# Etiology of obesity, causes of secondary obesity, genetics, monogenic obesity and syndromic obesity


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INTERNATIONAL HELLENIC UNIVERSITY

EASO European Association for the Study of Obesity

D&CVD Diabetes and Cardiovascular Disease EASD Study Group

International ILEP Lipid Expert Panel

HELLENIC ATHEROSCLEROSIS SOCIETY 25-5-02

# Conflict of interest

**411 publications in PubMed, 7,622 citations, H-index: 44**

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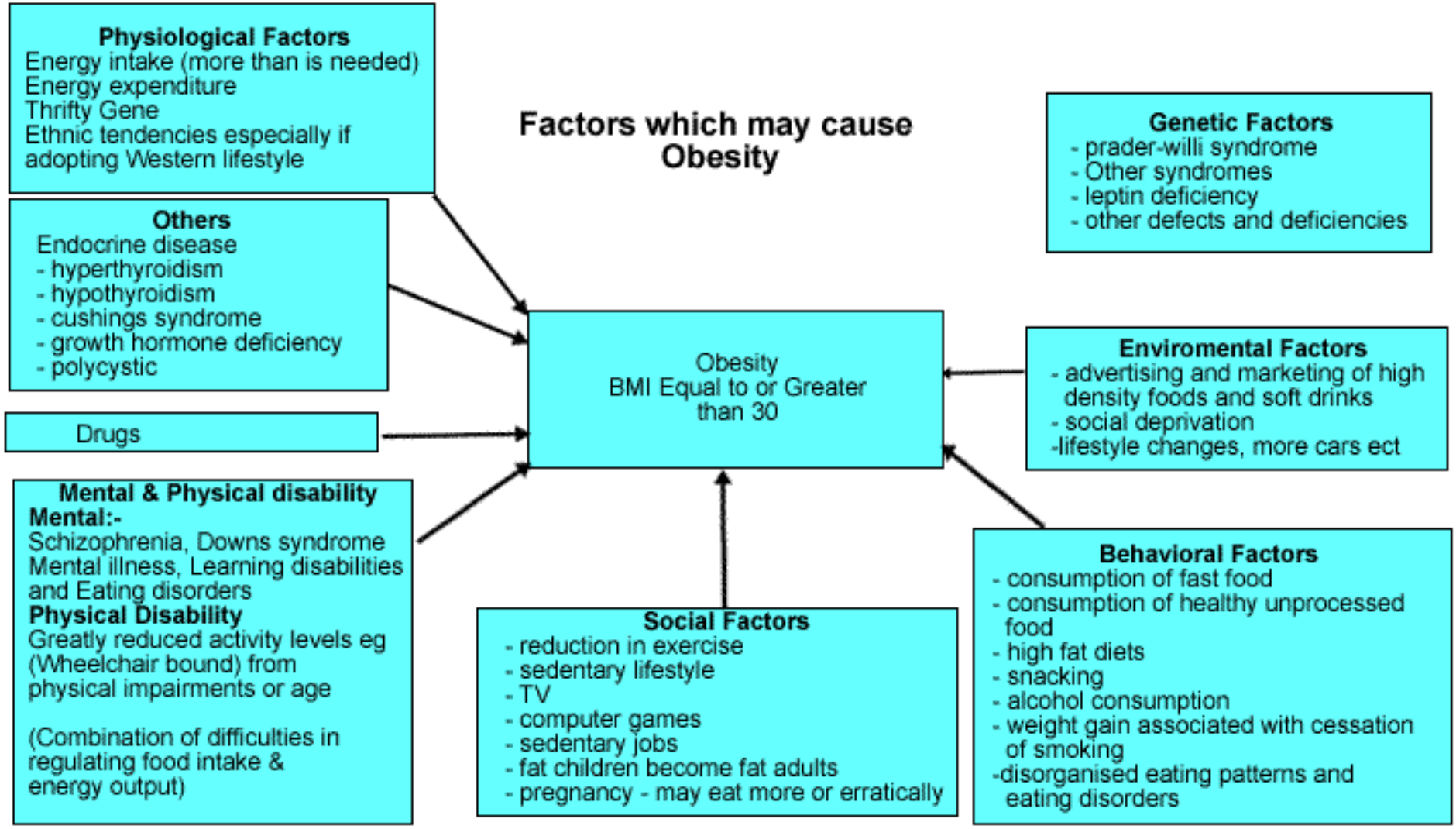

Factors which may cause Obesity
Physiological Factors
Energy intake (more than is needed)
Energy expenditure
Thrifty Gene
Ethnic tendencies especially if adopting Western lifestyle
Others
Endocrine disease
- hyperthyroidism
- hypothyroidism
- cushings syndrome
- growth hormone deficiency
- polycystic
Drugs
Mental & Physical disability
Mental:-
Schizophrenia, Downs syndrome Mental illness, Learning disabilities and Eating disorders
Physical Disability
Greatly reduced activity levels eg (Wheelchair bound) from physical impairments or age
(Combination of difficulties in regulating food intake & energy output)
Obesity
BMI Equal to or Greater than 30
Social Factors
- reduction in exercise
- sedentary lifestyle
- TV
- computer games
- sedentary jobs
- fat children become fat adults
- pregnancy - may eat more or erratically
Genetic Factors
- prader-willi syndrome
- Other syndromes
- leptin deficiency
- other defects and deficiencies
Enviromental Factors
- advertising and marketing of high density foods and soft drinks
- social deprivation
-lifestyle changes, more cars ect
Behavioral Factors
- consumption of fast food
- consumption of healthy unprocessed food
- high fat diets
- snacking
- alcohol consumption
- weight gain associated with cessation of smoking
-disorganised eating patterns and eating disorders

**Secondary causes of obesity, while less common, include:**

**Endocrine Disorders**
Cushing Syndrome
Hypothyroidism
Pseudohypoparathyroidism
Type 2 diabetes

**Genetic Syndromes**
Prader-Willi syndrome
Bardet-Biedel syndrome
Cohen syndrome

**Central Nervous System Disorders**
Hypothalamic Tumor
Trauma to or inflammation of the hypothalamic region

**Other**
**Drug induced** - atypical anti-psychotics, tricyclic antidepressants
Binge eating disorder
Bulimia nervosa

**Box 1. Endocrine and genetic causes of obesity.**

***Endocrine causes***

- Hypothyroidism
- Cushing disease
- Polycystic ovaries
- Growth hormone deficiency
- Hypothalamic obesity
- Hypogonadism
- Insulinoma
- Pseudohypoparathyroidism

***Genetic causes***

Monogenic obesity:

- Leptin and leptin receptor deficiency
- POMC deficiency
- Melanocortin Receptor 4 deficiency
- Prohormone convertase deficiency
- BDNF and TrkB insufficiency
- SIM 1 insufficiency

Syndromic obesity:

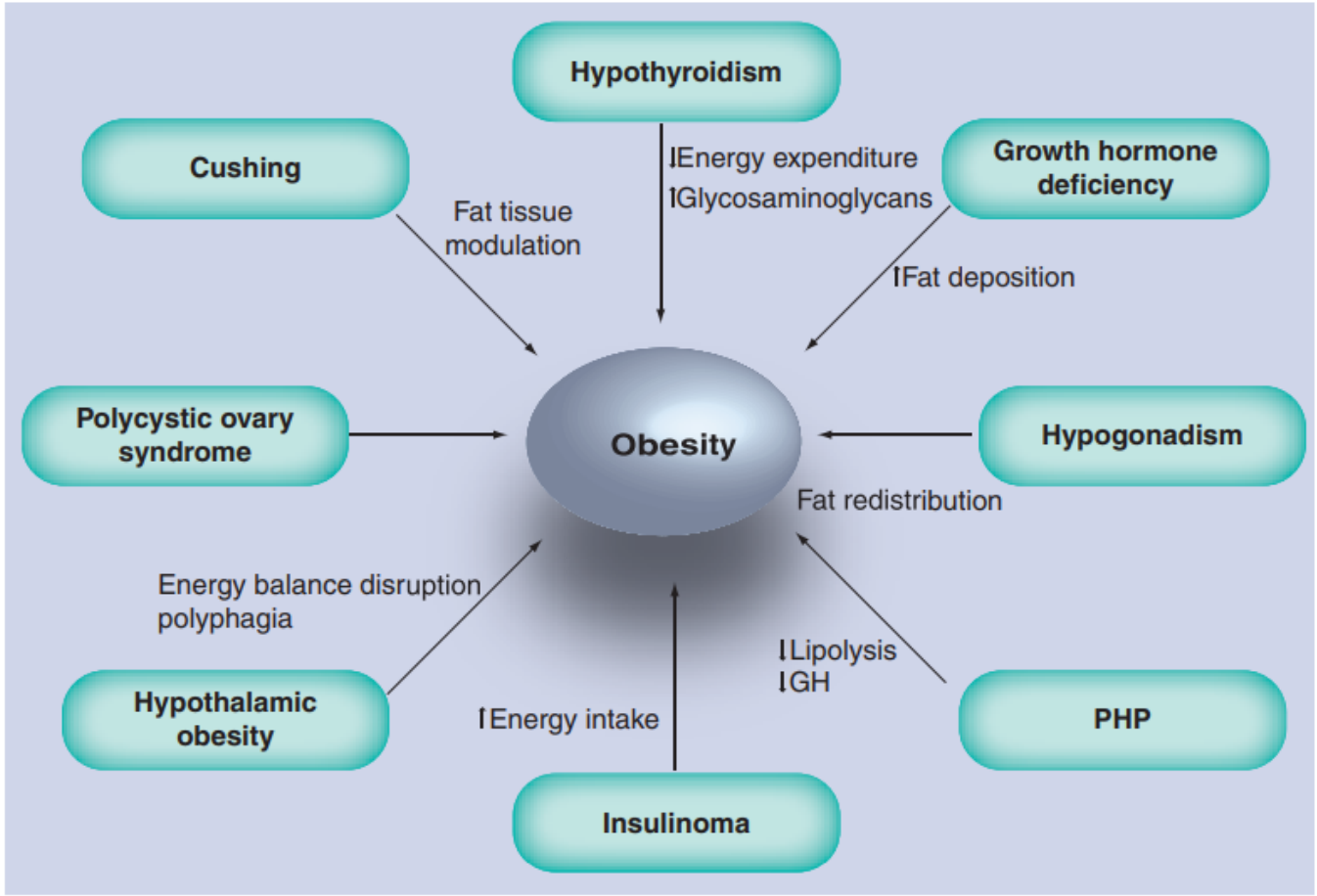
- Prader–Willi syndrome
- Bardet–Biedl syndromes
- Beckwith–Wiedemann syndrome
- Alstrom–Hallgren syndrome
- Carpenter syndrome
- Cohen syndrome

# Secondary causes of obesity

**Therapy 2007,4(5): 641-50**

# Secondary causes of obesity

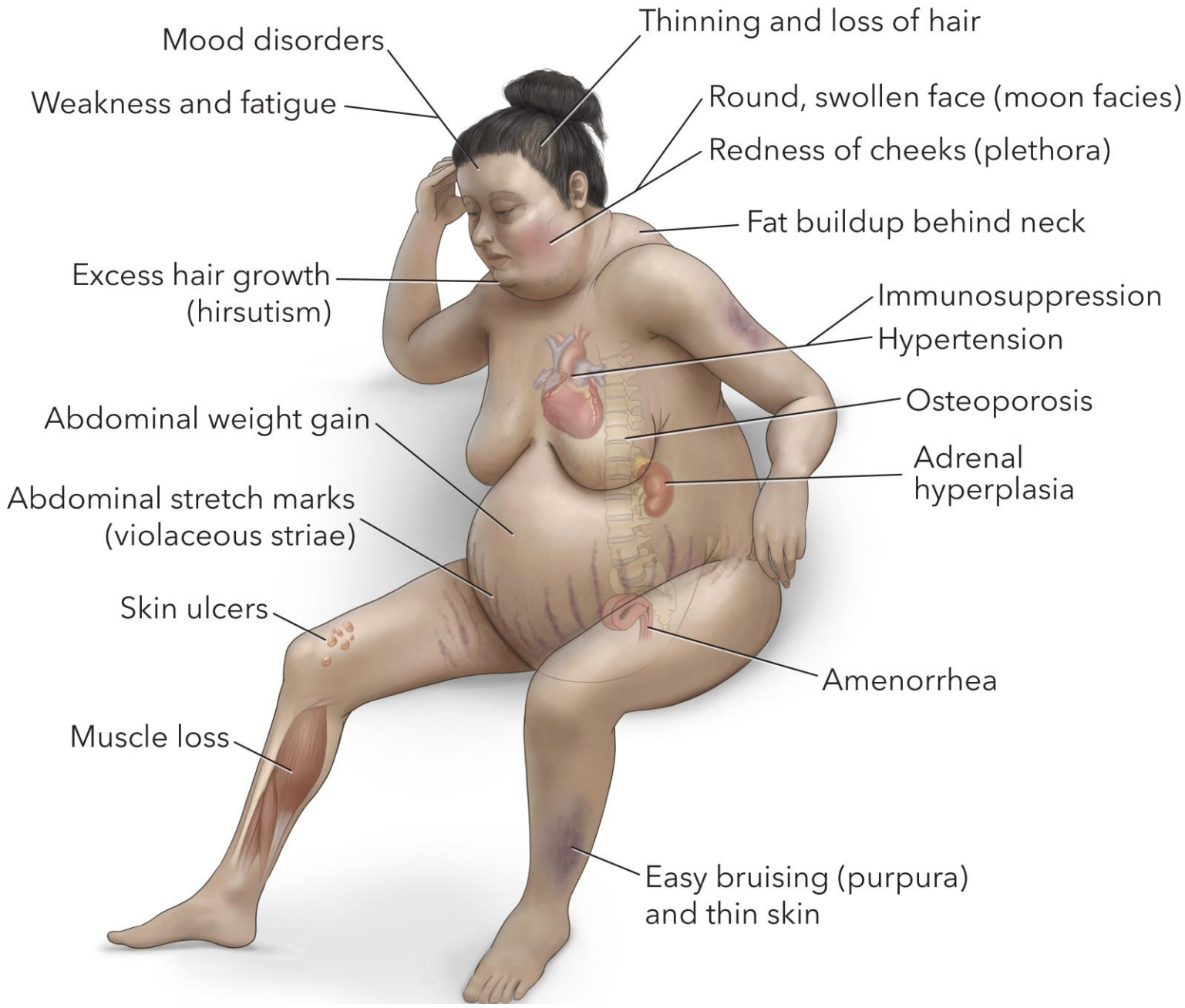
**Figure 1. Endocrinologic etiologies of obesity and related pathophysiology.**




PHP: Pseudohypopparathryoidism.

