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RESEARCH

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# Exploring obesity-related endocrine disorders beyond diabetes: a narrative review

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## Abstract

**Background** While insulin resistance and diabetes shine as the central stars in the constellation of obesity-related conditions, other common endocrine diseases are also closely associated with obesity and high body mass index.

**Main body** This review aims to illuminate the hormonal imbalances associated with obesity, beyond diabetes. It covers the prevalence, clinical presentation, screening, diagnosis, and treatment of some of these conditions.

**Conclusion** In obese patients, physicians must pay attention to hormonal disorders that may be associated with obesity.

**Keywords** Cushing syndrome, Adrenocorticotropic hormone, Diabetes mellitus

## Back ground

Obesity is associated with many metabolic and endocrinal disorders. Prediabetes and diabetes are the most frequent endocrine disorders encountered by physicians and endocrinologists. Other common endocrine disorders seen in endocrine clinics are hypothyroidism, Cushing syndrome androgen excess in women, and hypogonadism in men. A bidirectional relationship between obesity and endocrine disorders is suggested so that obesity may be the etiologic factor or the consequence of some of these disorders [1].

## Main text

### Hypothyroidism and obesity

Weight gain in hypothyroidism is attributed to many factors as increased fat accumulation as a result of decreased energy expenditure and physical activity in addition to water retention and glycosaminoglycans accumulation in different tissues [2, 3]. Contrary to the popular opinion, hypothyroidism associated weight gain is only of limited extent [3]. This was deduced from studies that found only limited weight reduction after thyroxine replacement in patients with overt hypothyroidism, usually less than 10% [4]. This weight reduction is primarily related to excess water excretion [5]. Therefore, excess weight gain is not directly caused by hypothyroidism.

Many studies found a positive correlation between TSH and body mass index [6, 7] and other studies described presence of small variations of THs, even in the normal range which may have a role in weight gain and [8] and impaired weight loss induced by diet [8] or after metabolic surgery [9]. On the contrary, other studies assumed that the THs changes associated with obesity are the result of weight gain rather than the cause. This opinion was supported by improving thyroid hormones abnormalities in obese persons after weight reduction after diets to lose weight [10] or bariatric procedures [9]. So it was assumed that TSH increase in obese individuals (in the absence of autoimmune thyroid disease) does not appear to be the primary etiologic factor for weight gain, but more likely a result of excess weight [11] and should be differentiated from autoimmune subclinical hypothyroidism (HT).

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### *The relationship between obesity and hypothyroidism (HT)*

The incidence of thyroid dysfunction is rising globally, affecting 30–40% of patients in endocrine clinics. Undiagnosed hypothyroidism affects around 5% of the general population. The prevalence of subclinical and overt HT in obese people was higher than general population 14.6% and 14.0% respectively. Positive anti-TPO antibody was found in 85% of hypothyroid patients with T2 diabetes and higher BMI [12]. The highest prevalence of hypothyroidism is in the USA, which is approximately 11.7%. In Europe, rates of overt hypothyroidism vary from 0.2% to 5.3%. Meanwhile, in Iran, subclinical and overt hypothyroidism prevalence stands at 7% and 0.4%, respectively [1]. In Egypt, subclinical hypothyroidism affected 44.4% of the population, while overt hypothyroidism (overt HT) was observed in 20.6%. Among pregnant women, approximately 8% had subclinical HT, and among postmenopausal women, 12% had subclinical HT, and 8% had overt HT [13].

### *Initial screening test for hypothyroidism in obese*

No study directly assessed the benefit of screening for hypothyroidism in obesity [14]. However, because HT is rather prevalent and has a potential to potentiate weight gain and worsen comorbidities in obesity, given these factors, a simple assessment of thyroid function is recommended for obese patients. TSH is the recommended screening test for hypothyroidism [15]. Measuring free T4 (FT4) is asked in individuals with high TSH levels or if disorders other than primary HT are suspected as thyroid hormones resistance or anterior pituitary insufficiency [16]. Secondary hypothyroidism (HT) represents no more than 1% of HT in which TSH levels are low-to-normal and free T4 is low. Neither total or free T3 are beneficial in hypothyroidism screening. T3 remains usually in the normal level due to the stimulatory effect of the elevated TSH on residual functioning thyroid tissue. In addition to the influence of other non-thyroidal illnesses on FT3 levels as nutritional status and inflammatory conditions, which result in reduced conversion of T4 to T3 (referred to as "euthyroid sick syndrome"), interpretation of FT3 in obesity is also complex, as higher FT3 levels have been observed in obese individuals compared to lean people, primarily due to differences in nutritional status [17].

