


A comprehensive diagnostic approach to detect underlying causes of obesity in adults

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Summary

Obesity is a worldwide growing problem. When confronted with obesity, many health care providers focus on direct treatment of the consequences of adiposity. We plead for adequate diagnostics first, followed by an individualized treatment. We provide experience-based and evidence-based practical recommendations (illustrated by clinical examples), to detect potential underlying diseases and contributing factors. Adult patients consulting a doctor for weight gain or obesity should first be clinically assessed for underlying diseases, such as monogenetic or syndromic obesity, hypothyroidism, (cyclic) Cushing syndrome, polycystic ovarian syndrome (PCOS), hypogonadism, growth hormone deficiency, and hypothalamic obesity. The most important alarm symptoms for genetic obesity are early onset obesity, dysmorphic features/congenital malformations with or without intellectual deficit, behavioral problems, hyperphagia, and/or striking family history. Importantly, also common contributing factors to weight gain should be investigated, including medication (mainly psychiatric drugs, (local) corticosteroids, insulin, and specific β -adrenergic receptor blockers), sleeping habits and quality, crash diets and yoyo-effect, smoking cessation, and alcoholism. Other associated conditions include mental factors such as chronic stress or binge-eating disorder and depression. Identifying and optimizing the underlying diseases, contributing factors, and other associated conditions may not only result in more effective and personalized treatment but could also reduce the social stigma for patients with obesity.

KEYWORDS

Diagnostics, genetic obesity, hormones, medication, secondary causes

1 | INTRODUCTION

Obesity (body mass index [BMI] ≥ 30.0 kg/m²) is a chronic disease¹ that is a worldwide growing problem.² In 2015, over 603 million adults had obesity, and 4.0 million deaths were yearly accountable to a high BMI.³ When facing a patient with obesity, most clinicians focus on

treating the associated comorbidities and/or simply recommend weight loss. The diagnostic phase, which is typically used when assessing other clinical problems, is often overlooked in obesity. Whereas in other clinical problems, such as hypertension, clinicians are alert to consider a wide variety of secondary causes.⁴ For obesity, a diagnostic phase to detect underlying diseases or other factors that

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hinder weight loss is recommended by some⁵ but not all clinical practice guidelines. The European guideline recommends a diagnostic phase; however, specific examples of diseases or factors that may contribute to obesity are lacking.⁵ Others do not mention the necessity to identify underlying contributing factors.^{6,7} This paper aims to help clinicians to deepen the diagnostic phase with a comprehensive overview of possible contributors to weight gain for an individual.

Currently, on a societal level, it is widely believed that obesity is simply the consequence of overconsuming unhealthy foods and lack of exercise. However, on an individual level, there are many other contributing factors or underlying diseases, which are often not identified and may prove significantly associated with weight gain and barriers to weight loss. We suggest that clinicians should first detect and address underlying diseases and contributing factors, before starting obesity treatment. Besides lifestyle-related factors, other factors include hormonal and genetic abnormalities, mental and socio-cultural factors, and side effects of medications. Identifying these underlying factors may lead to more personalized treatment strategies, can also increase patients' understanding of their obesity, and reduce their social stigma.

1.1 | Clinical presentation

1.1.1 | Clinical Case A

A 66-year-old man, known with type 2 diabetes mellitus and eczema, was referred because of obesity. Since the last decade, he became increasingly heavier, with a rapid weight gain of 30 kg in the last year. He noticed red striae under his armpits and suffered from mood swings and decreased libido. A detailed past medication list showed several episodes of using clobetasol cream, triamcinolone, desoximetasol, and one short course of prednisone in the last 8 years. Moreover, in the last year, he had used large amounts of mometasol cream on his whole back and arms because of severe eczema. We saw a man weighing 168 kg (BMI 59.5 kg/m²) with pronounced abdominal obesity with purple striae, hematomas, and severe non-pitting ankle edema. Laboratory results are shown in Table 1. We concluded that there was severe obesity, with multiple contributing causes: an exogenous Cushing syndrome due to the use of large amounts of dermal corticosteroids, late-onset hypogonadism (which can be a consequence of obesity but also poses an opportunity for treatment⁸), and non-pitting lymphedema. The subclinical hypothyroidism was considered a consequence of obesity.^{9,10} A multidisciplinary strategy comprised gradual tapering