Therapy 2007,4(5): 641-50

# Cushing syndrome



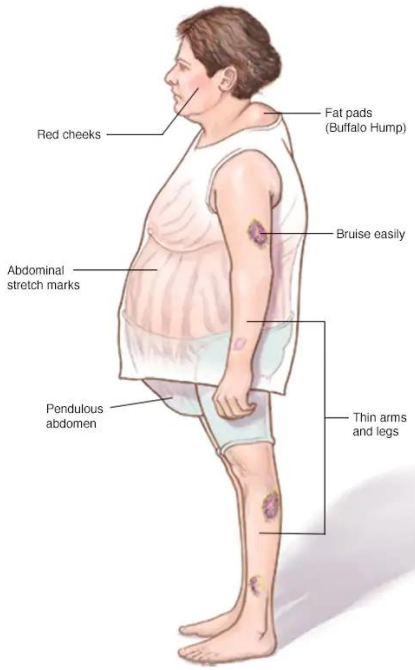
## The role of corticosteroid medications (exogenous Cushing syndrome)

Cushing syndrome can develop from taking oral **corticosteroid medications**, such as prednisone, in high doses over time.

**Oral corticosteroids** may be necessary to treat inflammatory diseases, such as **rheumatoid arthritis, lupus and asthma**. They may also be used to prevent from rejecting a **transplanted organ**.

It's also possible to develop Cushing syndrome from **injectable corticosteroids** — for example, repeated injections for joint pain, bursitis and back pain.

**Inhaled steroid** medicines for ***asthma*** and steroid **skin creams** used for skin disorders such as ***eczema*** are generally **less likely to cause Cushing syndrome** than are oral corticosteroids. But, in some individuals, these medications may cause Cushing syndrome, especially if taken in high doses.



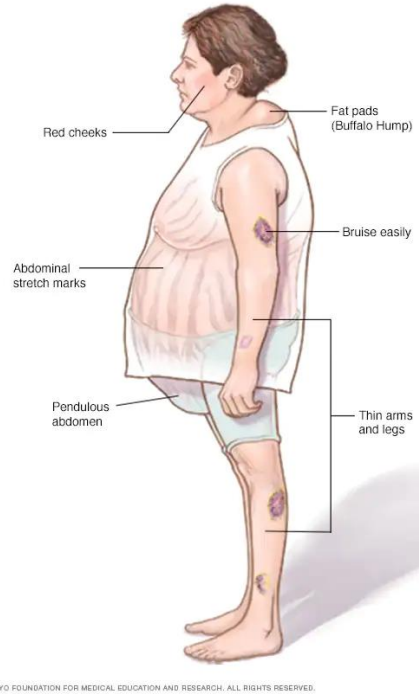


**https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/symptoms-causes/syc-20351310**

# Endogenous Cushing syndrome

producing **either cortisol** or **adrenocorticotropic hormone (ACTH)**, which regulates cortisol production

- A pituitary gland tumor (pituitary adenoma)- **Cushing disease**
- An ACTH-secreting tumor (*Ectopic ACTH Syndrome*)
- A primary adrenal gland disease
- Cancerous tumors of the adrenal cortex
- Familial Cushing syndrome





**https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/symptoms-causes/syc-20351310**

**A pituitary gland tumor (pituitary adenoma).** A noncancerous (benign) tumor of the pituitary gland produces an excess amount of ACTH, which in turn stimulates the adrenal glands to make more cortisol (***Cushing disease***). It occurs much more **often in women** and is the **most common form** of endogenous Cushing syndrome.

**An ACTH-secreting tumor**. **Rarely**, a tumor that develops in an **organ that normally doesn't produce ACTH** will begin to secrete this hormone in excess. These tumors, which can be ***noncancerous (benign) or cancerous (malignant)***, are usually found in the **lungs, pancreas, thyroid or thymus gland**.

**A primary adrenal gland disease**. The most common is a **noncancerous tumor** of the **adrenal cortex**, called an adrenal adenoma, but only a small fraction of adenomas produce too much cortisol. **Cancerous tumors** of the adrenal cortex are **rare**, but they can cause Cushing syndrome as well. Occasionally, benign, **nodular enlargement of both adrenal glands** can result in Cushing syndrome.

**Familial Cushing syndrome**. **Rarely**, people inherit a tendency to develop tumors on one or more of their endocrine glands, affecting cortisol levels and causing Cushing syndrome.

**https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/symptoms-causes/syc-20351310**

**The following tests can help determine if there are excessive levels of cortisol being produced:**

- The 24-hour urinary cortisol test
- The low-dose dexamethasone suppression test
- The late-night salivary cortisol test

The **24-hour urinary cortisol test** measures the amount of cortisol being produced within the urine over the course of an entire day.

Levels higher than **50-100 micrograms per day** in an adult suggest the presence of Cushing's syndrome.

Although the majority of patients with Cushing's syndrome have elevated levels of cortisol, it is becoming increasingly evident that many patients with a **mild case** of Cushing's syndrome may also **have normal levels of cortisol** resulting in several 24-hour urine collections to confirm a diagnosis.

The **low-dose dexamethasone suppression test** measures the response of the adrenal glands to ACTH and has been widely utilized for four decades.

It involves taking a small dose of a cortisol-like drug, **dexamethasone (1 mg), at 11 p.m.**, then having blood drawn to screen for **cortisol the following morning.**

In patients **without** Cushing's syndrome, the **morning level of cortisol is typically very low**, indicating that ACTH secretion was suppressed by the evening dose of dexamethasone.

In patients **with** Cushing's syndrome, the **morning cortisol level will be high**. It is evident that normal patients will suppress their cortisol to a very low level (1.8 mg/dl), whereas those suffering from Cushing's syndrome will not.

Using this strict criterion, this test should provide an estimated **95-97% diagnostic accuracy rate.** However, some patients with a mild case of Cushing's syndrome can suppress their cortisol to low levels making it difficult to fully diagnose utilizing this test.

The **late-night salivary cortisol test** is a relatively new test that checks for elevated **levels of cortisol in the saliva between 11 p.m. and midnight**.

Cortisol secretion is usually **very low** late at night, but in patients with **Cushing's syndrome**, the level will always be **elevated** during this time.

**Normal levels** of late-night salivary cortisol **virtually exclude** the diagnosis of Cushing's syndrome.

When administered correctly, this test should provide an estimated **93-100% diagnostic accuracy rate**.

After a definitive diagnosis has been made, the **source must then be determined.**

The first step in distinguishing the underlying cause is **the measurement of ACTH**. Patients with ACTH-secreting tumors will either have a normal or elevated level of ACTH. In contrast, **patients with an excess of adrenal cortisol will have a subnormal level**.

Performing a **high-dose dexamethasone suppression test** may be helpful in this situation. This test, similar to the low-dose dexamethasone suppression test, involves taking **a high dose of dexamethasone (8 mg) at 11 p.m**. then having blood drawn to screen for the **presence of cortisol the following morning**.

In normal patients, the morning level of cortisol will again be very low.

**Patients with pituitary tumors** will also **suppress their serum cortisol level**, but those **with adrenal tumors will maintain a high level** of cortisol production.

A **high level of cortisol** points to a **non-pituitary source**.

**Magnetic Resonance Imaging (MRI)** of the pituitary gland with gadolinium enhancement is a recommended approach. When an obvious pituitary tumor (5 mm) is identified with an MRI, further diagnostic evaluation may not be needed depending on the clinical presentation. However, about **50% of patients will have a "normal" MRI** of the pituitary, with **10% having incidental tumors unrelated to ACTH production**.

**Petrosal sinus sampling** is a test used to distinguish the source of ACTH secretion and should only be performed after the diagnosis of Cushing's syndrome has been confirmed. **ACTH and other pituitary hormones produced in the pituitary gland enter the blood stream by drainage through veins called the inferior petrosal sinuses**. To perform this procedure, a catheter is placed in both veins at the same time and blood is **sampled for ACTH before and after the administration of the corticotropin-releasing hormone (CRH)** and at two, five and 10 minute intervals. When administered correctly, this test should provide an estimated **95-98% diagnostic accuracy rate**.

## Treatment of Cushing's Syndrome

Treatment of Cushing's syndrome depends on the underlying cause of excess cortisol but may perhaps include **surgery, radiation, chemotherapy or the use of cortisol-inhibiting drugs**. If the cause is iatrogenic, from long-term use of glucocorticoid hormones to treat another disorder, the physician will **gradually reduce the dose of the externally administered steroid** to the lowest dose adequate for control of that disorder. Once control is established, the dose of glucocorticoid hormones may be given on alternate days to lessen side effects for the patient.

## Treatment of Cushing's Disease

**Microsurgical resection of an ACTH-secreting pituitary adenoma** is the optimum treatment for Cushing's disease with **cure rates of 80-90%** if a tumor is found. Surgery is most often done through a **transnasal transsphenoidal approach**, which will not leave a visible scar. Partial removal of the pituitary gland (subtotal hypophysectomy) may be used in patients without clearly identifiable adenomas.

**•In patients to whom a remission is not obtained after surgery, the use of various medications that can inhibit cortisol production may be used, such as:**

- Ketoconazole (Nizoral)
- Mitotane (Lysodren)
- Metyrapone (Metopirone)
- Mifepristone (Korlym)

These agents are considered a **second–line course of treatment**. In some patients who are particularly resistant to all forms of therapy, **removal of the adrenal glands bilaterally (bilateral adrenalectomy)** may be considered.

**Post-surgery**, with successful tumor removal, the production of **ACTH drops below normal**. This decrease is natural and temporary, and patients are **prescribed a synthetic form of cortisol** such as **hydrocortisone** or **prednisone** to compensate this change.

Most patients can **discontinue replacement therapy within 6-12 months**, but others may require the use of oral steroids for **several years** to, possibly, their **lifetime**.

Patients who need adrenal surgery may also require steroid replacement therapy.

**Primary causes of hypothyroidism** are much more common. The most frequent of these causes is an **autoimmune condition** called **Hashimoto's disease**. Also called Hashimoto's thyroiditis or chronic lymphocytic thyroiditis, this condition is **hereditary**.

The **other primary causes** of hypothyroidism can include:

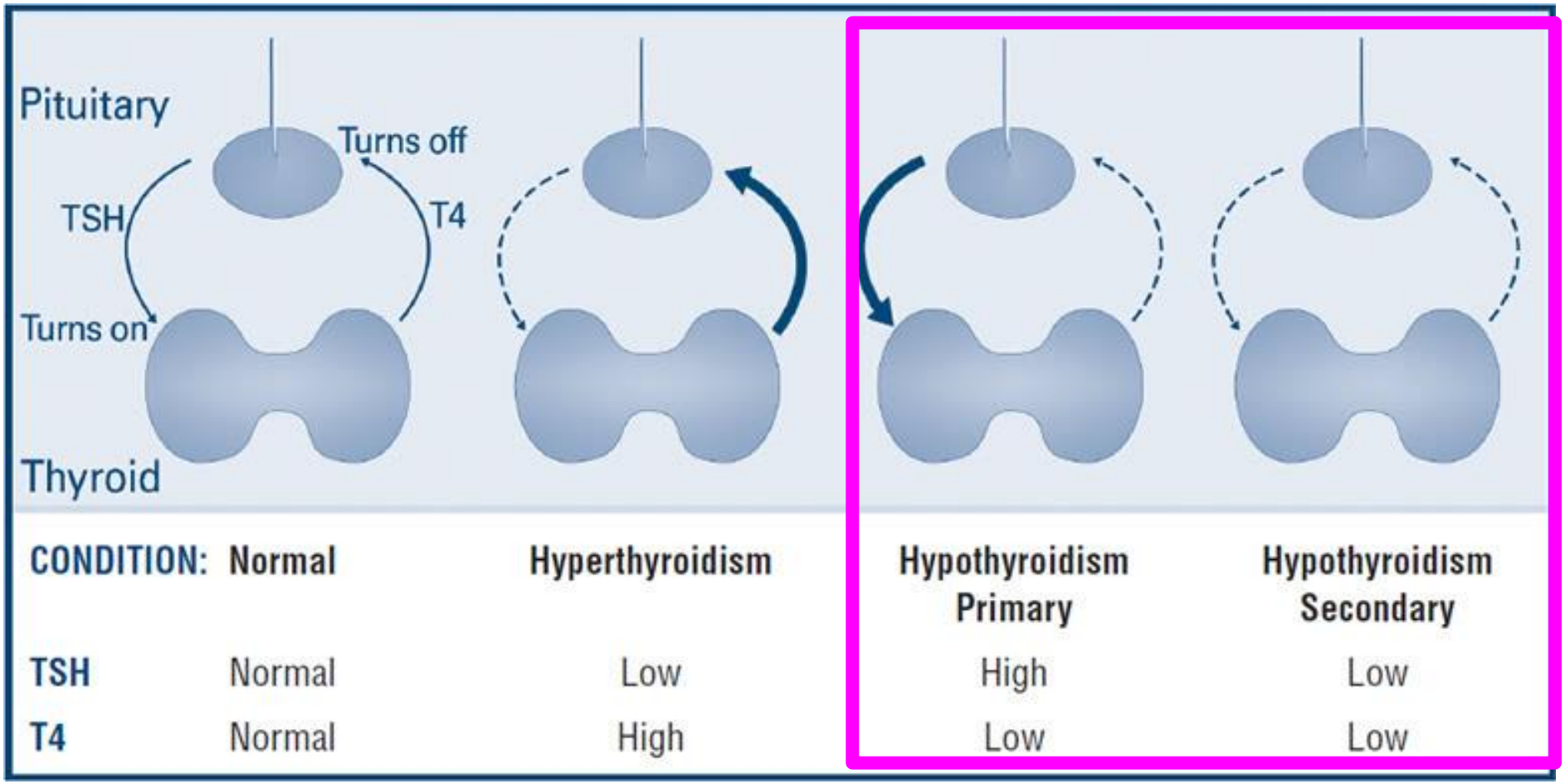
- **Thyroiditis** (inflammation of the thyroid).
- **Treatment of hyperthyroidism** (radiation and surgical removal of the thyroid).
- **Iodine deficiency** (a mineral the thyroid uses to make hormones).
- **Hereditary conditions**
- In some cases, thyroiditis can happen after a pregnancy (**postpartum thyroiditis**).