### *Is there specific reference ranges for thyroid for TSH in obese?*

TSH levels are usually higher in obese individuals than in normal-weight individuals, showing a positive correlation with BMI. However, the relationship between FT3 and FT4 is not consistent. An inverse relation between body mass index and FT4, and a positive correlation with FT3 with a decreased FT4/FT3 ratio has been observed [17]. The elevation of TSH may be related to low thyroid hormone levels, which may be related to plasma volume increase in one hand and an enhance thyroid hormone clearance in obesity. This leads to compensatory activation of the pituitary–thyroid axis. Additionally, elevated leptin and insulin levels have been suggested as potential mechanisms underlying alterations in thyroid hormone levels in individuals with obesity [3]. However, until now, there is no sufficient evidence whether to use a different reference range in obesity would be efficient to identify individuals who need treatment or not.

### *The relationship between obesity and thyroid autoimmunity*

Chronic autoimmune thyroiditis, often caused by thyroid antibodies like antithyroid peroxidase (anti-TPO), is a common reason for hypothyroidism. Elevated anti-TPO levels predict progression from subclinical to overt hypothyroidism [3]. However, testing for thyroglobulin antibodies in obese individuals lacks supporting evidence [18].

*Obesity and thyroid morphology* Obese individuals exhibit a greater incidence of thyroid morphological abnormalities on ultrasonography compared to lean individuals. These abnormalities include increased thyroid volume, hypoechogenicity, and thyroid nodules [19]. The underlying factors contributing to these changes involve heightened TSH (thyroid-stimulating hormone) stimulation or the production of inflammatory mediators in adipose tissue [3]. Additionally, obesity is associated with a higher frequency of thyroid cancer. Interestingly, anti-TPO (thyroid peroxidase antibody) has a similar predictive value as hypoechogenicity for the progression from subclinical to overt hypothyroidism. It is worth noting that thyroid nodules are common in old age (50% of individuals over 60 years old), but currently, there is no evidence supporting improved prognosis after early detection of thyroid cancer by ultrasound. Consequently, thyroid ultrasound examinations may lead to unnecessary invasive and expensive procedures [20].

### *Treatment of hypothyroidism in obese people*

Thyroid hormone replacement (THR) should be initiated in overt hypothyroidism (HT) or mild hypothyroidism (HTH) with a TSH level greater than 10 mIU/L. L-thyroxine (levothyroxine) is the preferred replacement hormone. There are no added benefits with the combination of L-thyroxine and L-triiodothyronine. TSH (thyroid-stimulating hormone) levels are used for monitoring THR. If there is no laboratory-specific normal range, a target range from 0.45 to 4.12 mIU/L for TSH is considered. FT3 (free triiodothyronine) and FT4 (free

thyroxine) are not recommended for treatment monitoring. In cases of overt HT, a lower starting dose and slower dose escalation should be considered, especially for elderly individuals or those with cardiovascular disease [15, 21]. A slight increase in TSH level (< 10 mIU/L) with normal FT4 is commonly seen in obesity and should not only relied on to diagnose primary hypothyroidism in persons with obesity in the absence of thyroid antibodies. It should be emphasized that the progression of subclinical hypothyroidism to overt hypothyroidism is 2–5% per year, with a lower rate in obesity. In a recent meta-analysis, L-thyroxine treatment in obese individuals with subclinical hypothyroidism did not improve weight loss [22].

