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Prevention and management of obesity in a lifetime perspective

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ABSTRACT

The prevalence of obesity is increasing across all geographies. Obesity develops due to a disruption of the energy balance regulation. However, the cause is not well understood. Identification of causal factors that may be modified is crucial to reduce the prevalence of obesity. However, the interventions needed will likely differ between life stages. Hence, obesity research should span from pre-conception to adulthood. In this review, we point to gaps and limitations in existing research, highlight recently initiated studies from which we are awaiting results and point to future directions.

KEY MESSAGES

- Prevention of obesity should focus on causal factors that may be modified or eliminated.
- Causes of obesity differ between life stages, and research should span the entire period from pre-conception to adulthood
- Prevention of obesity has failed in children and adults, but the pre-conception period looks promising
- Management of obesity in adults is lifelong and calls for a holistic, evidence-based and cost-effective programme.

Obesity is a global challenge with prevalence increasing across all geographies, and it is expected that 51% or four billion people of the global population (aged over five years) will have overweight or obesity by 2035, 24% of whom will have obesity [1]. The burden of obesity affects the health of the individual living with obesity but also impacts the sustainability of society through increased healthcare costs and decreased labour market attachment [2].

Obesity develops due to a disruption of normal energy balance regulation, which results in an excessive energy intake. However, the reason for the increased energy intake is not understood.

Obesity is a multifactorial condition that evolves over years and involves the interplay between genes, epigenetics, metabolism, microbiome and behaviour, and is triggered by environmental factors that are currently not well understood. Changes in food systems (e.g., energy dense, processed and highly palatable food) contribute, but it is likely an interplay with the person's innate biological factors that determines the individual's susceptibility to obesity. Except for rare cases of monogenic obesity, heritability is weak and caused by the combination of hundreds of polymorphisms that each have a small effect [3]. Moreover, research is providing evidence that the responsibility lies at the national, food system, educational, medical, public health, municipal, societal and parental level and only at the individual level when adequate resources are available [4]. Despite this, weight stigma remains high and likely influences mental health.

A strategy to prevent and manage overweight and obesity should focus on causal factors that may be modified or eliminated; otherwise, we simply treat the symptoms. Identification of such factors is crucial for the success of endeavours to reduce the prevalence of overweight and obesity. Therefore, it is necessary to develop mechanistic models that allow us to understand the perturbations in energy balance physiology that lead to a positive balance and weight gain. Conceptualising obesity as a disorder of energy balance restates a principle of physics. However, this tautology provides no insights into the biological causes of what is driving the excessive energy intake. It is more likely that environmental factors disrupt appetite regulation and change the set-point, so that energy intake is increased to a higher level than needed for maintenance of a normal body weight. Many examples exist of how external factors may interact with the body's normal physiology and affect both peripheral and central factors to change energy balance (e.g., smoking, glucocorticoids, glucagon-like peptide-1 (GLP1) analogues). It is necessary to identify the environmental factors responsible for the disruption of appetite regulation, whether these are dietary factors, a lack of sleep, pollutants, mental stress or other, yet unidentified, factors.

PREVENTION AND MANAGEMENT IN A LIFETIME PERSPECTIVE

The root causes of obesity are likely to vary between life stages and, hence, research within obesity prevention and management should span from pre-conception to adulthood.

Prenatal

In a review and meta-analysis of observational studies, children born of mothers with pre-conception overweight and obesity had a doubled and tripled increased risk, respectively, of developing obesity in childhood or adulthood [5]. Most studies are adjusted for education/household income, but it cannot be ruled out that the association was due to other confounding factors. Some evidence was reported from a non-randomised intervention. Here, the prevalence of obesity in 172 children, aged 2-18 years, born to 113 severely overweight mothers who had a large weight loss following a gastric bypass operation, was compared with the prevalence in 45 gender and age-matched siblings born before the weight loss. After the maternal weight loss, the prevalence of overweight in the offspring was reduced by 52% and of obesity by

45% [6]. Furthermore, a randomised controlled trial (RCT) recently found that a 10-kg pre-conceptional dietary weight loss among women with obesity reduced a composite of adverse pregnancy outcomes – including large for gestational age [7]. However, other similar studies have failed to find an effect [8, 9] .