**Primary hypothyroidism** occurs when the **thyroid gland** does not produce enough thyroid hormones: **triiodothyronine (T3) and thyroxine (T4)**. **Hashimoto's thyroiditis** causes 90% of primary hypothyroidism cases.

**Central hypothyroidism**

- **Secondary hypothyroidism**, is a condition in which the **pituitary gland** malfunctions, **decreasing TSH production** and, by extension, T3/T4 levels.
- **Tertiary hypothyroidism** is when the **hypothalamus** does not secrete enough **thyrotropin-releasing hormone** (TRH) to stimulate the pituitary gland, which ultimately leads to an underactive thyroid.

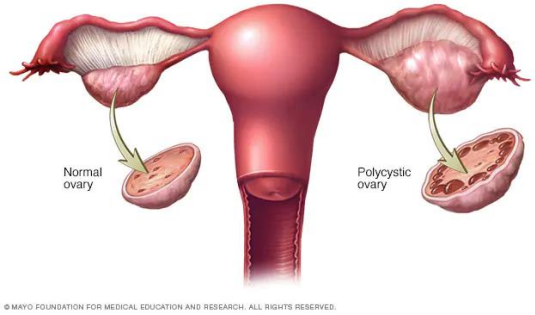
**Subclinical hypothyroidism** affects the pituitary gland just like secondary hypothyroidism, but the **thyroid hormone levels are within a normal range**. Subclinical hypothyroidism frequently clears up on its own. It is often **caused by inflammation**, like that experienced during a hospital stay. All other types of hypothyroidism besides this one can be called "overt hypothyroidism."




| CONDITION: | Normal | Hyperthyroidism | Hypothyroidism Primary | Hypothyroidism Secondary |
|---|---|---|---|---|
| TSH | Normal | Low | High | Low |
| T4 | Normal | High | Low | Low |

**Positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies** in a patient with hypothyroidism result in a diagnosis of **Hashimoto's thyroiditis**.

# Polycystic ovary syndrome

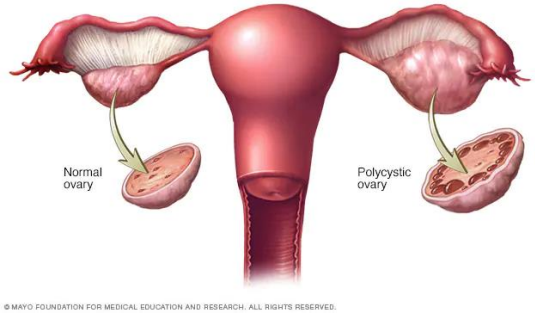



Symptoms of PCOS often start around the time of the **first menstrual period**. Sometimes symptoms develop later after you have had periods for a while.

A diagnosis of PCOS is made when you have at **least 2 of these:**

- **Irregular periods**. Infertility possible.
- **Hyperandrogenemia**. Hirsutism, severe acne and male-pattern baldness can happen, too.
- **Polycystic ovaries**.

# Polycystic ovary syndrome: treatment



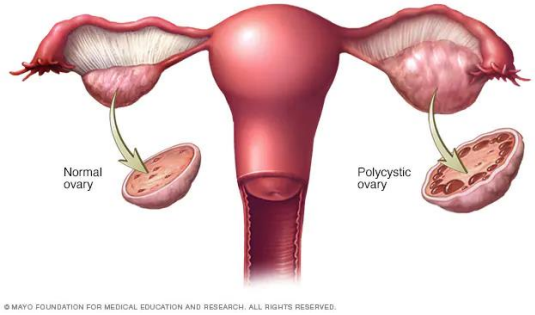

## Lifestyle changes

## Medications

To regulate your periods:

- **Combination birth control pills** (estrogen and progestin): decrease androgen production and regulate estrogen, thus lowering the risk of endometrial cancer and correct irregular bleeding, excess hair growth and acne.
- **Progestin therapy**. Taking progestin for 10 to 14 days every 1 to 2 months can regulate periods and protect against endometrial cancer.

# Polycystic ovary syndrome: treatment




## Medications

To help ovulation:

- **Clomiphene**. This oral anti-estrogen medication is taken during the first part of the menstrual cycle.
- **Metformin**. Improves insulin resistance and lowers insulin levels. In the presence of prediabetes, metformin can slow the progression to type 2 diabetes and help with weight loss.
- **Gonadotropins**.

To reduce excessive hair growth or improve acne:

- **Birth control pills**.
- **Eflornithine** (Vaniqa) cream.
- **Electrolysis and laser hair removal**
- **Acne treatments**. Medications, including pills and topical creams or gels, may help improve acne.

Genetic causes of obesity can be broadly classified into:

1. Monogenic causes: those caused by a single gene mutation, primarily located in the leptin- melanocortin pathway.
2. Syndromic obesity: severe obesity associated with other phenotypes such as neurodevelopmental abnormalities, and other organ/system malformations.
3. Polygenic obesity: caused by cumulative contribution of a large number of genes whose effect is amplified in a 'weight gain promoting' environment.

**Adolesc Med State Art Rev. 2017; 28(2): 379-405**

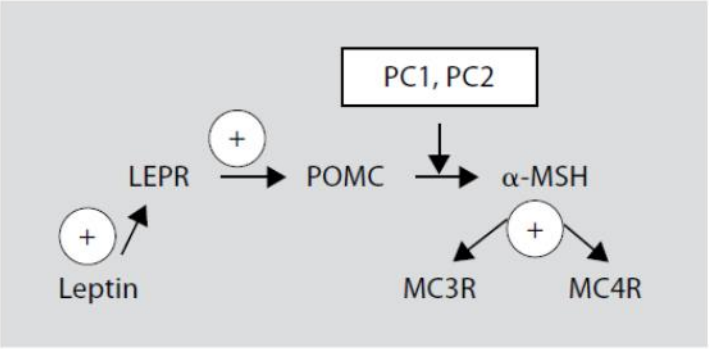



**Fig. 1.** Leptin-melanocortin pathway. Most monogenic obesities are frequently due to gene mutations within the leptin-melanocortin pathway (for description, see text).

## SINGLE GENES KNOWN TO BE INVOLVED WITH OBESITY

| NAME | GENE | MIM | MODE of INHERITANCE | CHROMOSOMAL POSITION |
|---|---|---|---|---|
| Leptin | *LEP* | 164160 | AR | 7q32.1 |
| Leptin receptor | *LEPR* | 601007 | AR | 1p31.2 |
| Proopiomelanocortin | *POMC* | 176830 | AR | 2p23.2 |
| Melanocortin 4 receptor | *MC4R* | 155541 | AD/AR | 18q21.32 |
| Single-minded Drosophila Homologue-1 | *SIM1* | 603128 | AD | 6q16.3 |
| Nurotrophic Tyrosine Kinase Receptor Type 2 | *NTRK2* | 600456 | AD | 9q21.33 |
| Kinase suppressor of Ras2 | *KSR2* | 610737 | AD | 12q24.22-q24.23 |
| Carboxypeptidase | *CPE* | 114855 | AD | 4q32.3 |
| Proconvertase 1 | *PCSK1* | 162150 | AR | 5q15 |
| Brain Derived Neurotropic factor | *BDNF* | 113505 | AD | 11p14.1 |
| SH2B adaptor protein | *SH2B1* | 608937 | AD | 16p11.2 |
| Tubby, Homogue of Mouse | *TUB* | 601197 | AR | 11p15.4 |

AD= Autosomal dominant, AR = Autosomal recessive.

**Adolesc Med State Art Rev. 2017; 28(2): 379-405**

# Genetic causes of obesity

**Rarely**, obesity occurs in families according to a clear inheritance pattern caused by changes **in a single gene**. The **most commonly** implicated gene is **MC4R**, which encodes the **melanocortin 4 receptor**. Changes in MC4R that **diminish its function** are found in a **small fraction (<5%) of obese** people in various ethnic groups. Affected **children feel extremely hungry** and become obese because of consistent **overeating (hyperphagia**). So far, rare variants in some genes have been implicated in **single-gene (monogenic) obesity.**

In **most obese** people, **no single genetic cause** can be identified. Since 2006, genome-wide association studies have found **more than 50 genes** associated with obesity, most with very small effects. Several of these genes also have variants that are associated with monogenic obesity, a phenomenon that has been observed in many other common conditions. Most obesity seems to be **multifactorial**, that is, the result of complex interactions among many **genes and environmental factors.**

**Table 1.** General and specific features of single gene mutations

| General features | Specific features | Gene |
|---|---|---|
| Early-onset obesity and hyperphagia | Low levels of circulating leptin | *LEP* |
| | Impaired immunity (high rate of childhood infections) | *LEP, LEPR* |
| | Hypogonadism | *LEP, LEPR, PC1* |
| | Adrenal insufficiency (e.g. hypoglycemia, convulsion), pale skin, red hair, jaundice | *POMC* |
| | Malabsorption (intestinal dysfunction), glucose homeostasis disturbances, low levels of insulin | *PC1* |
| | Variable effect on body weight in heterozygous mutation carriers | *MC4R* |
| | Developmental delays | *SIM1, BDNF, NTRK2* |

Obesity due to a single gene mutation is usually severe and characterized by early-onset accompanied by hyperphagia. Mutation carriers manifest with additional specific features which may help in genetic diagnosis of morbid obesity in an individual [modified according to Choquet H et al. [30]]. LEP = leptin; LEPR = leptin receptor; PC1 = prohormone convertase 1; POMC = pro-opiomelanocortin; *MC4R* = melanocortin type 4 receptor; SIM1 = single-minded homolog 1; BDNF = brain-derived neurotrophic factor; NTRK2 = neurotrophic tyrosine kinase receptor type 2.

**Table 1.** Rare monogenic forms of human obesity

| Gene | Mutation type | Prevalence | Obesity | Associated phenotypes |
|---|---|---|---|---|
| Leptin | Homozygous mutation | Diagnosed in fewer than 100 patients worldwide | Severe, from the first days of life | Gonadotropic and thyrotropic insufficiency<br>Alteration in immune function |
| LEPR | Homozygous mutation | 2–3% of patients with severe early-onset obesity | Severe, from the first days of life | Gonadotropic, thyrotropic and somatotropic insufficiency<br>Alteration in immune function |
| POMC | Homozygous or compound heterozygous | Diagnosed in fewer than 10 patients worldwide | Severe, from the first months of life | ACTH insufficiency<br>Mild hypothyroidism and ginger hair if the mutation leads to the absence of POMC production |
| PCSK1 | Homozygous or compound heterozygous | Diagnosed in fewer than 20 patients worldwide | Severe obesity occurring in childhood | Adrenal, gonadotropic, somatotropic and thyrotropic insufficiency<br>Postprandial hypoglycemic malaises<br>Severe malabsorptive neonatal diarrhea<br>Central diabetes insipidus |
| SIM1 | Translocation between chr 1p22.1 and 6q16.2 in the *SIM1* gene | Diagnosed in fewer than 50 patients worldwide | Severe obesity occurring in childhood | Inconstantly, neurobehavioral abnormalities (including emotional lability or autism-like behavior) |
| NTRK2 | De novo heterozygous mutation | Diagnosed in fewer than 10 patients worldwide | Severe obesity from the first months of life | Developmental delay<br>Behavioral disturbance<br>Blunted response to pain |