TABLE 1 Laboratory results patient 1

	Value	Reference Value
TSH	6.030 mU/L	0.4-4.3 mU/L
FT4	15.4 pmol/L	11-25 pmol/L
Urinary cortisol first measurement	39 nmol/24 h	5-133 nmol/24 h
Urinary cortisol second measurement	48 nmol/24 h	
Testosterone	5.05 nmol/L	10-30 nmol/L
SHBG	40 nmol/L	10-70 nmol/L
Calculated free testosterone	0.0839 nmol/L	>220 pmol/L ^a

^aIn the presence of symptoms.^{9,3}

of topical corticosteroids and lymphedema compression therapy by his dermatologist, testosterone supplementation, and an exercise program. After 2 years, he had lost 35 kg, his clinical condition improved, and testosterone and TSH levels had normalized. This case shows the importance of a combined approach taking into account all factors that contribute to obesity and counteract weight loss.

1.1.2 | Clinical Case B

A 48-year-old woman was referred because of severe obesity with type 2 diabetes, with no long-term effect of previous diets. Her overweight started around her first year of life, and later she had been treated in a mental health institute for her eating behavior. Since she was a baby, she always had an increased appetite. Several family members, mostly from her mother's side, had obesity. Interestingly, she reported that even during the Dutch extreme famine of 1945, her maternal grandfather had obesity. We saw a woman with red hair, weighing 117 kg (BMI 41.5 kg/m²). No other physical abnormalities were found.

We suspected a monogenetic cause of her obesity, because of the young age of onset, hyperphagia, red hair, and family history. Diagnostic screening of 52 obesity associated genes revealed two mutations in the melanocortin 4 receptor gene (*MC4R*) gene, of whom one is known to be pathogenic (c.[105C > A], p.[Tyr35*]), whereas the other is a variant of unknown significance (VUS). Her daughter, who had obesity since the age of three, had inherited both *MC4R* mutations. Her father, who developed obesity at an older age, had no *MC4R* mutations.

In patients with pathogenic *MC4R* mutations long-term weight maintenance is difficult to achieve.¹¹ The response to bariatric surgery seems to be positive; however, long-term results are still being investigated.¹² Additionally, new pharmacological treatment options are arising that target *MC4R*.¹³ Recently, effective pharmacological treatment for another type of monogenetic obesity, caused by pathogenic *POMC* gene mutations, has become available.¹⁴ It is therefore relevant to identify underlying monogenic causes of obesity, which also may reduce the patient's obesity stigma.

2 | METHODS

Due to the comprehensive nature of the subject, we selected subtopics based on clinical experience. For each subtopic, we searched databases such as the Cochrane library (February 2018) and MEDLINE library for relevant articles. We preferably selected publications of the last 5 years. Older publications were included if commonly referenced, highly regarded, or relevant to the topic. Reference lists of relevant identified articles were also searched.

3 | ASSESSMENT OF OBESITY—CLINICAL HISTORY

Weight gain occurs when the energy homeostasis is chronically "out of balance." This occurs either due to changes in total energy intake or in total energy expenditure, the latter being the sum of a person's resting energy expenditure plus a person's thermogenesis during activities.¹⁵ A clinical consult addressing obesity should therefore focus on what

