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THEORIES OF THE CAUSES OF OBESITY

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An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

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1. INTRODUCTION

Allison et al (2023) described how obesity is viewed as unlike other diseases because the cause is simple or obvious: "Often, obesity is attributed to gluttony and sloth, two of the canonical seven deadly sins, and thus historically cast as a result of moral failure of righteous willpower. The focus of much of the history of obesity science on energy intake and expenditure has perhaps inadvertently fed into such beliefs. Although energy intake and expenditure are vitally important, scientists have increasingly come to appreciate that appeals to conscious control neither seem logically defensible nor commensurate with decades of accumulating data regarding long-term regulation of food intake or energy expenditure" (p1).

Also unlike other diseases, "obesity and its purported causes are closely related to personal anecdotal experiences with eating, nutrition, exercise, and body habitus. Thus, anecdotal experiences often replace expertise, evidence, or the product of deep study" (Allison et al 2023 p1).

Trying to understand the causes of obesity, for Allison et al (2023), immediately faces two problems; what is meant by "cause", and by "obesity". In reference to the former: "Do we mean evolutionary explanations such as how did we as a species get to be what we are? or do we mean mechanisms whereby we ask by what physical processes does something occur? or do we adopt the Rubin causal model [Imbens 2010] and mean counterfactuals, ie: how would things have been different had it not been for this postulated causal factor and define that difference as the causal effect? There are yet other ways of conceiving of cause, but these are some of the most common" (Allison et al 2023 p2). The term "obesity" refers to "a degree of excess body fat, but more than a degree of excess body fat. It also implies an excess of body fat where excess itself must be defined and is typically defined as an amount that causes deleterious health effects or reduced lifespan" (Allison et al 2023 p2).

2. EVOLUTION AND GENES

"From an evolutionary perspective, our susceptibility to excess weight must broadly derive from the human genome. While fatness is sensitive to environmental factors, obesity has substantial heritability, demonstrated by twin and adoption studies. To date, around 60 genome-wide association studies (GWAS) have linked over 1100 loci with adiposity phenotypes, though they explain only a small minority of the heritability. Like height, adiposity appears to be a quintessential polygenetic trait, whereby numerous alleles each contribute a very small magnitude of effect to phenotypic variance" (Wells 2023 p1).

An evolutionary explanation looks at the benefits of certain genes, as in the "thrifty genotype" hypothesis of diabetes susceptibility (Neel 1962). This hypothesis "assumed that ancestral humans experienced selective pressures from 'cycles of feast and famine', through periods of energy-plenty and energy-scarcity. Those more regularly exposed to such conditions were hypothesised to have evolved an enhanced capacity for fat accumulation during times of surplus, which could then be oxidised during famines. In contemporary settings of unlimited food availability, accordingly, thrifty genotypes would drive development of obesity and diabetes" (Wells 2023 p2). No specific genes have been found to support this theory, however (Wells 2023) [1].

The complete alternative is the "drifty genotype" hypothesis (Speakman and Elmquist 2022), with the emphasis on the absence of evolutionary pressures. It proposed that "the emergence of the capacity to use fire and weapons for defence among the genus Homo would have relaxed the selective pressure of predation, weakening upper constraints on body mass and allowing random mutations to accumulate" (Wells 2023 p2).

Concentrating on human adiposity (ie: the amount of adipose tissue), Wells (2023) combined the two hypotheses above as the "crafty genotype" hypothesis. Humans have greater levels of body fatness than other apes, and so this would suggest that adiposity had strong evolutionary pressures. The genus Homo evolved in unpredictable environments, so specific genes may not be as beneficial as the ability to deal with variability - eg: large energy stores in the form of adipose tissue. Along with

[1] Challenges to the thrifty gene idea include that "most famines are too short to provide sufficient natural selection pressures to result in the emergence of a survival gene that would determine the fate of a species. Some have also argued that if thrifty genes existed, then everyone today should be obese" (Johnson et al 2023 p10).

the evolution of the large brain, adiposity act as "risk management" systems in volatile environments. Flexibility is the product of multiple genes.

Evolutionary explanations often emphasise that the human body is in the wrong environment of today with the constant food availability of the West, and thus obesity. Wells (2023) partly agrees. The problem for him is that sensitivity to the environment in terms of adiposity has evolved, particularly short-term changes. Put simply, a short-term lack of food leads to the storage of fat, with no "thinking ahead" to the negative consequences, because the individual may not survive in the long-term.

In summary, "selection has favoured a crafty genotype, where the role of numerous alleles helps stabilise the genetic basis of phenotype in order to underpin enhanced plasticity, a strategy that is appropriate for a long-lived organism occupying volatile environments. The crafty genotype allows the fitness value of fat to vary in association with endogenous characteristics and life-course experience" (Wells 2023 p6).