**Obes Facts 2016;9:158-73**

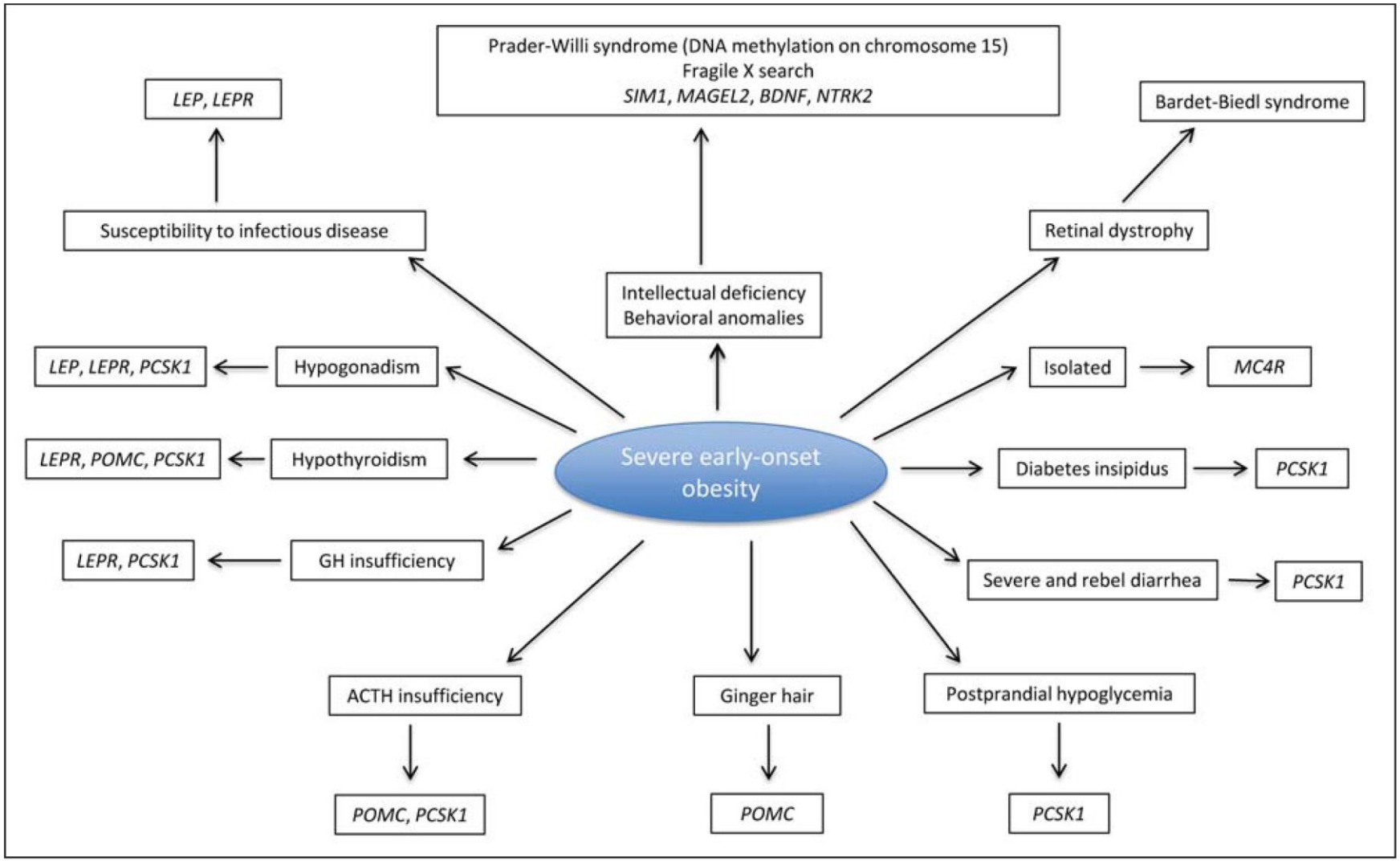



**Fig. 3.** Genetic diagnosis prioritization for severe early-onset obesity [4–7, 20, 22, 26, 36, 75]. BDNF = brain-derived neurotropic factor; LEP = leptin; LEPR = leptin receptor; MAGEL2 = MAGE-like 2; MC4R = melanocortin 4 receptor; NTRK2 = neurotrophic tyrosine kinase receptor 2; PCSK1 = proprotein convertase subtilisin/kexin type 1; POMC = proopiomelanocortin; SIM1 = single-minded 1.

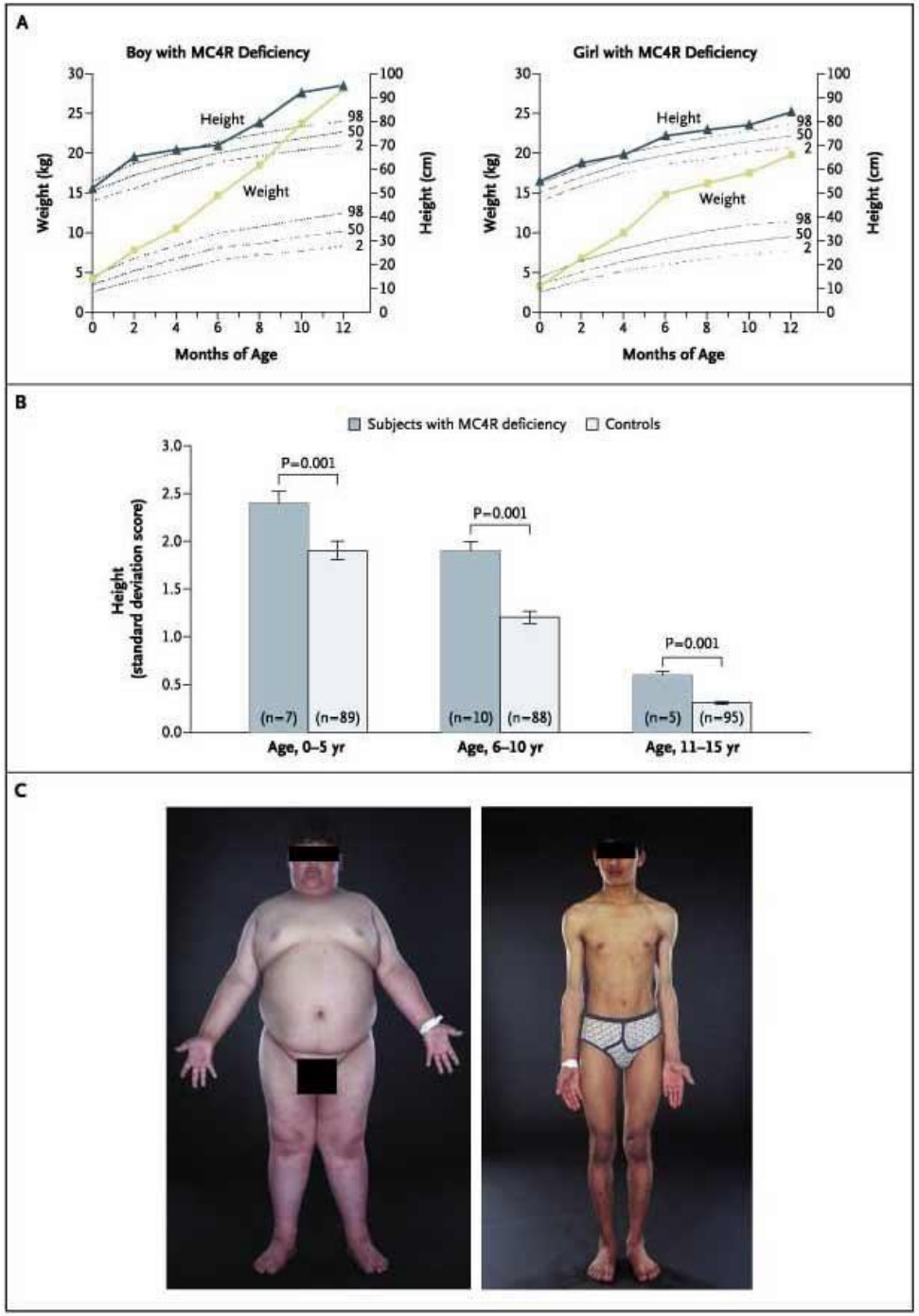



**Figure 3. Growth (Panels A and B) and Body Composition (Panel C) in Subjects with Melanocortin 4 Receptor (MC4R) Deficiency.**

Panel A shows growth charts for two children with MC4R deficiency during the first year of life, as compared with normal reference values in the United Kingdom (2nd, 50th, and 98th percentiles).

Panel B shows mean (±SD) standard-deviation scores for height at different ages in subjects with MC4R deficiency and obese subjects with a normal MC4R genotype who were matched for age and body-mass index.

Panel C shows a **9-year-old boy** who was **homozygous** for a mutation in MC4R (left-hand side) and his **16-year-old brother**, who had a normal genotype (right-hand side).

N Engl J Med 2003; 348:1085-1095

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# New treatment for obesity caused by rare genetic disorders

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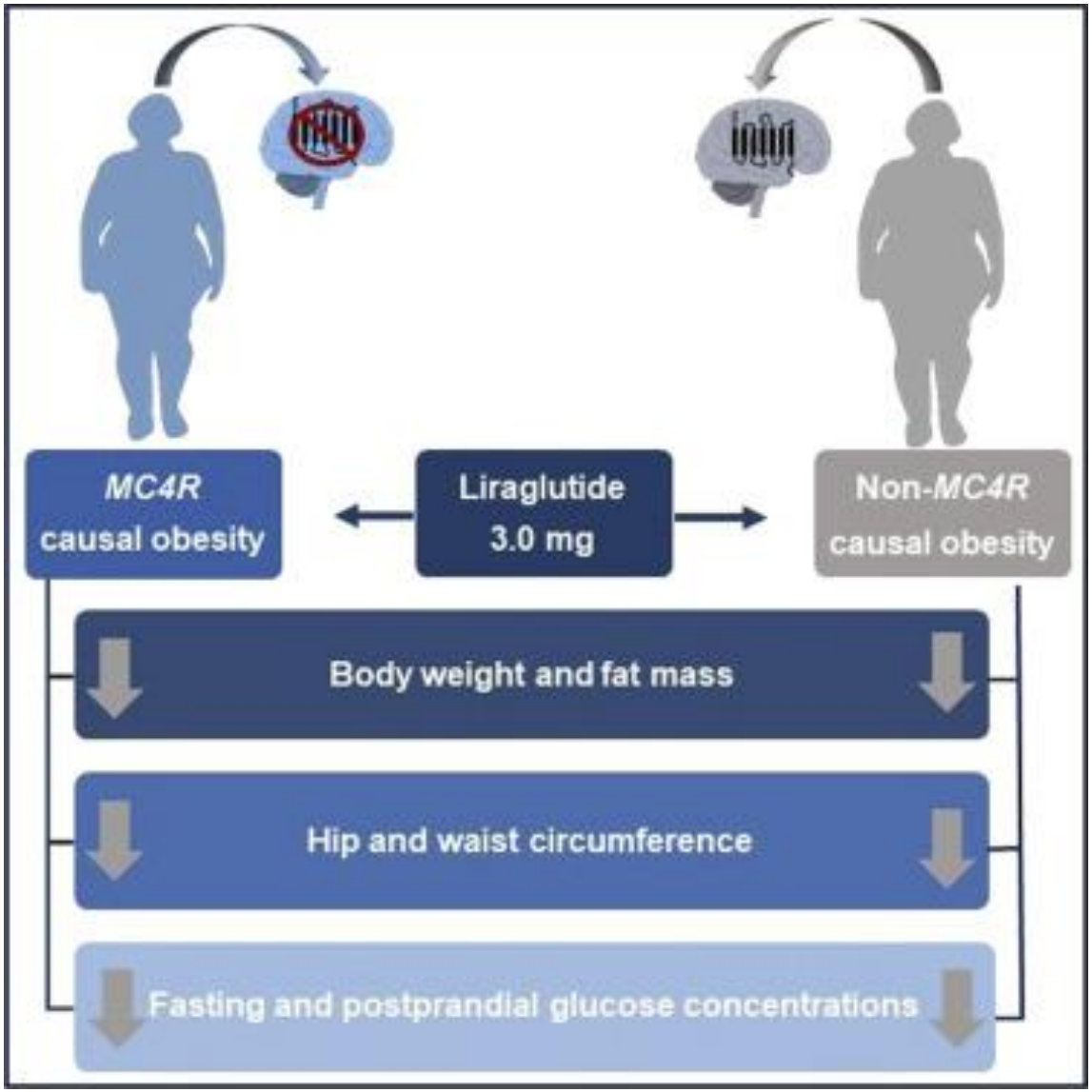
## MC4R agonist

News 21/05/2021

EMA has recommended granting a marketing authorisation in the European Union (EU) for Imcivree (setmelanotide) to support weight loss and -management in patients from 6 years of age with obesity caused by the following rare genetic disorders: pro-opiomelanocortin (POMC) deficiency – including proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency – and leptin receptor (LEPR) deficiency in adults and children. These conditions must be confirmed by genetic testing before a patient can start treatment with Imcivree.

POMC, PCSK1 or LEPR deficiency affect the melanocortin 4 receptor (MC4R) pathway which is responsible for transmission of signals about when to eat and when to stop eating. Patients with these deficiencies continuously feel hungry and become severely obese early in life – often beginning in infancy. These conditions are extremely rare. Fewer than 50 patients with POMC deficiency, 90 with LEPR deficiency and 50 with PCSK1 deficiency have been reported worldwide thus far.