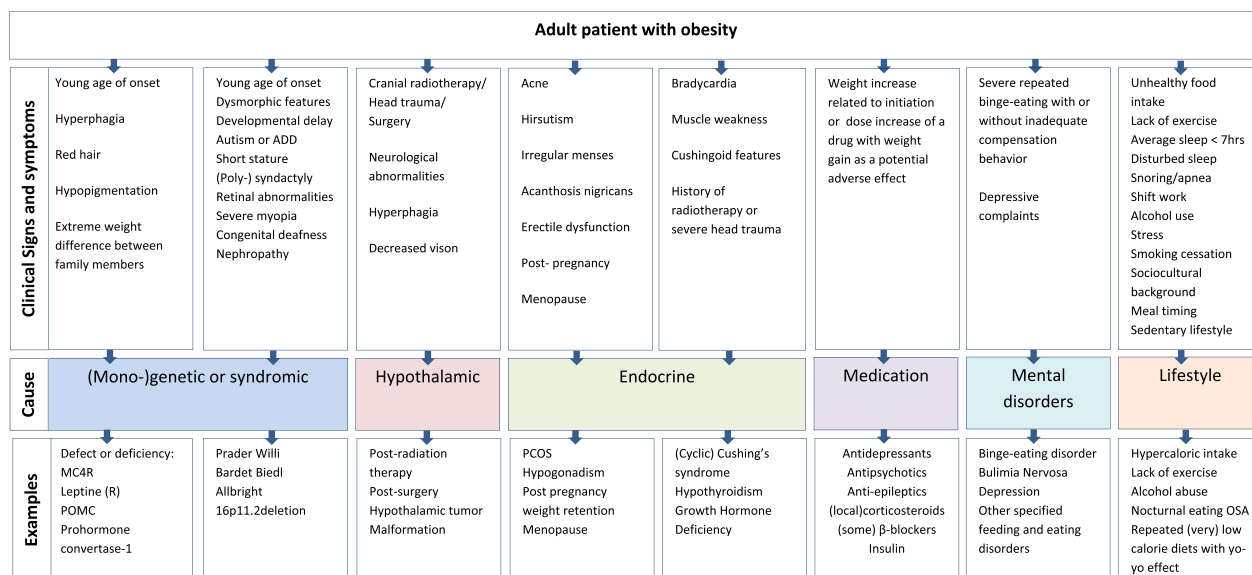


FIGURE 1 Recognizing underlying causes of obesity in adults. ADD, attention deficit disorder; PCOS, polycystic ovarian syndrome; MC4R, melanocortin 4 receptor; POMC, proopiomelanocortin; PPI, proton pump inhibitors; OC, oral contraceptives; OSA, obstructive sleep apnea; OSFED, other specified feeding and eating disorders [Colour figure can be viewed at wileyonlinelibrary.com]

causes this excess and what maintains it. Examples to guide the clinical approach of identifying underlying causes and contributing factors, roughly grouped in lifestyle-related factors, medication, (neuro-)endocrine factors, genetic factors, and mental factors, are shown in Figure 1.

3.1 | Lifestyle-related factors involved in weight gain

Globally, the obesity pandemic is largely the consequence of increased energy consumption.¹⁶ However, in individual patients, there may be several reasons why a person has an increased caloric intake or decreased energy expenditure, which may even be modifiable. Often, there is a complex interplay of multiple social, psychological, and biological factors altogether resulting in excess energy intake.

For example, in some cultures, exorbitant amounts of food are associated with hospitality. Also, some patients may be unable to prioritize weight management in light of financial problems, relationship issues, or other circumstances requesting their attention. On an individual level, patients may overeat because they experience increased hunger or appetite. For example, this occurs in patients who have been on very low calorie-diets without exercise or behavioral therapy, often referred to as the “yo-yo-effect.” The weight regain that follows may be associated with altered “hunger hormones” (eg, ghrelin) and satiety hormones’ (eg, leptin and peptide YY [PYY]) that can remain altered even a year after ending the diet.¹⁷ Some individuals may overeat as a coping strategy for other, psychological factors such as emotions.¹⁸ Next, a decreased quantity or quality of sleep can induce weight gain.¹⁹ This may lead to a desire for high caloric food,²⁰ imbalance of appetite hormones (eg, ghrelin and leptin),²¹ as well as increased hypothalamic–pituitary–adrenal-axis reactivity²² yielding higher cortisol levels which may also enhance obesity.^{23,24} Circadian misalignment, such as in shift work, is associated with a decreased daily energy expenditure and increased caloric intake.^{25,26} As for sleep quality, obstructive sleep apnea (OSA)

is especially notable as it seems to have a bidirectional relation with obesity. OSA occurs more frequently in obesity, but the sleep disturbances belonging to it may again promote weight gain enhancing behavioral, metabolic, and/or hormonal.²⁷ It is not fully clear whether OSA treatment has an effect on body weight.^{28–30}