Replacement of thyroid hormone treatment should not be started due to the mere presence of slightly increased TSH levels in obese individuals with the only intention of reducing weight. In non-obese individuals, starting thyroid hormone replacement in cases of slightly elevated TSH (< 10 uIU/L) with normal FT4 is considered when additional factors are present as the presence of thyroid antibodies, history of destructive thyroiditis, or prior radioiodine therapy for hyperthyroidism, particularly in young subjects. Also in childbearing period, L-thyroxine treatment should be considered. On the other hand, older individuals (> 70 years), especially those with cardiovascular disease, should lean toward a follow-up strategy [15]. The "Trust Thyroid Trial" did not find a clear benefits with levothyroxine replacement on clinical symptoms in older people with subclinical hypothyroidism [23], although no specific trial has been conducted in older obese individuals. Several studies have demonstrated only minor effects on weight change, increased urinary nitrogen excretion (which indicates indicating loss from lean mass), adverse effects on bone metabolism, and alterations in affective status. Additionally, an increased risk of cardiac arrhythmia, heart failure, and ischemic events has been reported in obese patients who are already at risk for cardiovascular disease [24, 25].

Females in the childbearing period with subclinical HT are at increased risk of infertility, pregnancy complications, and neurocognitive deficits in neonate. On the other hand, thyroid hormone replacement is associated with reduced risk of pregnancy loss and premature delivery in pregnant females with TSH levels higher than 4.0 mIU/L [26]. The American Thyroid Association (ATA) recommends thyroxine replacement in women planning pregnancy and during conception if TSH level is more than 2.5 mIU/L and have positive serum thyroid peroxidase antibodies (TPOAb) [15]. In pregnant women, the target TSH level should be based on trimester-specific levels (less than 2.5 mIU/L during the first trimester, 3 mIU/L during the second trimester, and 3.5 mIU/L during the last trimester). It should be emphasized that no specific trials have addressed whether there is a different target TSH range in obese females or not.

## Endogenous hypercortisolism and obesity

### *The relationship between obesity and endogenous hypercortisolism (Cushing syndrome CS)*

In most studies, the diagnosis of Cushing's syndrome (CS) in individuals with obesity may reach 0.7% [27]. However, a higher prevalence (approximately 2–3%) has been reported in patients with type 2 diabetes who have poor metabolic control [28]. Also, a higher prevalence of subclinical Cushing's syndrome (CS) was found in people with obesity than nonobese individuals [29].

### *Is any obese patient needs screening for endogenous hypercortisolism?*

Given the high prevalence of obesity, its diverse causes, and the reduced incidence of Cushing's syndrome (CS) in obese individuals, applying screening tests for CS to unselected obese patients results in unacceptably high false positive rates. Therefore, only obese patients exhibiting more specific signs of the disorder should undergo CS screening. In this context, catabolic signs such as skin thinning, wide purple striae, spontaneous ecchymosis, proximal myopathy, and osteoporosis warrant consideration for CS screening [30]. The presence of certain features in combination is associated with a 95% probability of diagnosing Cushing's syndrome (CS). However, upper body adiposity, T2 diabetes, hypertension, or depression—while common in Cushing's syndrome—are not specific features exclusive to endogenous hypercortisolism; they are also prevalent in obesity. Screening for Cushing's syndrome (CS) is warranted in resistant hypertension or uncontrolled hyperglycemia despite intensive therapy. particularly in young patients [31]. Additionally, other conditions such as urinary stones, recurrent infections, and hypokalemia may increase the probability of CS, although less specific than catabolic features. In candidates for bariatric surgery, it is crucial to pay special attention to ruling out Cushing's syndrome (CS) in patients exhibiting suspicious clinical signs. This approach helps prevent outcomes such as suboptimal weight loss, recurrence of hypertension or diabetes, and weight regain. Additionally, screening for CS is essential to mitigate potential post-surgery complications related to hypercoagulability, catabolic state, and increased cardiovascular risk [32].

### *Laboratory screening and diagnosis of CS*

Pseudo-Cushing's syndrome, a condition characterized by biochemical features (with or without physical manifestations) resembling Cushing's syndrome (CS), can be caused by obesity, endogenous depression, and

alcoholism. It is typically excluded by demonstrating reversibility after addressing the underlying causes and occasionally through more sophisticated biochemical tests.