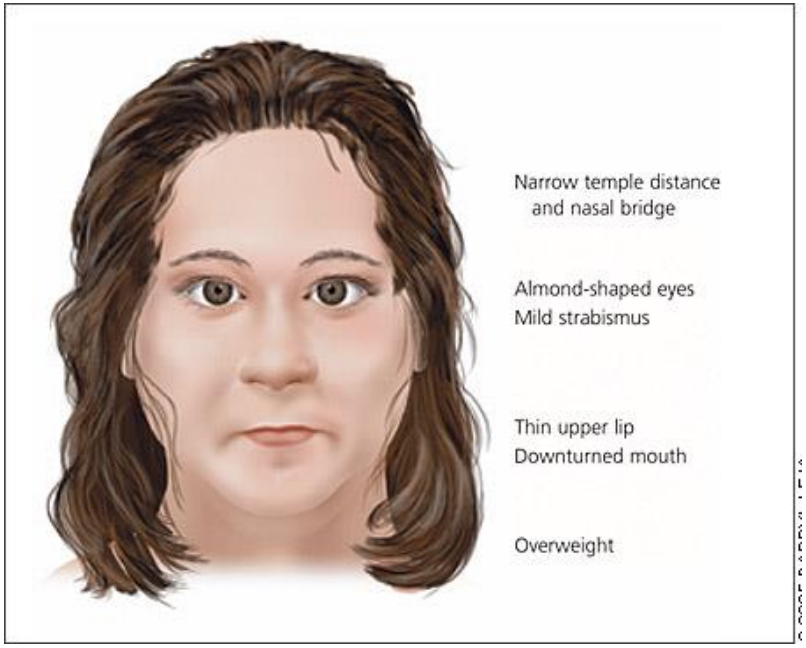
## Sibutramine – Bariatric surgery

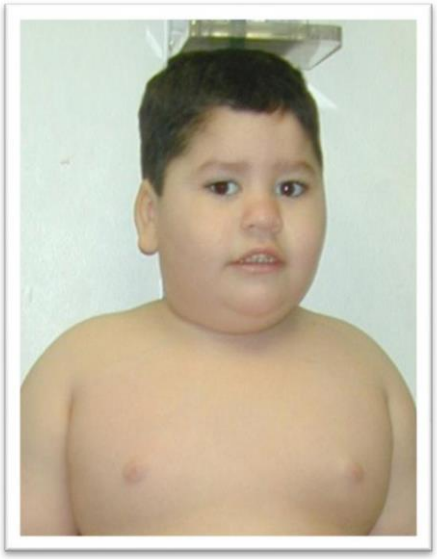


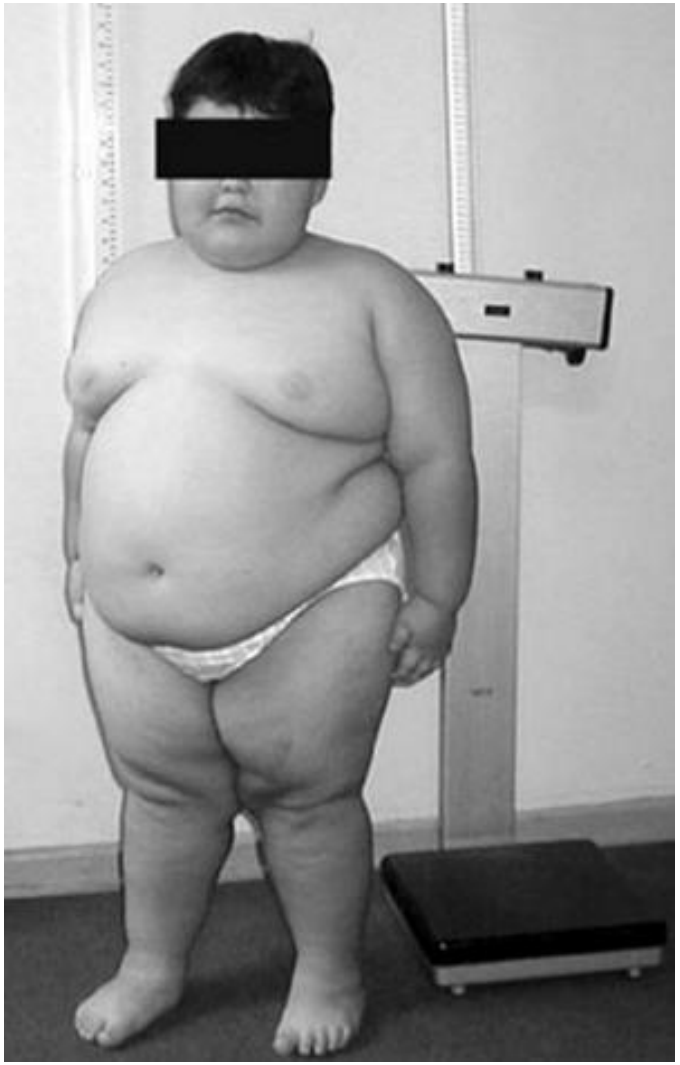

Cell Metab. 2018;28(1):23-32

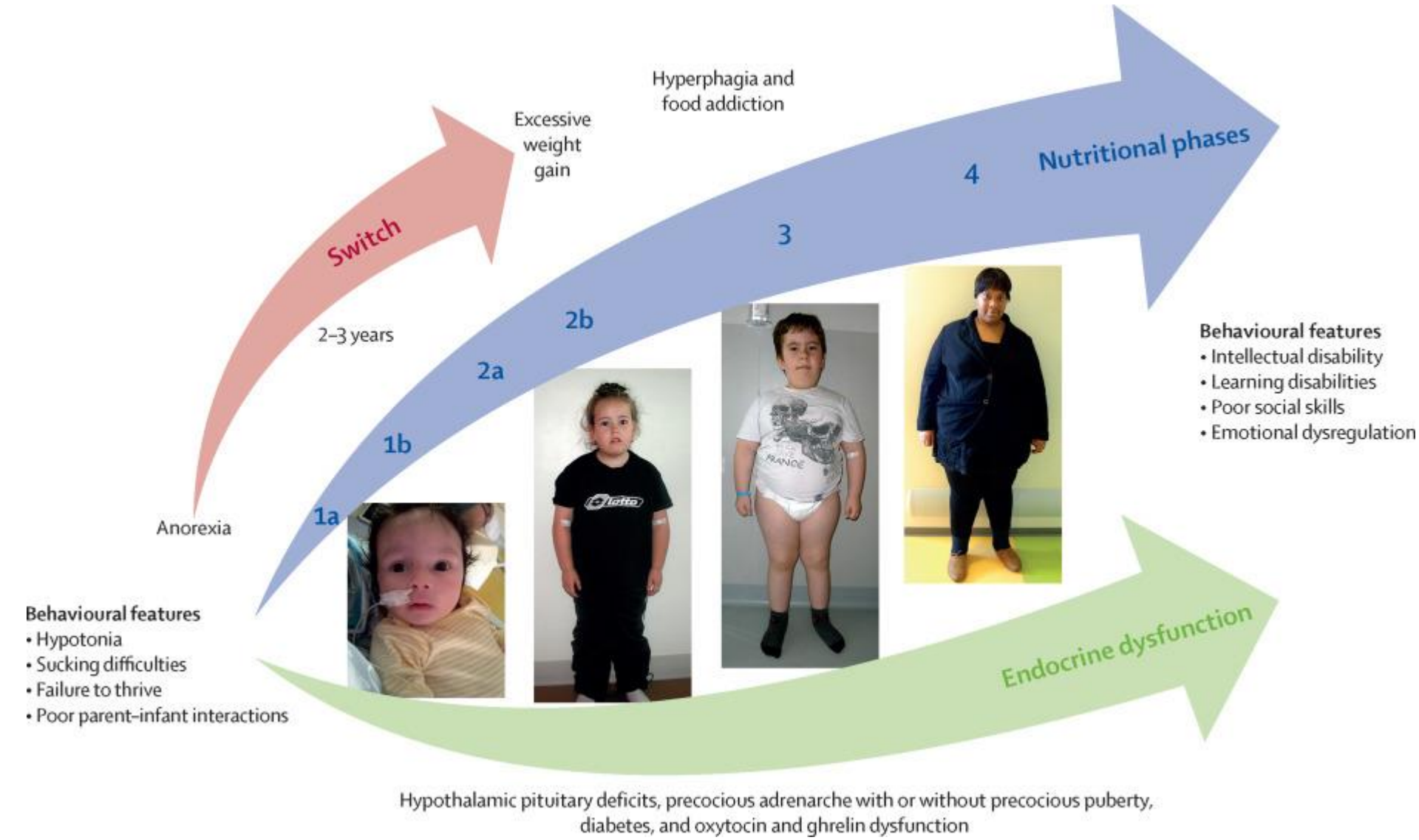
**Table 2.** Main syndromic forms of obesity

| Syndrome | Clinical features in addition to obesity | Prevalence | Genetic |
|---|---|---|---|
| Prader-Willi | Neonatal hypotonia, mental retardation, hyperphagia, facial dysmorphy, hypogonadotrophic hypogonadism, short stature | 1/25,000 births | Lack of the paternal segment 15q11-q13 (microdeletion, maternal disomy, imprinting defect or reciprocal translocation) |
| Bardet-Biedl | Mental retardation, retinal dystrophy or pigmentary retinopathy, dysmorphic extremities, hypogonadism, kidney anomalies | 1/125,000 to 1/175,000 births | BBS1 (11q13); BBS2 (16q12.2); BBS3 (*ARL6*, 3q11); BBS4 (15q24.1); BBS5 (2q31.1); BBS6 (*MKKS*, 20p12); BBS7 (4q27); BBS8 (*TTC8*, 14q31); BBS9 (*PTHB1*, 7p14); BBS10 (*C12ORF58*, 12q21.2); BBS 11 (*TRIM32*, 9q33.1); BBS12 (*FLJ35630*, 4q27); BBS13 (*MKS1*, 17q23); BBS14 (*CEP290*, 12q21.3); BBS15 (*WDPCP*, 2p15); BBS16 (*SDCCAG8*, 1q43); BBS17 (*LZTFL1*, 3p21); BBS18 (*BBIP1*, 10q25); BBS19 (*IFT27*, 22q12) |
| Cohen | Retinal dystrophy, prominent central incisors, dysmorphic extremities, microcephaly, cyclic neutropenia | Diagnosed in fewer than 1,000 patients worldwide | Autosomal recessive *COH1* gene (chr 8q22-q23) |
| Alström | Retinal dystrophy, neurosensory deafness, diabetes, dilated cardiomyopathy | Diagnosed in about 950 patients worldwide | Autosomal recessive *ALMS1* gene (chr 2p13-p14). |
| X fragile | Mental retardation, hyperkinetic behavior, macroorchidism, large ears, prominent jaw | 1/2,500 births | X-linked *FMR1* gene (Xq27.3) |
| Borjeson-Forssman-Lehmann | Mental retardation, hypotonia, hypogonadism, facial dysmorphy with large ears, epilepsy | Approximately 50 reported patients | X-linked *PHF6* gene (Xq26-q27) |
| Albright hereditary osteodystrophy | Short stature, skeletal defects, facial dysmorphy, endocrine anomalies | 1/1,000,000 births | Autosomal dominant *GNAS1* gene (20q13.2) |
| 16p11.2 deletion syndrome | Developmental delay, intellectual disability, autism spectrum disorders, impaired communication, socialization skills | Approximately 3/10,000 births | Autosomal dominant Microdeletion of 16p11.2 |
| Kinase suppressor of Ras2 (KSR2) variants | Hyperphagia in childhood, low heart rate, reduced basal metabolic rate, severe insulin resistance | Approximately 65 reported patients | Rare *KSR2* variants (12q24.22-q24.23) |
| *TUB* mutation | Night blindness, decreased visual acuity and electrophysiological features of a rod-cone dystrophy | Identified in 3 affected sibs from a consanguineous Caucasian family | Homozygous *TUB* mutation (11p15.4) |
| *ACP1*, *TMEM18*, *MYT1L* deletion | Hyperphagia, intellectual deficiency, severe behavioral difficulties | Approximately 13 reported patients | Paternal deletion encompassing the *ACP1*, *TMEM18*, *MYT1L* genes (2p25) |


Narrow temple distance
and nasal bridge
Almond-shaped eyes
Mild strabismus
Thin upper lip
Downturned mouth
Overweight








**Lancet Diabetes Endocrinol. 2021;9(4):235-46**

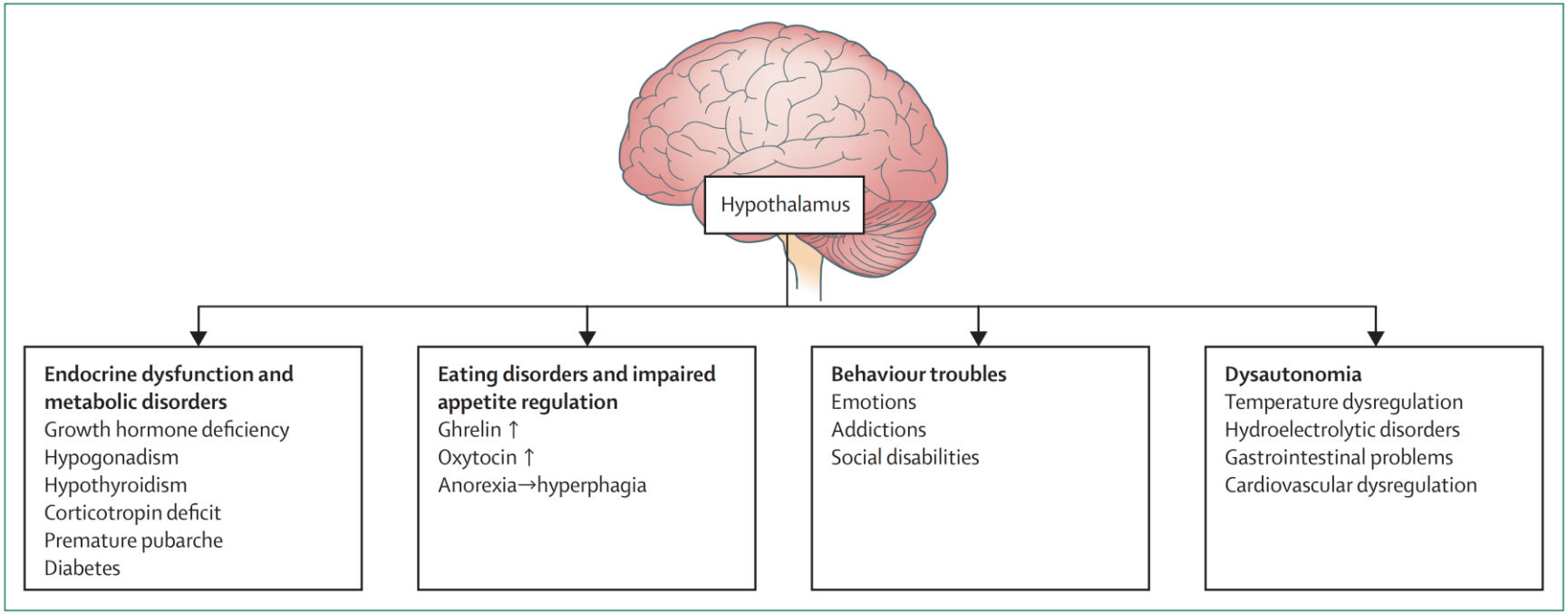



***Figure 4:*** **Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome**

The hypothalamus controls endocrine and metabolic function, appetite regulation, emotion, and behaviour and is linked to the autonomic nervous system. Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome.