When there is no notable change in energy intake, the problem may be altered energy expenditure, which can be either the result of decreased activity or decreased resting metabolism.

Recently, several possible influencers of resting metabolism have been identified. For example, weight loss itself can already affect the total energy expenditure, as this decreases more than is expected from the change in body composition only. This may be due to adaptive thermogenesis, that may hinder further weight loss.³¹ Also, an important contributor to a decreased metabolism is a sedentary lifestyle.³² Interesting associations have been found for options to interrupt the continuous sitting, eg, by intermittent standing, moving, or fidgeting, also called nonexercise activity thermogenesis (NEAT).³³ Another possible determinant and future target regarding resting energy expenditure is the activity of brown adipose tissue (BAT).³⁴ BAT, which was found to be also present in adult humans and basically burns calories into heat, can be stimulated by physical activity or cold exposure. This has been shown to result in a significant decrease in fat mass, with maintenance of lean mass.³⁵ Nicotine can also stimulate BAT,³⁶ possibly explaining the subtle weight gain that patients who quit smoking experience (together with increased appetite and psychological factors). Importantly, this modest weight gain does usually not outweigh the beneficial effects of smoking cessation. Education and guidance may limit the weight gain when patients quit smoking.³⁷

3.2 | Medication

Medication can affect the energy homeostasis mainly by promoting hunger or by decreasing resting metabolism. In our clinical experience,

we find it helpful to taper or stop medication with weight gaining effects³⁸ prior to a weight-reducing intervention, as this may enhance the weight reduction. An overview of medication that may induce weight gain is provided in Table 2.

Drugs that are frequently used in psychiatry, such as specific selective serotonin reuptake inhibitors or antipsychotic agents, are well-known to promote weight gain. The strongest weight change is seen in amitriptyline, mirtazapine, and paroxetine.³⁹ As for antipsychotic drugs, olanzapine and clozapine induce the highest weight gain.⁴⁰ Also, several anti-epileptic drugs should be noted. Although most prescribers are aware of these side effects, in patients with severe obesity, a medication switch to less obesogenic drugs should be considered if possible.³⁸

It is well-known that systemic corticosteroids can cause weight gain. For the treatment of rheumatoid arthritis, for example, it was found that low-dose prednisone is associated with a weight increase of 4% to 8%.⁴¹ Corticosteroids can be administered in many forms. Often overlooked are the local forms, which we recently reported to be associated with increased BMI and waist circumference when compared with non-corticosteroid users in a large population-based cohort.⁴² Local corticosteroids may also have systemic effects resulting in weight gain, in a similar matter as local corticosteroids having other systemic effects, such as adrenal insufficiency,⁴³ which needs further research. A weight gaining systemic effect of local corticosteroids is

likely in patients using large quantities on a frequent basis, particularly if they show additional Cushingoid features, such as abdominal obesity, peripheral atrophy, plethora, and purple striae, as demonstrated by clinical case A.

The initiation of insulin therapy or sulphonylurea derivatives in patients with type 2 diabetes can be accompanied by weight gain.³⁸ Blood-glucose lowering drugs without weight inducing effects, such as glucagon-like peptide-1 analogues, metformin, and sodium-glucose cotransporter-2 inhibitors,³⁸ can be good alternatives if weight loss is desired.