Overall, good evidence suggests that epigenetic programming of the foetus occurs, and that this influence may have a biological effect on the child's weight and potential obesity. However, randomised studies are needed to infer causality, and such studies have been initiated, e.g., the Dutch 'TOP-mums' [10], the Australian 'PRE-BABE' [11] and two large Danish trials 'PRE-STORK' [12] and 'PREPARE-CHILD' [13].

Pregnancy

A meta-analysis of 162,129 mothers and their children from 37 pregnancy and cohort studies [14] examined the role of maternal Body Mass Index (BMI) prior to conception and gestational weight gain for risk of overweight or obesity in offspring in early (2-5 years), middle (5-10 years) and late childhood (10-18 years). It was found that 20.1% of overweight and obesity for ages 10-18 years could be attributed to maternal overweight prior to conception, and 21.6% to maternal obesity prior to conception. An additional 19.2% was attributed to excessive gestational weight gain. Overall, the analysis suggests that around 60% of the prevalence of overweight and obesity in children and adolescents could be prevented if overweight or obese women reduce their weight to a BMI < 25 kg/m^2 before conception and prevent excessive gestational weight gain [14]. These findings are largely confirmed by a major German cohort (n= +34,000 children) that reported parental overweight at the time of conception to be the single most important factor for childhood overweight (42.5%) [15].

Numerous studies have documented that limiting gestational weight gain through diet change and exercise reduces complications for mother and child [14, 16-19]. However, no randomised studies have documented that the prevalence of obesity in the offspring may be reduced by limiting gestational weight gain during the second and third trimester in overweight women – as concluded by the recent participant data meta-analysis including six randomised trials with follow-up at 3-5 years of age [20]. Therefore, the spotlight has largely changed to the first trimester and the pre-conception period. However, a longer follow-up may be needed to identify the potential programming of childhood obesity that occurs during pregnancy, and recently funded follow-ups of completed RCT studies in Denmark count a three-year follow up on the FitMum [21], a 5-year follow-up on APPROACH [19], a 12-year follow-up on the "Treatment of Obese Pregnant women" (TOP) study [22] and a 15-year follow-up on the "Lifestyle in Pregnancy" (LIP) study [23].

Infancy (0-1 years old)

Infants are breastfed or given formula and are then gradually introduced to transitional food. Observational studies indicate that a high protein intake is associated with overweight later in life [24]. In addition, fibre and whole grains must be balanced in this age group, and fat may be

actively added to increase the energy density of transitional food. These dietary recommendations differ in many ways from those of older children and adults.

Numerous observational studies have identified early risk factors for childhood overweight and obesity. However, the number of studies that have aimed to modify the risk factors in RCTs to show causality and effect sizes is still relatively low. Although some of the studies have shown effects on a few of the behavioural risk factors (e.g., breastfeeding, transitional diet, the child's diet, the parents' approach to the child's nutrition, screen time and sleep), these changes are rarely translated into an effect on the child's weight status. Thus, an overall conclusion for this age group is that a significant challenge exists in terms of ensuring that risk factors are on the causal chain.

Childhood (1-18 years old)

Regardless of age group, children react the same way physiologically to the obesogenic society, and recommendations for healthy lifestyles should, therefore, in theory, be the same for children in nursery, kindergarten, school and for adolescents.

Numerous studies have attempted to prevent overweight and obesity in children, and a meta-analysis of RCTs focusing on improved diet and physical activity found a reduction in BMI of 0.11 kg/m2 as compared with control groups [25]. Most of these implementation trials are school-based and are conducted in US populations up to the age of 12 years, often from socially disadvantaged areas. Generally, studies from both Denmark and the Nordic countries are few, and those that have been published generally have a negative outcome. Therefore, it was recently concluded that the efforts known so far cannot be expected to have any decisive effect in preventing obesity among children and young people, wherefore new initiatives involving more comprehensive interventions should be developed [26]. The evidence points to a need to combine high-intensity interventions with diet, exercise, sleep and screen time; and to target both schools and homes. Moreover, teaching and educational elements should be involved. To achieve a long-term effect, interventions need to exceed the usual 6 to 12 months and to comprise weekend behaviours [27]. Such a project involving 2,500 6–9-year-old school children will be initiated shortly [28]. Furthermore, a proof-of-concept sleep RCT is needed to confidently continue working with sleep as a causal factor involved in the development of obesity – another project, which will be initiated shortly [29].