**Lancet Diabetes Endocrinol. 2021;9(4):235-46**

## Growth hormone treatment

A seminal review on growth hormone treatment in Prader-Willi syndrome was published in 2013.[93] Treatment is now usually initiated between 3 months and 12 months of age.

## Sex-steroid treatment and fertility

Puberty is usually induced with sex steroids at normal pubertal age.

Thyroid function testing is required at routine visits, particularly before starting growth hormone treatment and during follow-up of growth hormone treatment,[123] so that levothyroxine can be started if indicated.

**Lancet Diabetes Endocrinol. 2021;9(4):235-46**

# Secondary causes of obesity

## Executive summary

- Secondary causes of obesity are rare and can be divided into endocrinological, genetic and iatrogenic etiologies.
- Endocrinologic diseases leading to obesity include hypothyroidism, Cushing's syndrome, polycystic ovaries syndrome, hypogonadism, growth hormone deficiency, hypothalamic diseases and pseudohypoparathyroidism.
- Early-onset obesity with abnormal eating behavior are suggestive of monogenic obesity, such as leptin deficiency, MCR4 deficiency and pro-opiomelanocortin deficiency.
- Prader–Willi syndrome is characterized by severe obesity in early age with insatiability, mild mental retardation and hypogonadism.
- Several centrally acting medications and antidiabetic agents can be associated with obesity.
- Physicians should recognize potentially treatable secondary causes of obesity.

**Therapy 2007,4(5): 641-50**

# Drug-induced obesity and its metabolic consequences: a review with a focus on mechanisms and possible therapeutic options

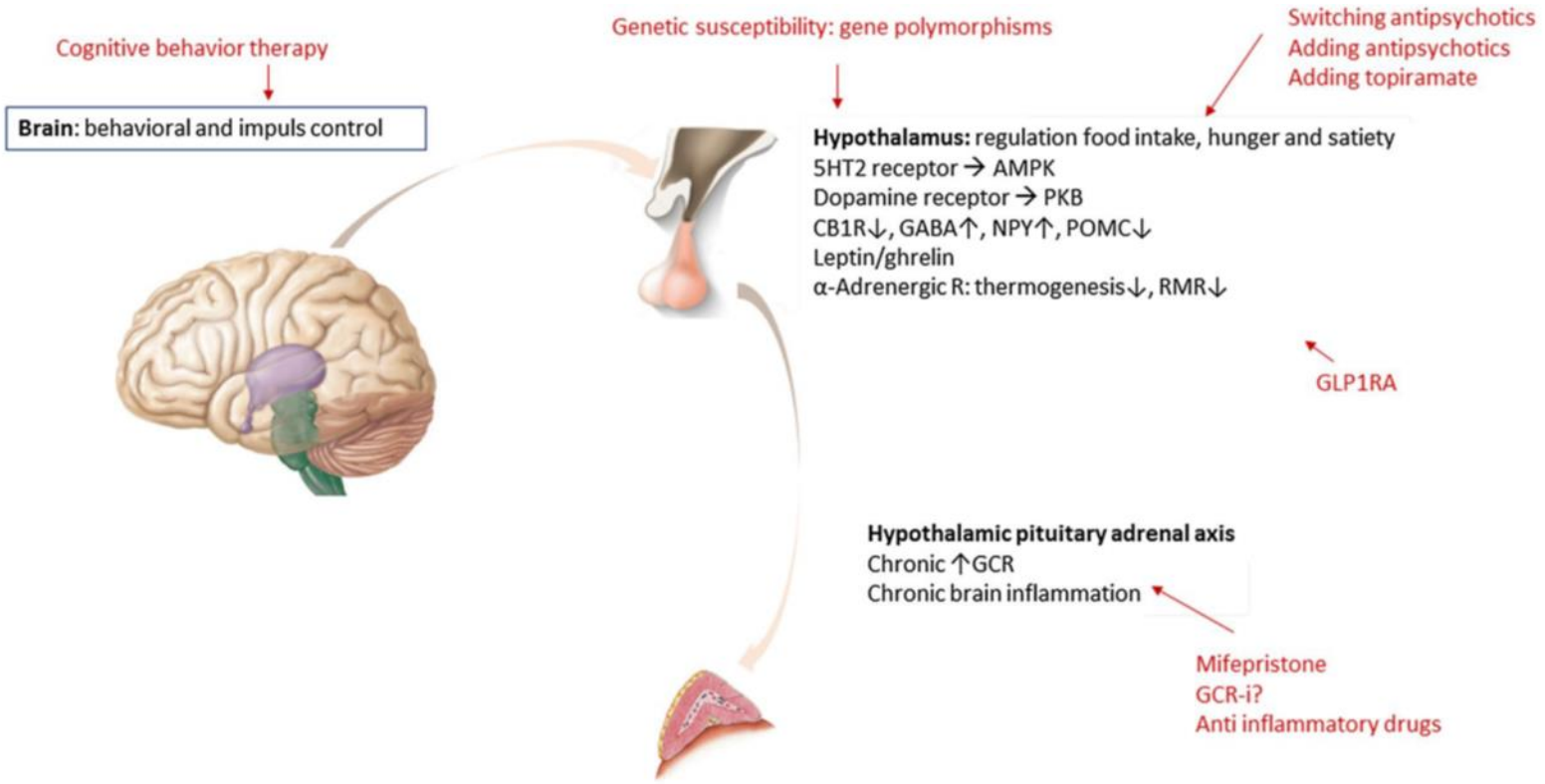



**Fig. 2** Central nervous mechanisms of antipsychotic-induced weight gain and metabolic side effects. Current and future preventive and therapeutic options. *5HT2* serotonin receptor type 2, *AMPK* AMP-activated protein kinase, *PKB* protein kinase B, *CB1R* cannabinoid receptor type 1, *GABA* gamma-aminobutyric acid, *NPY* neuropeptide Y, *POMC* pro-opiomelanocortin, *RMR* resting metabolic rate, *GLP1RA* glucagon like peptide-1 receptor agonist, *GCR* glucocorticoid receptor, *GCRi* glucocorticoid receptor inhibitor, ↑ increase, ↓ decrease

J Endocrinol Invest. 2017;40(11):1165-74

# Antipsychotic-associated weight gain: management strategies and impact on treatment adherence

**Table 1** Likelihood of weight gain with antipsychotics

| Antipsychotic | Propensity to cause weight gain |
|---|---|
| Clozapine | High |
| Olanzapine | High[a,b] |
| Chlorpromazine | Moderate |
| Quetiapine | Moderate[b] |
| Risperidone | Moderate[b] |
| Paliperidone | Moderate |
| Aripiprazole | Low[c] |
| Amisulpride | Low[c] |
| Asenapine | Low |
| Haloperidol | Low[d] |
| Ziprasidone | Low[c,d] |
| Lurasidone | Low[d] |

**Notes:** [a]Significantly greater increase in weight at >38 weeks, when compared with <6 weeks period in both antipsychotic previously prescribed and naïve groups in the meta-analysis by Bak et al.[13] [b]Significant weight gain seen in antipsychotic naïve group even <6 weeks in the meta-analysis by Bak et al.[13] [c]Weight neutral with duration of antipsychotic use in the meta-analysis by Bak et al.[13] [d]No significant difference in weight when compared with placebo in multiple treatment meta-analysis by Leucht et al.[10] Data from studies.[9–11,13]

**Neuropsychiatr Dis Treat. 2017;13:2231-41**

# Drug-induced obesity and its metabolic consequences: a review with a focus on mechanisms and possible therapeutic options

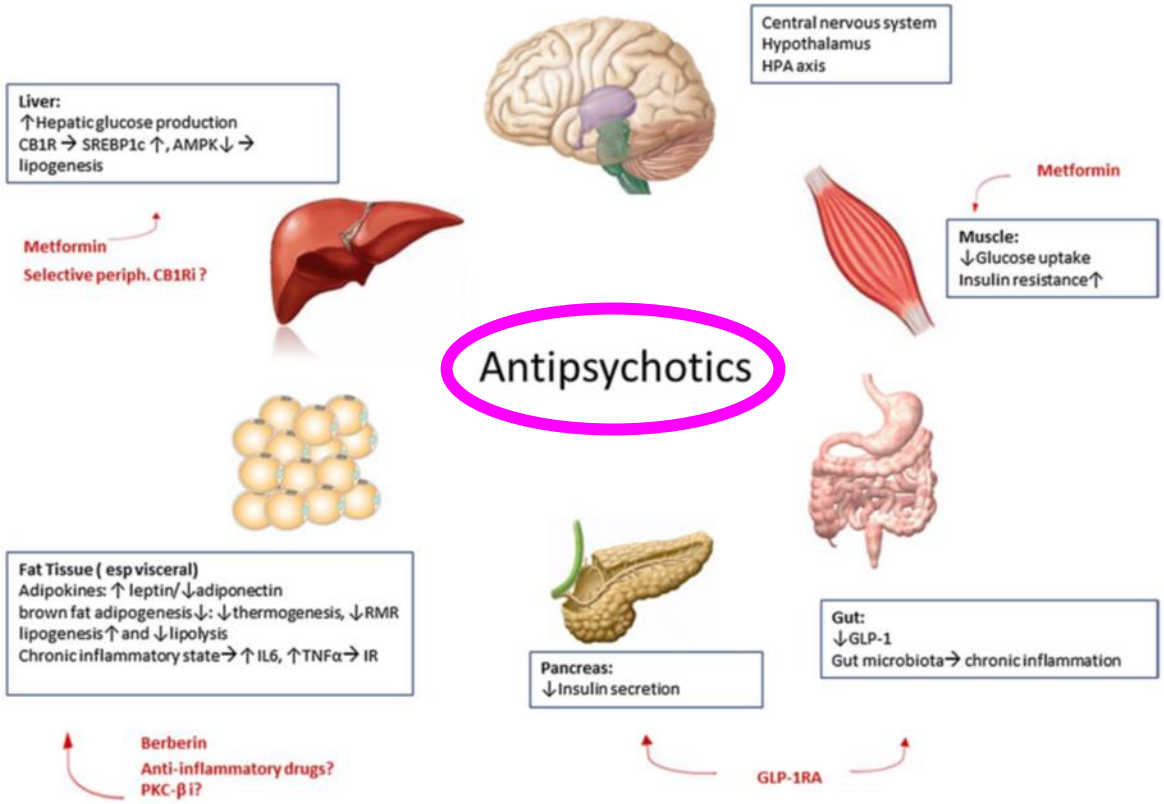



**Fig. 1** Mechanisms of antipsychotic-induced weight gain and metabolic side effects. Current and future preventive and therapeutic options. *HPA axis* hypothalamic–pituitary–adrenal axis, *GLP-1* glucagon like peptide-1, *GLP1RA* GLP-1 receptor agonist, *RMR* resting metabolic rate, *IL6* interleukin-6, *TNF-α* tumor necrosis factor-α, *IR* insulin resistance, *PKC-βi* protein kinase C-β inhibitor, *CB1R* cannabinoid receptor type 1, *periph CB1Ri* peripheral cannabinoid receptor type 1 inhibitor, *SREBP1c* sterol regulatory element-binding proteins type 1c, *AMPK* AMP-activated protein kinase, ↑ increase, ↓ decrease

J Endocrinol Invest. 2017;40(11):1165-74

# Effect on weight of diabetes medications

**Weight gain**

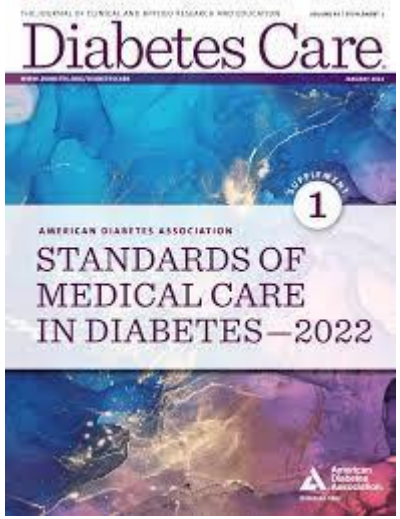
- Insulin
- Sulfonylureas
- Thiazolidinediones

**Weight neutral**

- Dipeptidyl peptidase-4 inhibitors
- Metformin
- Acarbose

**Weight loss**

- Glucagon-like peptide-1 agonists
- Sodium-glucose cotransporter-2 inhibitors



# Antidiabetic Medications and Weight Gain: Implications for the Practicing Physician

**Table 2. Postulated mechanisms of weight gain with insulin therapy**

| |
|---|
| Correction of glycosuria leading to reduced energy loss and catch-up process of regaining weight loss of uncontrolled diabetes |
| Anabolic effects of insulin and increased lipogenesis |
| Attenuation of insulin-evoked satiety leading to increased food intake |
| Frequent hypoglycemic episodes leading to defensive snaking |
| Excessive reliance on insulin to normalize glucose readings leading to false sense of freedom to eat |
| Genetic factors associated with greater visceral adiposity and dyslipidemia |