Other drugs that have been shown to induce obesity are non-selective β -adrenergic receptor blockers.^{38,44} If prescribed for hypertension, one could consider replacing them with other antihypertensive agents such as ACE-inhibitors or angiotensin receptor blockers.⁴⁴ The weight increase is more profound in metoprolol than in carvedilol. Interestingly, the weight increase was worse in subjects who already had severe obesity.^{45,46} In HIV patients, the start of protease inhibitors has also been associated with weight gain and increased deposition of visceral adipose tissue.³⁸ Another association has been found in users of H1 anti-histamines, who were more likely to be overweight than non-users.⁴⁷

Regarding hormonal contraceptives, there is no large effect on weight, although available evidence is insufficient.⁴⁸ However, we cannot rule out that some women experience excessive weight gain due to individual differences.

TABLE 2 Drugs that may induce weight gain

Drug Class	Examples of Specific Agents	Estimated Weight Gaining-Effect per Agent	References
Antidepressants	Citalopram	26% higher chance of an episode of 5% weight gain Mean weight gain during >4 months of treatment 1.69 kg	38,39,94
	Mirtazapine	50% higher chance of an episode of 5% weight gain Mean weight gain 2.59 kg during >4 months treatment	
	Amitriptyline	17% higher chance of an episode of 5% weight gain Mean weight gain 2.24 kg during >4 months treatment	
	Paroxetine	Mean weight gain after >4 months of treatment 2.73 kg 5% higher chance of an episode of 5% weight gain	
Antipsychotics	Olanzapine	3.8 kg to 16.2 kg in youth	38,40,95,96
	Lithium	29% increases $\geq 7\%$ in body weight	
	Clozapine	4-12 kg weight increase	
	Quetiapine	0.9-9.5 kg in youth	
	Risperidon	2.3-6.1 kg in youth	
	Ziprasidone	25% increases $\geq 7\%$ in body weight 1.9-7.2 kg in youth 18% increases $\geq 7\%$ in body weight 9.8% increases $\geq 7\%$ in body weight	
Anti-epileptics	Carbamazepine	7-15 kg weight gain	38,96,97
	Gabapentin	57% gains $\geq 5\%$ of baseline weight	
	Valproic acid	47% gains >10% of baseline weight, 24% gains 5-10% weight 0.5-6 kg weight gain on average	
Anti-diabetics	Insulin SU derivatives	1.78-6 kg weight gain in the first year 2-4 kg over 1 year of treatment	96,98,99
Anti-hypertensives	α -Adrenergic blockers	0.4-2.0 kg	100
	B-Adrenergic blockers	1.2-kg mean weight difference when compared with other antihypertensives	44
Corticosteroids	Systemic corticosteroids	Depending on doses, indication, and large individual variation Rheumatoid arthritis: weight increase 4% to 8% 70% of patients report weight gain	38,101
	Local corticosteroids	Unknown association of higher BMI in women	42
Others	Proton pump inhibitors	Possible association with weight gain	50,102,103
	Protease inhibitors	Lipodystrophy Average weight gain 8kg in a study of 10 patients	38,104,105
	Anti-histamines	Association with higher weight and waist circumference	38,47,103

Also, for several other agents, such as proton pump inhibitors and alpha blockers, weight gaining effects have been reported.^{49,50}

3.3 | Genetic causes of obesity

An overview of (mono)genetic obesity disorders is summarized in Table 3. The genetics of obesity are complex. In the general population, the fat-mass and obesity associated gene (*FTO*) has shown the strongest association to obesity.⁵¹ Besides these polygenic associations that have not been fully elucidated as yet, only a small percentage of the patients with obesity can be classified as having a monogenic or syndromic obesity disorder.⁵²