2.1. FRUCTOSE SURVIVAL HYPOTHESIS

Using evolutionary ideas, Johnson et al (2023) discussed a protective mechanism, that they called "the survival switch", "that is initiated before resources become scarce... [which] is mediated by fructose, and that, unlike glucose whose primary biologic function is to provide an immediate fuel, that the primary function of fructose is to aid in the storage of fuel" (p1). The survival switch is overactive for the modern world with the availability of food, and thus the rise on obesity.

Fructose is a "simple sugar" generated in the body from glucose (in a process called the "polyol pathway", and controlled by an enzyme called "adipose reductase" (AR)). AR is activated by stress, or starvation, for instance, while fructose generation in the liver is stimulated by salty foods, alcohol, and high fructose corn syrup (HFCS) (used in many modern processed and ultra-processed foods), among others (Johnson et al 2023).

Animal studies that administer fructose produce weight gain and adiposity, similar to animals preparing for hibernation. Fructose encourages behaviour change to increased the search for food and water, as well as energy conservation, a "low power mode" (eg: reduced oxygen need), preservation of key body functions, and

activation of the immune system (Johnson et al 2023).

The "paired feeding study" is a common design with rats, where groups are fed the same composition and caloric content food, except for one change, like the absence or presence of fructose. One such study (Roncal-Jimenez et al 2011) found no difference in weight gain between the fructose and non-fructose groups, but there were changes in behaviour that increased caloric intake (eg: leptin resistance, where leptin acts a stop mechanism for food intake) in the fructose group. Even when caloric intake was restricted, the fructose group showed changes in the body associated with obesity (eg: severe fatty liver; insulin resistance) (Johnson et al 2023).

Applying these ideas to humans today, Johnson et al (2023) summed up: "One of the most serious consequences of continued activation of the fructose-mediated switch is not obesity and weight gain, but the metabolic effects that involve many of the common diseases occurring in western society" (p8).

2.2. GENETIC INFLUENCE

Establishing the genetic influence on the susceptibility to weight gain within an obesogenic environment involves identical twins reared separately [2]. In such studies (eg: Allison et al 1996), the heritability factor is 40-70% (Farooqi 2023).

Another method is to compare adopted children to their biological and adoptive parents (eg: Sorensen et al 1989). The children were similar in body weight to their biological parents (with whom they shared genes) rather than the adoptive parents (with whom they shared the environment) (Farooqi 2023).

Genomic studies have allowed the search for specific genes. For example, mutations in the genes encoding leptin and the leptin receptor cause an intense drive to eat and severe obesity in early life (eg: Clement et al 1998) (Farooqi 2023). These are monogenic disorders (ie: changes in single genes), but severe obesity has been seen in the rare variants of multiple genes in animal models (eg: zebrafish; mouse) (Farooqi 2023).

[2] Over 1500 genetic variants have been found to have an association with body weight (Heeran et al 2023).

2.3. GENETIC SUSCEPTIBILITY

Childhood obesity is "of particular concern" (eg: 1 in 10 4-5 year-olds starting school and 1 in 5 10-11 year-olds in England in 2021) (Llewellyn et al 2023). "Once developed in childhood, obesity is difficult to reverse, with strong tracking into adolescence and adulthood. What is more, weight development during the infancy period is especially important; rapid weight gain in the first 2 years of life... is associated with a nearly 4 times increased risk of overweight or obesity in childhood or adulthood" (Llewellyn et al 2023 p1).

Genetic susceptibility to childhood obesity is seen as important (as found in twin studies). For example, a meta-analysis by Silventoinen et al (2016) found that 40-85% of individual differences in weight in the early years was due to genetic variation (Llewellyn et al 2023).

How does the genetic susceptibility to early obesity manifest itself? The answer is neurobiological processes controlling appetite regulation and thus eating behaviour, according to the "Behavioural Susceptibility Theory" (BST) (eg: Wardle et al 2001). Two key aspects are responsiveness to food cues (eg: wanting to eat when seeing, smelling, or tasting food), and sensitivity to fullness (satiety) signals. The susceptible individuals are high on the former and low on the latter. Together these can be called "appetite avidity". The opposite pattern could lead to underweight issues (Llewellyn et al 2023).