Prevention is crucial and the Novo Nordisk Foundation, together with the Danish Ministry of Health, have recently launched the 1.1 DKK billion ‘Centre for Childhood Health’ [30]. This centre will primarily focus on prevention but will also develop and evaluate non-pharmacological management (lifestyle interventions) for children who become obese.

Adulthood (18+ years)

Obesity in adulthood is a gateway to other non-communicable diseases, such as type-2 diabetes (T2DM), cardiovascular disease and cancer, and to mechanical issues such as osteoarthritis and

sleep apnoea, together compounding quality of life. Therefore, finding effective prevention and management strategies is a burning platform. Bariatric surgery has so far been the most effective offer for people with severe obesity. However, an alternative to bariatric surgery has emerged over the past decade; pharmacotherapies primarily based on GLP1 that are safe and highly effective treatments (10-20% weight loss) for obesity and likely to be even more effective (>20% weight loss) in combination with, e.g., amylin or glucose-dependent insulinotropic polypeptide (GIP) [31, 32]. Lifestyle and behavioural interventions aimed at reducing calorie intake and increasing energy expenditure have historically shown limited effectiveness to prevent and manage obesity. Nevertheless, landmark studies have recently shown that a low-calorie diet-induced weight loss of 10-15 kg may be achieved and sustained over two years and that this is sufficient to induce remission of, e.g., T2DM in most individuals [33]. Furthermore, it has been shown in several randomised controlled trials that diet composition plays an important role in weight loss and weight loss maintenance [34, 35]. E.g., the DioGenes study found that a modest increase in protein content and reduction in the glycaemic index produced an improvement in maintenance of weight loss after a large initial weight loss [34]. Moreover, SHOPUS found a New Nordic Diet containing more dietary fibre and wholegrain to improve weight loss – with both studies finding the effect to be recorded almost exclusively among prediabetics [36]. Of note, the DioGenes research findings have been translated and adopted commercially in France with more than 50 participating centres and have been shown to be effective also in a non-controlled setting [37]. Furthermore, recent reviews [38, 39] have highlighted the potential for diets with a lower glycaemic load for T2DM, which should be a priority going forward. The great heterogeneity and interpersonal variation in weight loss response may potentially indicate that obesity is not one condition but, in fact, various “obesities”. Thus, stratification of obesity into distinct subtypes (e.g., according to fasting glucose and insulin sensitivity [39], enterotype [40] and genetics or epigenetic profiling) will no doubt be a breakthrough in the future of obesity research. This may potentially, in turn, pave the way for “precision prevention” and “precision management” strategies; a paradigm shift that has the potential – together with a systems approach – to bend the curve of the obesity epidemic.

Currently a push is being made towards holistic (individualised, multidisciplinary and equitable), evidence-based weight management strategies that may be embedded in existing healthcare systems (i.e. must be scalable and cost-effective). The LightCOM project aims to embrace this approach by developing, implementing and evaluating a new intensive weight loss intervention including lifestyle and pharmacotherapy (based on combining current best-practices in an individualised manner) that is delivered in a pragmatic trial setting both in Denmark and the United Kingdom [41].

Up until now - after more than 40 years of dedicated obesity research - it has still not been possible to identify the causal factors of obesity and we have thus far been unable to reverse, or even halt, the obesity epidemic. Remember that the problem with pharmacotherapy and short-term lifestyle interventions (e.g., low calorie diets) is that we are not focusing on the causal factors of obesity but

simply treating the symptoms. Therefore, weight loss maintenance will be the major issue to tackle going forward. This calls for new and disruptive thinking while supporting novel early-stage high-risk/high-gain projects to identify causal biological and physiological factors of obesity, which may, in turn, pave the way for new and effective prevention and management strategies in the future.

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