Curr Diab Rep. 2009;9(3):249-54

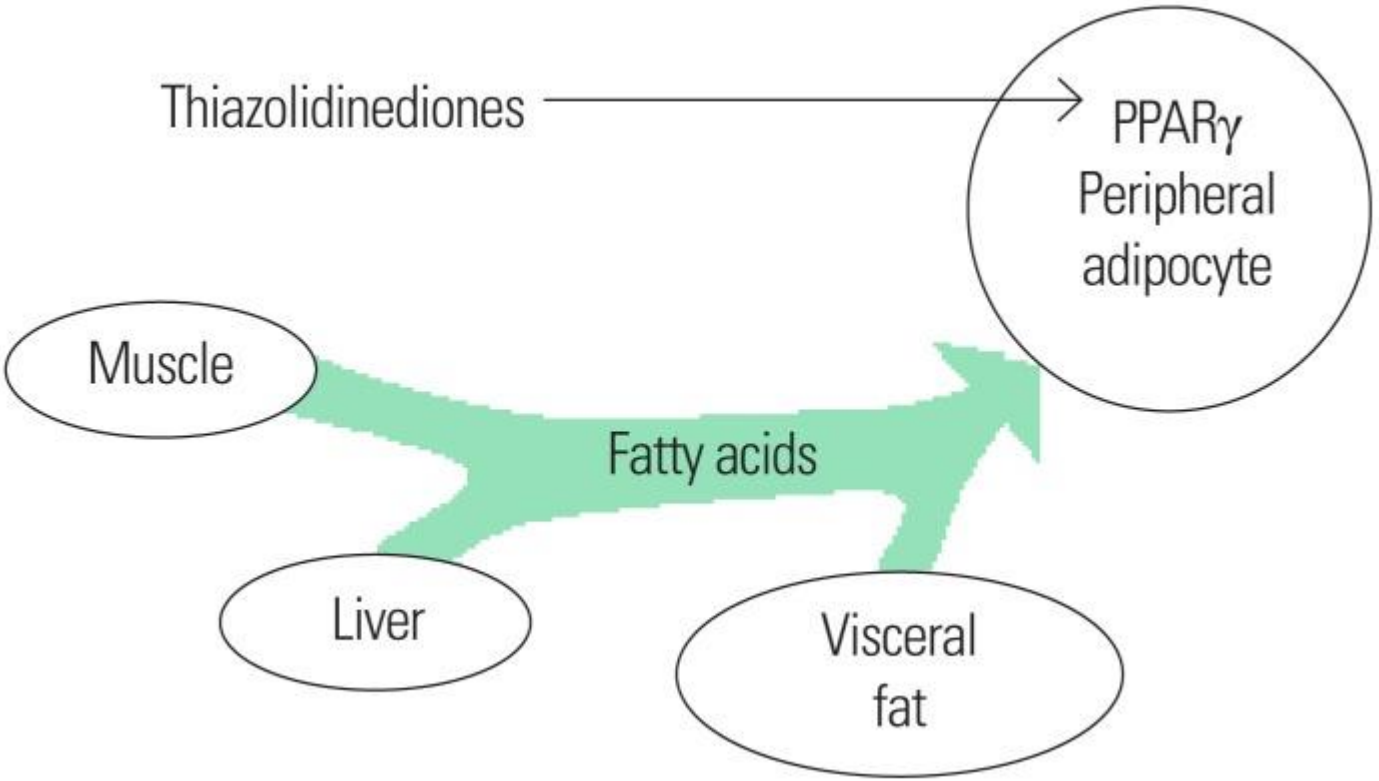
# Sulfonylureas

- Increased and sustained insulin secretion
- Decreased glycosuria
- Increased hypoglycemia
- No independent effects on adipose deposition or appetite

# TZD: pioglitazone

- Fat cell proliferation
- Fluid retention
- Decreased glycosuria
- Increased appetite

# Depot-specific effects on regional adiposity of thiazolidinediones




TZDs induce **body fat redistribution** in the direction **of reducing** (or at least not accumulating) **visceral fat** and **increasing subcutaneous fat**

**J Obes Metab Syndr. 2017;26(2):102-6**

# Rethinking pioglitazone as a cardioprotective agent: a new perspective on an overlooked drug

Cardiovasc Diabetol. 2021;20(1):109

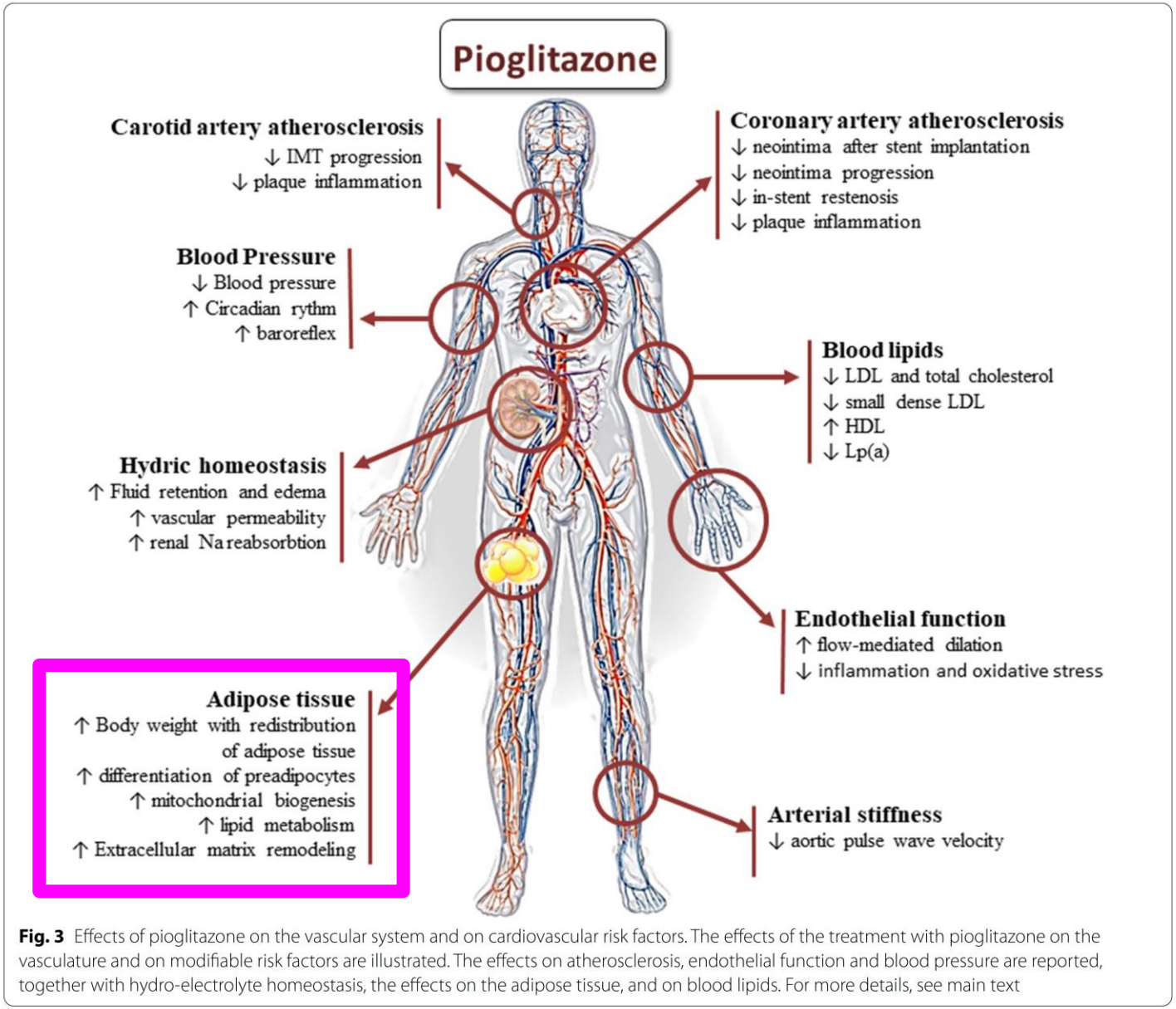



**Fig. 3** Effects of pioglitazone on the vascular system and on cardiovascular risk factors. The effects of the treatment with pioglitazone on the vasculature and on modifiable risk factors are illustrated. The effects on atherosclerosis, endothelial function and blood pressure are reported, together with hydro-electrolyte homeostasis, the effects on the adipose tissue, and on blood lipids. For more details, see main text

# Drugs Commonly Associated With Weight Change: A Systematic Review and Meta-analysis

**Results:** We included 257 randomized trials (54 different drugs; 84 696 patients enrolled). Weight gain was associated with the use of amitriptyline (1.8 kg), mirtazapine (1.5 kg), olanzapine (2.4 kg), quetiapine (1.1 kg), risperidone (0.8 kg), gabapentin ( 2.2 kg), tolbutamide (2.8 kg), pioglitazone (2.6 kg), glimepiride (2.1 kg), gliclazide (1.8 kg), glyburide (2.6 kg), glipizide (2.2 kg), sitagliptin (0.55 kg), and nateglinide (0.3 kg). Weight loss was associated with the use of metformin (1.1 kg), acarbose (0.4 kg), miglitol (0.7 kg), pramlintide (2.3 kg), liraglutide (1.7 kg), exenatide (1.2 kg), zonisamide (7.7 kg), topiramate (3.8 kg), bupropion (1.3 kg), and fluoxetine (1.3 kg). For many other remaining drugs (including antihypertensives and antihistamines), the weight change was either statistically nonsignificant or supported by very low-quality evidence.

J Clin Endocrinol Metab. 2015;100(2):363-70

**Table 4** Treatment-emergent weight changes associated with antihypertensives

| Drug name | Weight effect |
|---|---|
| **Alpha-blockers** | |
| Clonidine[155,156] | +[a] |
| Prazosin[157,158] | Neutral |
| **ACE inhibitors** | |
| Enalapril[131–133] | – –[a] |
| Lisinopril[124,137,138] | –[a] |
| Perindopril[134–136] | + & – –[a] |
| Ramipril[139–141] | –[a] |
| **ARBs** | |
| Irbesartan[161,165,166] | Neutral |
| Losartan[131,163,164] | – –[a] |
| Olmesartan[161,162,165] | Neutral |
| Telmisartan[159–162] | –[a] |
| Valsartan[167–169] | +[a] |
| **Beta-blockers** | |
| Acebutolol[153,154] | Neutral |
| Atenolol[143–145] | + +[a] |
| Metoprolol[148,149] | +[a] |
| Propranolol[146,147] | +[a] |
| Timolol[150–152] | –[a] |
| **CCBs** | |
| Amlodipine[170–172] | Neutral |
| Diltiazem[173–175] | +[a] |
| **Direct renin inhibitors** | |
| Aliskiren[176–178] | Neutral |
| **Diuretics** | |
| Chlorthalidone[122,125,126,a] | –[a] |
| Furosemide[122,123,130a] | – – |
| Hydrochlorothiazide[121–124,a] | –[a] |
| Indapamide[127–129,a] | –[a] |

**Notes:** +=>1 kg. Neutral=±1 kg. –=<–1 kg. Additional + or – refers to ≥3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s).
**Abbreviations:** ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

**Diabetes Metab Syndr Obes. 2018;11:427-38**

**TABLE 2**

## Antihypertensives and weight[3]

| Weight gain | Weight neutral |
|---|---|
| Alpha-adrenergic blockers | ACE inhibitors |
| Beta-adrenergic blockers (atenolol, metoprolol, nadolol, propranolol) | Angiotensin receptor blockers |
| | Beta-adrenergic blockers (carvedilol, nebivolol) |
| | CCBs |
| | Thiazides |

ACE, angiotensin-converting enzyme; CCBs, calcium channel blockers.

# PRACTICE RECOMMENDATIONS

Choose **weight-loss-promoting medications**, such as **metformin, sodium-glucose co-transporter 2 inhibitors, and glucagon-like peptide-1 agonists**, and weight-neutral medications, such as **DPP-4 inhibitors**, as first- and second-line agents for patients with type 2 diabetes who are overweight or obese.

Prescribe **angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers** as first- and second-line antihypertensive therapy for patients who are overweight or obese.

Select **antidepressants** that promote weight loss, such as **bupropion**, or weight-neutral agents, such as **fluoxetine and sertraline**, for patients who are overweight or obese and require treatment for depression.

**Table 5** Treatment-emergent weight changes associated with corticosteroids

| Drug name | Weight effect |
|---|---|
| Cortisone[187–189] | + + |
| Prednisolone[185,186] | + + |
| Prednisone[182–184] | + + |

**Notes:** +=>1 kg. Additional + refers to ≥3 kg weight change.

**Diabetes Metab Syndr Obes. 2018;11:427-38**


Early diagnosis and treatment!
OBESITY

EASO
European Association for the Study of Obesity

# European Guidelines for Obesity Management in Adults

## Clinical Evaluation of the Obese Patient

A comprehensive history, physical examination and laboratory assessment relevant to the patient's obesity should be obtained [25–27] {Recommended Best Practice (RBP)}.

*History Taking*

- Ethnicity
- Family history
- Dietary habits
- Physical activity frequency and nature
- Eating pattern and possible presence of an eating disorder (binge eating disorder, night eating syndrome, bulimia)
- Presence of depression and other mood disorders
- Other determinants, e.g., genetic, drugs, endocrine abnormalities, psychosocial factors, chronic stress, smoking cessation etc.
- Health consequences of obesity (table 2)
- Patient expectations and motivation for change
- Previous treatments for obesity.

***Obes Facts* 2015;8:402-24**

**Table 4.** Obesity-related health risks and complications

| |
|---|
| *I. Metabolic complications* |
| Diabetes |
| insulin resistance |
| Dyslipidaemia |
| Metabolic syndrome |
| Hyperuricaemia |
| Gout |
| Low-grade inflammation |
| *II. Cardiovascular disorders* |
| Hypertension |
| Coronary heart disease |
| Congestive heart failure |
| Stroke |
| Venous thromboembolism |
| *III. Respiratory disease* |
| Asthma |
| Hypoxemia |
| Sleep apnoea syndrome |
| Obesity hypoventilation syndrome |
| *IV. Cancers* |
| Oesophagus, small intestine, colon, rectum, liver, gallbladder, pancreas, kidney, leukaemia, multiple myeloma, and lymphoma |
| In women: endometrial, cervix uteri, ovary, breast cancer after menopause |
| In men: prostate |
| V. Osteoarthritis |
| Knee and an increase in pain in the weight bearing joints |
| *VI. Gastrointestinal* |
| Gallbladder disease |
| Non-alcoholic fatty liver disease |
| Non-alcoholic steatohepatitis |
| Gastro-esophageal reflux |
| Hernia |

# European Guidelines for Obesity Management in Adults

*Physical Examination*

- Measure weight and height (from which BMI is calculated), WC, blood pressure (appropriate size cuff) {grade 3}
- Assess the presence and impact of obesity-related diseases (diabetes, hypertension, dyslipidaemia; cardiovascular, respiratory and joint diseases; non-alcoholic fatty liver disease (NAFLD), sleep disorders etc.) {RBP}
- Look for the presence of acanthosis nigricans as a sign of insulin resistance {RBP}.