Screening for these conditions is not routinely done in clinical practice. As new therapies are arising that target specific types of obesity, we here plead for screening for genetic obesity in a subgroup of patients who have a high clinical suspicion for these types of genetic obesity. A recent study found a confirmed diagnosis of genetic obesity in 3.9% of patients who were clinically suspected of genetic obesity.⁵³ Indications for genetic screening include an early age of onset, below 5 years of age,^{54,55} (or in adult populations a prepubertal onset), a family history with striking weight differences between family members (which may indicate monogenic obesity), and severe hyperphagia (which can be seen in monogenic obesity-with and without intellectual deficit). Furthermore, characteristics such as intellectual deficit or developmental delay, congenital malformations, visual impairment and/or deafness, and abnormal growth parameters (head circumference and height) may be indicative for syndromic obesity. Examples of syndromic obesity are Prader-Willi syndrome (characterized by hypotonia and feeding problems in infancy, and later in life hyperphagia and obesity, short stature, intellectual deficit and hypogonadotropic hypogonadism⁵⁶), Bardet-Biedl syndrome (intellectual deficit, retinal dystrophy or pigmentary retinopathy, polydactyly, hypogonadism, and nephropathy), and the 16p11.2 deletion syndrome (intellectual deficit, speech development problems, autism, macrocephaly, and epilepsy). There is a large variability of these symptoms among affected patients.⁵⁷ Mild to moderate intellectual disability is also seen in patients with pseudohypoparathyroidism type 1 (PHP1a), caused by maternally inherited heterozygous mutations in *GNAS*. PHP1a is associated with the clinical phenotype of Albright's hereditary osteodystrophy (AHO), which encompasses short stature, round facies, and skeletal abnormalities⁵⁸

Monogenic (non-syndromic) causes of obesity are characterized by a young age of onset and hyperphagia,^{12,54} with usually no intellectual deficit. Additionally, other clinical signs of monogenic obesity may differ depending on the affected gene. These include red or ruddy hair, pale skin, and adrenocorticotrophic hormone (ACTH) deficiency (pro-opiomelanocortin [*POMC*] gene defects), central hypothyroidism, hypogonadotropic hypogonadism and frequent infections (leptin deficiency, caused by autosomal recessive *LEP* gene mutations), increased linear growth and increased lean mass, severe hyperinsulinemia, and mild central hypothyroidism (caused by autosomal dominant or recessive *MC4R* mutations) and neonatal diarrhea, recurrent hypoglycemia,

and global endocrine dysfunction (caused by prohormone convertase-1 [*PCSK1*] mutations).^{54,59}

3.4 | Neuroendocrine causes

3.4.1 | Hormonal causes

A relatively sudden increase in weight may suggest a neuroendocrine cause. We screen for hypothyroidism, as this is associated with a modest weight gain. This is especially recommended if patients present with other symptoms such as dry skin, feeling cold, etc. However, the weight gain in hypothyroidism seems mostly due to additional edema.⁶⁰ Also, obesity is often associated with a slightly increased TSH that is most often the result of excess adipose tissue rather than the cause of obesity. This can be explained by the presence of peripheral thyroid resistance and also by increased levels of leptin, stimulating TRH and subsequently TSH.^{9,10} Weight loss usually reverses this form of hyperthyrotropinemia.⁶¹

To identify Cushing syndrome (CS), specific signs of CS including easy bruising, facial plethora, proximal myopathy, and recent purple striae⁶² should be considered, as most patients with obesity will have the more non-specific CS signs such as central obesity, fatigue, hypertension, and decreased libido. Due to the large number of corticosteroid users,^{63,64} iatrogenic CS should also be considered.

Another common endocrine condition associated with obesity is the polycystic ovarian syndrome (PCOS), a constellation of hyperandrogenism, oligoovulation or anovulation, and polycystic ovaries. Male hypogonadism has a complex, bidirectional relation with obesity. Testosterone therapy in patients with obesity or diabetes with evident testosterone deficiency causes improvement of body composition and components of the metabolic syndrome.^{8,65} On the other hand, obesity induces hypogonadotropic hypogonadism, and a healthy diet and physical activity can increase bound and unbound testosterone levels and completely normalize the hypogonadism.⁶⁶