The 1 mg overnight dexamethasone suppression test (ONDST) serves as the recommended initial screening test for Cushing's syndrome. It is straightforward, well-standardized, and widely used in previous studies. The test is sensitive enough to exclude hypercortisolism, with a threshold of post-dexamethasone levels ≤ 1.8 μg/dL. There is no compelling evidence to adopt different methodologies or cutoffs for obese patients. Recent research found no advantage in using a 2 mg suppression test over the 1 mg test in obese individuals. False-positive results can indeed occur in severe obesity and other conditions as depression, alcoholism, chronic stress, and obstructive sleep apnea. It is essential to consider these factors when interpreting test results [33, 34]. Despite a false positive is seen in severe obesity, the specificity of 1 mg ONDST remains high ( 92%) in severely obese individuals in a recent trial. If 1 mg ONDST is positive, other test such as urinary-free cortisol (UFC) or midnight serum or salivary cortisol is needed to confirm or exclude the diagnosis. However, it should be considered that elevated UFC may be seen in obesity and may show a positive correlation with body mass index and waist circumference. When it comes to ACTH (adrenocorticotropic hormone) measurements, they are not significantly altered by obesity. However, it is essential to perform these measurements to differentiate between ACTH-dependent (high or normal) and non-ACTH-dependent (low) Cushing's syndrome (CS). This differentiation helps guide the choice of imaging methods and appropriate treatment measures [31, 35].

Despite the fact that hypercortisolism contributes to weight gain, normalization of body weight is not achieved in most cases after specific treatment of Cushing syndrome. This may suggest that endogenous hypercortisolism is one contributing factor rather than the only etiologic factor for weight gain. Treatment in CS should target endogenous hypercortisolism as the essential treatment goal rather than BMI reduction [36].

#### Gonadal dysfunction and hyperandogenism in females

In females, obesity can lead to obesity-related hyperandrogenemia, particularly during adolescence [37]. Many underlying pathogenic mechanisms are responsible as hyperinsulinemia and insulin resistance coupled with insulin effects on steroidogenic cells which retain insulin sensitivity [38]. Low-grade inflammation in obese is another factor. Obesity is also associated with fertility problems and an increased miscarriage rate, even in the absence of polycystic ovary syndrome [37]. Although obesity-associated gonadal dysfunction is due to hypothalamic dysfunction, primary ovarian failure may also promote weight gain.

Obese and overweight women with acne, hirsutism, or androgenic alopecia, as well as those experiencing menstrual abnormalities or infertility, should undergo endocrine evaluation. This evaluation aims to confirm or exclude hyperandrogenemia, anovulation, polycystic ovary syndrome (PCOS), and insulin resistance. Additionally, it aids in identifying other secondary causes of female gonadal dysfunction.

Polycystic ovary syndrome (PCOS) is prevalent in approximately one-third of female patients with obesity. The PCOS is diagnosed according to the Rotterdam criteria, which require any two of the following: hyperandrogenism (clinical or biochemical), chronic anovulation, and polycystic ovarian appearance on ultrasound. Furthermore, PCOS is associated with metabolic abnormalities such as dysglycemia, hypertension, dyslipidemia, an increased risk of cardiovascular disease, and endothelial dysfunction [39–41]. When dealing with androgen excess, it is crucial to exclude other clinical conditions beyond PCOS as congenital adrenal hyperplasia and other adrenal causes, insulin resistance syndromes, and androgenizing drugs. Furthermore, women suffering from menstrual abnormalities or infertility require screening for thyroid dysfunction, hypercortisolism, and hyperprolactinemia. In obese or overweight females, presence of feature of hyperandrogenism, menstrual irregularity, or infertility warrant measures serum gonadotrophins, sex hormones (total testosterone, androstenedione, estradiol, and progesterone), as well as serum sex hormone binding globulin (SHBG) and prolactin levels.

In PCOS, total testosterone, free T3, free T4, and androstenedione are elevated, while SHBG is low. Additionally, a high LH/FSH ratio may be observed, although it is not present in all cases. In addition to ovarian ultrasonography, HbA1c and oral glucose tolerance tests are also required [42]. Late-onset congenital adrenal hyperplasia although less common than PCOS may simulate the later clinical picture, so plasma 17-hydroxyprogesterone should be measured to eliminate the possibility of 21-hydroxylase deficiency [43].

