume	12	−0.32(−0.52, −0.12)	.002
Sperm concentration	14	−0.15(−0.32,0.02)	.088
Total sperm count	10	−0.77(−1.31, −0.23)	.005
Forward progression (%)	7	−0.95(−1.70, −0.19)	.014
Viability (%)	4	−0.812(−1.532,0.093)	.027
Normal sperm morphology (%)	12	−0.17(−0.66,0.32)	.487



Donkin et al. show that spermatozoa from obese men carry a distinct epigenetic signature compared to lean men, in particular at genes controlling brain development and function. The sperm methylome is dynamically remodeled after gastric-bypass-induced weight loss,notably at gene regions implicated in the central control of appetite.

Donkin et al., 2016, Cell Metabolism23, 369–378

Relationship between erectile dysfunction (ED) severity and various parameters including excess adipose tissue



Corona G, et al., Erectile dysfunction and central obesity: an Italian perspective. Asian J Androl 2014;16:581-91.

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