Women may report weight gain after pregnancy⁶⁷ or menopause.⁶⁸ The average weight change from preconception to the first year postpartum is referred to as "postpartum weight retention." This is on average relatively small (0.5 to 1.5 kg). However, there is a large variability, as 13% to 20% of women are 5 kg or more above their preconception weight by 1-year postpartum.⁶⁹ Although menopause is frequently reported as a contributing factor by women, and experimental evidence suggests estrogen depletion is associated with abdominal fat accumulation, epidemiological evidence in humans indicates that the steady weight gain of 0.5 kg annually is due to age rather than the menopause itself.⁷⁰

In specific patients with a history of pituitary disease, surgery or irradiation in these areas, severe head trauma, or evidence of other pituitary hormone deficiencies,⁷¹ endocrine evaluation is indicated, including growth hormone (GH) deficiency as it may contribute to obesity and treatment options are available.^{72,73}

3.4.2 | Hypothalamic disorders

Hypothalamic obesity, typically accompanied by hyperphagia, can occur after various insults leading to damage of the hypothalamic

TABLE 3 Examples of relevant genetic obesity disorders

Syndrome	Syndrome	Clinical Symptoms ⁵⁵	Dysmorphic Features	Estimated Prevalence ¹⁰⁶	Reference
Syndromic obesity with developmental delay	Prader-Willi syndrome	Developmental delay and intellectual disability, (prenatal) hypotonia, feeding difficulties Failure to thrive, hyperphagia, neurologic, and cognitive disturbances Hypogonadism	Almond-shaped eyes, strabismus, thin upper lip, downturned corners of the mouth Short stature Genital hypoplasia	1/15,000–1/30,000	Cassidy and Driscoll ¹⁰⁷
	Bardet-Biedl syndrome	Developmental delay Intellectual disability Retinal dystrophy Renal dysfunction Hypogonadism Cardiac abnormalities	Post-axial polydactyly Dental crowding High-arched palate Hypodontia Malocclusion Enamel hypoplasia Micropenis	1/160,000 (northern European) 1/13,500 (specific populations)	Forsythe et al ¹⁰⁸
	16p11.2 deletion syndrome	Developmental delay Mild intellectual disability Autism spectrum disorders	Variable presentation Macrocephaly	3 in 10,000	Dell'edera et al ¹⁰⁹
	Albright hereditary osteodystrophy	Short stature, subcutaneous ossifications Maternally inherited GNAS mutations: Hormone resistance (eg, parathyroid hormone)sometimes developmental delay and intellectual disability	Round facies Brachydactyly fourth/fifth metacarpals	0.79 in 100,000	Haldeman-Englert et al ¹⁵⁸
Genetic obesity without developmental delay	MC4R deficiency	Hyperphagia Accelerated linear growth Disproportionate hyperinsulinemia Low/normal blood pressure	Not apparent	2%–5% of subjects with extreme pediatric obesity	Martinelli et al ^{110,111}
	Leptin (receptor) deficiency	Extreme hyperphagia Frequent infections Hypogonadotropic hypogonadism Mild hypothyroidism	Not apparent	Leptin receptor deficiency: 2%–3% in severely obese subjects Leptin deficiency: Fewer than 100 patients worldwide Unknown	Farooqi et al ¹¹² Krude et al ¹¹³
	POMC deficiency	Hyperphagia, ACTH deficiency, pale skin, and red hair	Not apparent	Unknown	RamosMolina et al ¹¹⁴
	PCSK1 deficiency	Adrenal, gonadotropic, somatotrophic, and thyrotropic insufficiency severe malabsorptive neonatal diarrhea central diabetes insipidus	Not apparent	Unknown	

region. It is seen in patients with abnormalities in the hypothalamic region, eg, craniopharyngeoma (especially following surgery), inflammatory processes such as sarcoidosis and tuberculosis, vascular damage, head trauma, or after cranial radiotherapy, but also some of the genetic mutations that were previously mentioned can be considered hypothalamic obesity.⁷⁴ In severe cases, it can lead to multiple endocrine symptoms such as impaired reproductive function with amenorrhea or impotence, diabetes insipidus, and thyroid or adrenal insufficiency (obesity that results in hormonal abnormalities is discussed in the previous paragraph). Also, neurological symptoms can be seen, including convulsions, hypothermia or hyperthermia, or somnolence.⁷⁵