Women with anovulation measuring LH, FSH, estradiol, progesterone, and prolactin are asked to assess gonadal dysfunction and to differentiate between secondary and primary hypogonadism. High circulating gonadotrophins levels are seen in primary hypogonadism, in contrast to the low levels in central hypogonadism. Special focus should be directed to circulating FSH level, which is differentially elevated in primary ovarian failure and is low in typical PCOS and central hypogonadism. In contrast, elevated LH levels are present in primary

hypogonadism and in some women with PCOS due to hypothalamic–pituitary dysfunction, either primary or secondary to peripheral androgen imbalance [44].

It is well established that hyperprolactinemia is associated with female infertility and anovulation, so measuring plasma prolactin is mandatory, and if present further investigations should be carried out to determine its cause. Mid-luteal phase progesterone should also be measured if assessment of ovulation is recommended [44]. Hormonal evaluation in women with regular menstrual periods is better done in the early follicular phase (day 1 to day 5 in menstrual cycle) and at any time in those with amenorrhea or irregular menstruation.

Complete assessment of the hypothalamic–pituitary function should be performed if the cause of infertility is well-matched with secondary hypogonadism and imaging of sellar and para-sellar region is carried out to exclude the presence of tumors and to differentiate from other potential causes of functional disturbances in hypothalamic pituitary hormonal axis as severe systemic illnesses, chronic stress, and eating disorders.

Metformin is an insulin sensitizer which improves hepatic, muscular, and adipose tissue insulin sensitivity, thus improving cardiometabolic risk profile, menstrual disturbances, and fertility in females with PCOS. Because of the potential role of insulin resistance plays hyperandrogenism and anovulation, metformin can be a suitable therapeutic approach in females with PCOS with prediabetes or T2 diabetes in addition to life style interventions targeting weight reduction. However, in the absence of diabetes or prediabetes, metformin should not be prescribed to promote weight reduction as the only indication. Instead, other anti-obesity drugs such as GLP1-receptor agonists as liraglutide or semaglutide or orlistat are used with the primary purpose of weight loss in addition to lifestyle interventions [45]. Furthermore, metformin should not be used as the sole treatment for restoring ovulatory cycle and fertility and improving signs of hyperandrogenism, Metformin is used as an adjuvant with other drugs, e.g., clomiphene in women seeking fertility [44].

Administration of combined oral contraceptives is the initial step in addition to weight reduction to reduce androgen excess signs in women with PCOS and to induce shedding of the thick endometrium lining. Formulations containing low doses of estrogens and progestin with no androgenic or antiandrogenic effects are preferred. Low estrogen formulations are preferred associated with low risk of venous thromboembolism. Antiandrogens are added if no or poor response after 6 months treatment with oral contraceptives. After menopause estrogen is not recommended if weight reduction is the only purpose for its use [46–48].

**Hypogonadism in males**

In moderately to severely obese men, male-secondary hypogonadism prevalence is approximately 35–64%. A higher prevalence of hypogonadism has been found in obese males with T2 diabetes and metabolic syndrome [49]. In morbidly obese men waiting for metabolic surgery, 75% had hypogonadism based on low plasma testosterone concentrations. Hence, severe obesity is regarded as one of the causes of functional secondary hypogonadism [50, 51]. Moreover, impaired sperm concentration, motility, and morphology were found in obese [52].

The relationship between male obesity and hypogonadism is rather a complex implicating role of obesity, excess abdominal fat, insulin resistance, inflammatory cytokines, oxidative stress, and T2 diabetes in its pathophysiology [49, 52]. There is a reciprocal relationship between obesity and hypogonadism: excess body fat can lead to low androgen levels and functional hypogonadism, while androgen deficiency can promote increased fat mass and metabolic syndrome. Increased fat mass and reduced fat free mass is common in androgen deficient males, although rarely produce a significant effect on BMI [53]. Hence, dysmetabolic hypogonadotropic hypogonadism is another term for this condition. Moreover, increased adipose tissue aromatase activity leads to excess conversion of testosterone to estradiol, resulting in inhibition of LH secretion and consequent reduction of secretion of testosterone. In addition, hypothalamic–pituitary–adrenal axis dysregulation with functional hypercortisolism has been postulated in obesity resulting in inhibition of gonadotrophin and testosterone secretion [35]. Despite the association of obesity and male hypogonadism, there are no available recommendations for routine hormonal screening in obese men in the absence of clinical suspicion for hypogonadism [54].