***Obes Facts* 2015;8:402-24**

# European Guidelines for Obesity Management in Adults

*Laboratory Examinations*

The minimum data set required will include {RBP}:

- Fasting blood glucose
- Serum lipid profile (total, HDL and LDL cholesterol, triglycerides)
- Uric acid
- Thyroid function (thyroid-stimulating hormone (TSH) level)
- Liver function (hepatic enzymes)
- Cardiovascular assessment, if indicated {RBP}
- Endocrine evaluation if Cushing's syndrome or hypothalamic disease suspected
- Liver investigation (ultrasound, biopsy) if abnormal liver function tests suggest NAFLD or other liver pathology
- Sleep laboratory investigation for sleep apnoea.

***Obes Facts* 2015;8:402-24**

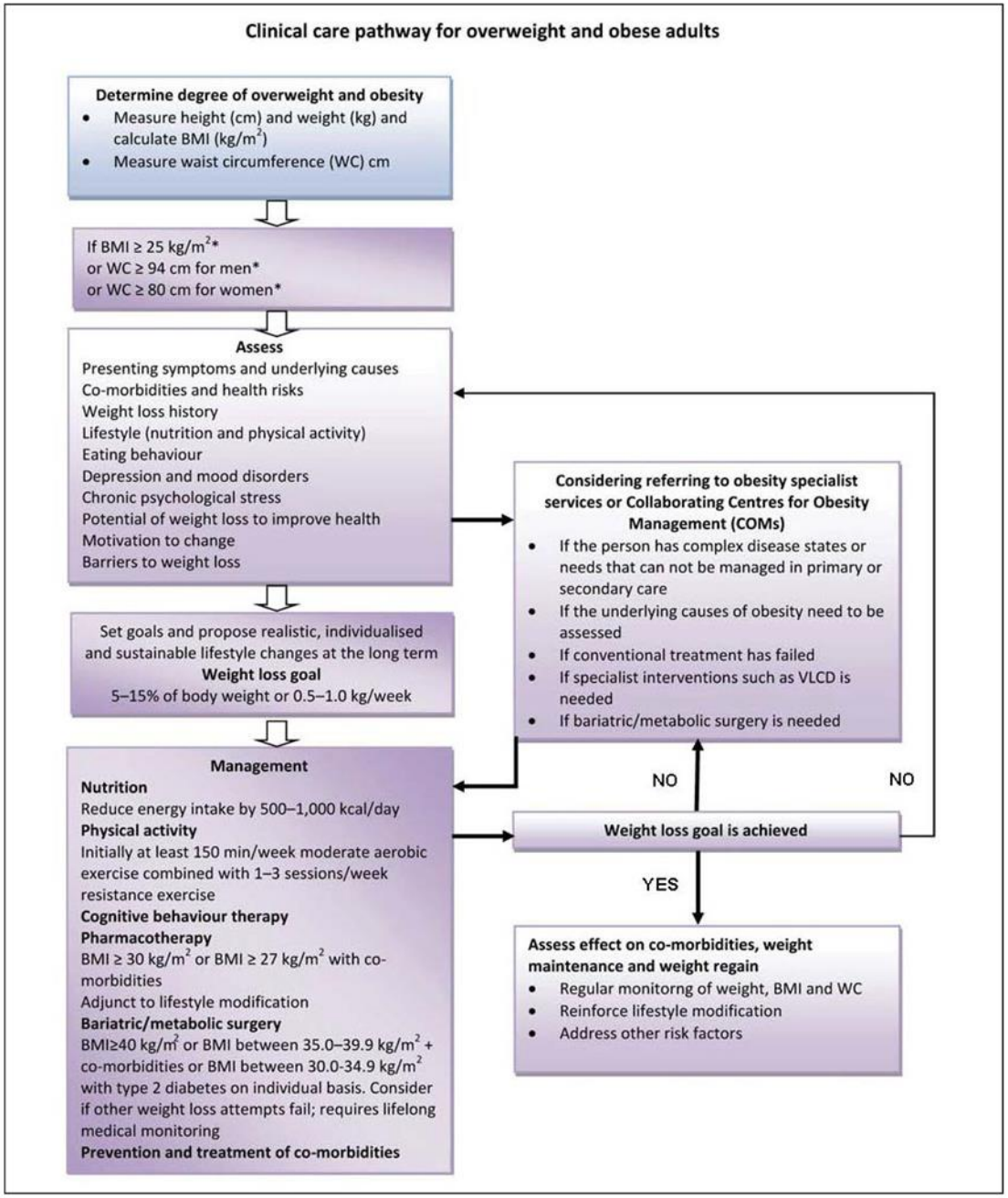
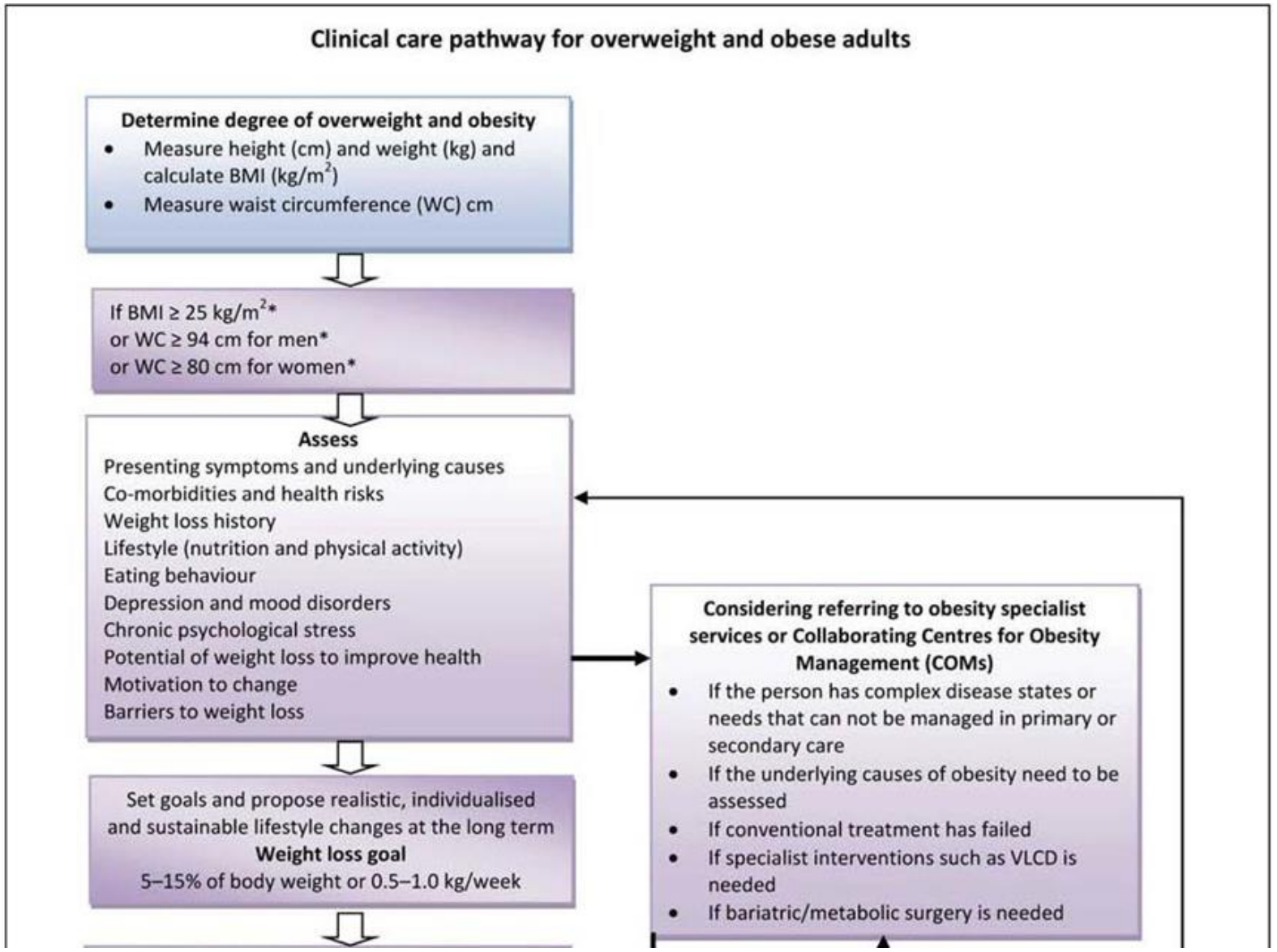



**Fig. 2.** Algorithm for the assessment and stepwise management of overweight and obese adults. *BMI and WC cut-off points are different for some ethnic groups (see text).


Clinical care pathway for overweight and obese adults
Determine degree of overweight and obesity
• Measure height (cm) and weight (kg) and calculate BMI (kg/m2)
• Measure waist circumference (WC) cm
If BMI ≥ 25 kg/m2*
or WC ≥ 94 cm for men*
or WC ≥ 80 cm for women*
Assess
Presenting symptoms and underlying causes
Co-morbidities and health risks
Weight loss history
Lifestyle (nutrition and physical activity)
Eating behaviour
Depression and mood disorders
Chronic psychological stress
Potential of weight loss to improve health
Motivation to change
Barriers to weight loss
Set goals and propose realistic, individualised and sustainable lifestyle changes at the long term
Weight loss goal
5–15% of body weight or 0.5–1.0 kg/week
Considering referring to obesity specialist services or Collaborating Centres for Obesity Management (COMs)
• If the person has complex disease states or needs that can not be managed in primary or secondary care
• If the underlying causes of obesity need to be assessed
• If conventional treatment has failed
• If specialist interventions such as VLCD is needed
• If bariatric/metabolic surgery is needed

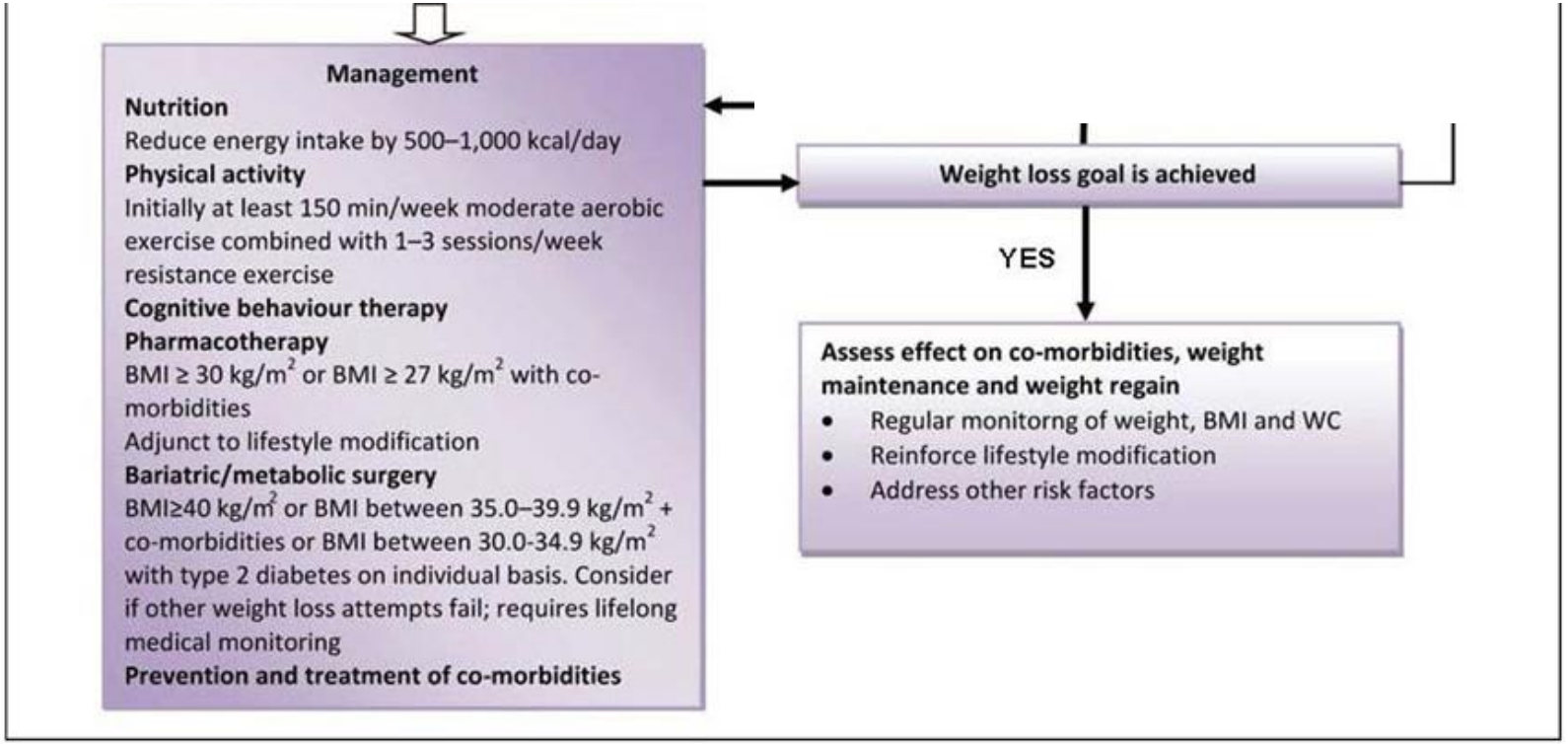



**Fig. 2.** Algorithm for the assessment and stepwise management of overweight and obese adults. *BMI and WC cut-off points are different for some ethnic groups (see text).

# Ευχαριστώ πολύ για την προσοχή σας