3.5 | Mental factors

In patients with obesity, attention to mental factors should be paid. Numerous studies showed that depression is linked to obesity, in a bidirectional manner.⁷⁶⁻⁷⁸ This is not surprising, as changes in food intake are considered symptoms of depression.⁷⁹ The associations are stronger for patients with a symptom profile that is often labeled as "atypical."⁷⁸ Also, anxiety disorders are cross-sectionally associated with obesity.⁸⁰

Binge-eating disorder⁸¹ is characterized by recurrent binge-eating episodes where more food is consumed than is normal for most people and where feelings of lack of control and distress play a role. Importantly, binge-eating can also be a sign of hyperphagia and may thus be a diagnostic clue for either genetic or hypothalamic obesity, as demonstrated in Clinical Case B.

Evidence is mounting that stress leads to more appetite (in comfort food), induces abdominal obesity,²⁴ and may counteract the effects of a healthy diet.⁸²⁻⁸⁴ Additionally, the weight stigma that individuals with obesity often suffer from may also lead to extra weight gain.⁸⁵ It is therefore conceivable that a non-stigmatizing attitude, as well as stress reduction, is beneficial when treating obesity.

Furthermore, events during early life have been identified as risk factors for obesity. Adolescents with a history of childhood sexual abuse have a higher risk of obesity (in men) or disordered eating (in women)⁸⁶

4 | LABORATORY DIAGNOSTICS AND FURTHER EVALUATION

General laboratory evaluation can be considered in all patients with obesity, including fasting glucose (and insulin in case of acanthosis nigricans), lipids, liver enzymes, and thyroid screening (TSH, and FT4 on indication).⁵ In case of clinical clues, this can be extended by testing gonadal function and/or Cushing diagnostics. Diagnostics for (mono) genetic obesity should be reserved for individuals with a high clinical suspicion (eg, early onset obesity, with or without intellectual deficit, dysmorphic features/congenital malformations, behavioral problems, hyperphagia, and/or striking family history, Figure 1⁵³).

5 | SOCIETY-RELATED OBESOGENIC FACTORS AND FUTURE TARGETS FOR PUBLIC HEALTH INTERVENTIONS

The assessment of obesity can be complicated further by considering disruptors of energy homeostasis on a societal level. These currently have limited value in clinical practice but are interesting possible targets for public health interventions. These include endocrine disruptors, such as chemicals in pesticides/herbicides, industrial and household products, plastics, detergents, flame retardants, and ingredients in personal care products, that can affect the endocrine system and interfere with various metabolic processes.^{87,88} In addition, both low birthweight and high birthweight in boys and high birth weight in girls have been associated to obesity,⁸⁹ indicating that intra-uterine factors may be important to weight. Also, early childhood infections have recently been shown to contribute to obesity.⁹⁰ In this context, an interesting emerging field of research is "infectobesity," which is the study of microbial agents as a cause of obesity. For example, intriguing associations between obesity and the adenovirus-36 have been found.⁹¹ The changing gut microbiome seems more and more important in the pathogenesis of obesity.⁹²

6 | CONCLUSIONS

Obesity is a complex clinical problem where adequate diagnostics are often overlooked. We plead for a comprehensive approach of obesity, including adequate diagnostics prior to treatment. This includes, besides evaluation of lifestyle factors, a detailed past and present medical history, medication use, a global outline of the sociocultural environment, and a thorough physical examination. In case of abnormalities suggestive of an underlying disease, we recommend specific testing for these causes, as some conditions may be treatable. Furthermore, modifiable contributing factors, such as the use of weight gaining medication, lack of sleep, chronic stress etc. may be optimized before starting a lifestyle intervention or bariatric surgery. This may lead to more effective treatment for individuals with obesity. Additionally, knowing the cause of the obesity can help to reduce the social stigma that many individuals with obesity suffer from.

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