***Investigating hypogonadism***

Total testosterone plasma concentrations represent the initial tool. Total testosterone (TT) is measured, while the patient is fasting state in the morning at 7–11 am (as testosterone has circadian rhythm) [55]. Two low morning samples are needed to confirm low testosterone. Free testosterone (FT) and SHBG levels are measured if TT is near the low normal range [51]. FT is best measured by equilibrium dialysis, and, if not available, calculated testosterone is estimated from TT, SHBG, and albumin (bioavailable testosterone) [51]. The commonly present low SHBG with excess body fat and insulin resistance adds to the complexity for the interpretation of testosterone concentrations in obese [51]. If testosterone level is low, measuring levels of pituitary gonadotrophins (LH and FSH) is ordered to differentiate central from primary hypogonadism. Reduced levels of LH and FSH levels

are present functional secondary hypogonadism associated with obesity in contrast to the high levels in primary hypogonadism. Different disorders associated with hypogonadotropic hypogonadism should be eliminated before diagnosing functional secondary hypogonadism of obesity, especially hyperprolactinemia, leptin signaling abnormalities, syndromic, or hypothalamic obesity. Hypothalamic pituitary MRI may also be required, and if negative, leptin assessment and specific genetic testing are considered [51].

### *Management of obesity associated male secondary functional hypogonadism*

Weight loss should be the first-line treatment aiming to correct functional hypogonadism associated with obesity. However, lifestyle modification includes dietary measures and increased physical activity; achieving 5% weight reduction may not be enough for normalizing plasma testosterone. Also, persistent improvement of gonadal function induced by caloric restriction and increased physical activity only is small, and weight regain is very common. In morbidly obese men, loss weight reducing surgery is followed by achieving meaningful and sustained weight reduction, recovery of the hypothalamic – pituitary gonadal axis dysfunction, and significant increase in testosterone levels. However, despite the improvement in gonadal function, the improvement in sperm characteristics is doubtful [56].

In obese men with functional secondary hypogonadism associated with obesity, if life style interventions are not effective in weight reduction, improving symptoms of hypogonadism or normalizing testosterone levels androgen replacement may be considered on individual basis after comparing the benefits versus possible harms. Testosterone replacement therapy (TRT) can be given either as injectable form or transdermal gel or patch. TRT is associated with some potential risks as erythrocytosis, breast cancer, prostate cancer, and sleep apnea. Contraindications are erythrocytosis, prostate cancer, micturition difficulties due to prostate enlargement, breast cancer, and severe heart failure or sleep apnea. Also, it should be emphasized that TRT inhibits gonadotrophin secretion and results in suppression of spermatogenesis. Therefore, it should be avoided in men with hypogonadotropic hypogonadism seeking fertility, and gonadotropins should be the first-line therapy to ensure or improve spermatogenesis [51].

## Conclusion

Obesity is intricately linked to hormonal changes, extending beyond the well-known insulin resistance. Other endocrine diseases also closely associate with obesity and high body mass index. These include hypothyroidism, endogenous hypercortisolism, male hypogonadism, and excess androgens in females. As we deepen our understanding of obesity, recognizing the role of fat cells in hormone production becomes crucial. Physicians managing obese patients should remain vigilant for hormonal disorders beyond diabetes, ensuring comprehensive care.

#### Abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotropic hormone |
| Anti-TPO | Antithyroid peroxidase |
| BMI | Body mass index |
| CS | Cushing syndrome |
| CT | Computed tomography scan |
| CVD | Cardiovascular disease |
| DM | Diabetes mellitus |
| FT3 | Free T3 |
| FT4 | Free T4 |
| HbA1c | Hemoglobin A1c |
| HT | Hypothyroidism |
| OHT | Overt hypothyroidism |
| ONDST | Overnight 1mg dexamethasone suppression test |
| PCO | Polycystic ovary syndrome |
| SCHT | Subclinical hypothyroidism |
| TT | Total testosterone |
| UFC | Urinary- free cortisol |

#### Authors' contributions

All Authors contributed to study design, screening of all citations from full-text papers retrieved, data collection, and final revision of the manuscript.

#### Availability of data and materials

No datasets were generated or analysed during the current study.

## Declarations

#### Competing interests

The authors declare no competing interests.

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