The "Child Eating Behaviour Questionnaire" (CEBQ) (Wardle et al 2001) and the "Baby Eating Behaviour Questionnaire" (BEBQ) (Bjorklund et al 2022) were developed to measure the behavioural susceptibility. The findings from research with these questionnaires have led to four conclusions (Llewellyn et al 2023):

i) Appetite avidity and obesity in early life - eg: a meta-analysis (Kininmonth et al 2021) of 72 cross-sectional studies using measures like BMI and adiposity.

ii) Appetite avidity and overeating in early life - A particular pattern of overeating has been observed (eg: Carnell and Wardle 2007), including eating in the absence of hunger, faster eating, lack of caloric compensation (eg: eating less later or increasing exercise), and eating more in ad libitum situations (ie: no restrictions). Other characteristics include larger "meal size", and higher "eating frequency" (ie: more eating

occasions per day), found in food diary studies (eg: 21 month-olds in Britain; Mooreville et al 2015) (Llewellyn et al 2023).

iii) The genetic basis to appetite behaviour - Supported by twin studies, and genomic studies.

iv) The gene-environment interaction - ie: the behavioural susceptibility in a particular environment. Llewellyn et al (2023) explained: "In environments with a limited food supply, such as in the UK during and immediately after World War II, there will be observable variation in weight, but most of the population will remain lean and genetic susceptibility to obesity is still, largely, buffered. However, in an abundant food supply such as the modern food environment, variation in weight is large as genetic predisposition to higher or lower weight is maximally expressed" (pp5-6).

Llewellyn et al (2023) commented: "An important limitation in all research relating to BST is that it has been largely undertaken in samples from affluent, high income western countries. More research is needed in socio-economically and ethnically diverse samples, and countries in transition, to establish the validity of BST in populations with high levels of food insecurity and cultural differences in eating behaviour and parental feeding practices, which might differentially impact appetite development and, in turn, risk of developing obesity. More longitudinal studies are also needed, including in genetically sensitive designs" (p8).

2.4. ADIPOSITY-FORCE THEORY

The "overflow" theories describe adiposity as a product of greater energy input than expenditure which is stored as fat, whereas the "adiposity-force theory" (Sorensen 2023) sees the body as responding to future social threats by storing fat.

Sorensen (2023) proposed that "the body responds to social disruptions as threats of a future lack of food by an adiposity force building a reserve of energy independent of the regulation of the energy balance. It is based on the assumption that our evolutionary development required collaboration in gathering and sharing of food, combined with precautionary measures against anticipated failing food supplies. Social challenges are perceived as such threats, which activate

the adiposity force through the brain to instigate the growth of fat and lean mass by neuro-hormonal signalling. If both perceived social threats and food abundance continue, the adiposity force pushes the fat accretion process to continue without inhibition by feedback signals from the fat mass, eventually leading to more obesity, and more so among the genetically predisposed" (p1).

An important distinction is that social threats are subjectively perceived (ie: unrelated to objective threats). So "mental challenges" can be perceived as threats. "These challenges may be various cognitive-emotional states, eg: disappointments, frustrations, stress and low self-esteem due to mismatch of expectations to oneself or other people in the social environment (parents, siblings, friends, peers colleagues etc) and the perceived relations and achievements. Thus, among individuals who are socially privileged, but subjectively experience such mental challenges, the adiposity force may be activated and produce obesity" (Sorensen 2023 p5).

2.5. FOOD INSECURITY-OBESITY PARADOX

The "food insecurity-obesity paradox" is a term coined to describe poor individuals who lack money to buy food and so eat cheap, energy-dense food to overcome hunger (Bateson and Pepper 2023). Food insecurity (FI) refers to the "periodic experience of insufficient quantity and quality of food and anxiety about future food scarcity, but not chronic energy deficit" (Bateson and Pepper 2023 p1).

So, there are three elements to FI (Bateson and Pepper 2023):

a) Uncertainty about food in the future (eg: item: "I was worried my food would run out before I got money to buy more").

b) Inadequate quality of food (eg: "I couldn't afford to eat balanced meals").

c) Insufficient quantity of food (eg: "The food that I bought just didn't last, and I didn't have money to get more").

It has been calculated that FI individuals were 1.21 times more likely to be overweight or obese than non-FI

individuals, and in the high risk group (FI adult women in developed countries) 1.50 times more likely (Bateson and Pepper 2023).

In relation to evolution, there are proximate and ultimate explanations for physiology and behaviour. "Ultimate explanations are concerned with why a response evolved, whereas proximate explanations are concerned with the mechanisms underlying the response within an individual" (Bateson and Pepper 2023 p2). FI individuals eating higher-energy density foods is an example of a proximate mechanism, while the body adapting to store fat against future food shortages is an ultimate explanation (Bateson and Pepper 2023). The latter has been called the "insurance hypothesis" (Nettle et al 2017).

"The insurance hypothesis is based on the assumption that fat provides a buffer against energy shortfall during periods when food is not available. However, carrying fat has costs as well as benefits; increased fat increases energy requirements, reduces locomotor performance and increases the risks of injuries resulting from having a heavier body. In humans, increased fat also has social costs arising from stigma and discrimination. It follows that the optimal amount of fat depends on the unpredictability of food: the greater the probability of energy shortfall, the higher the optimal fat stores. Thus, the set point (or zone) around which body weight is regulated should be higher under FI" (Bateson and Pepper 2023 p2).

What is the evidence for FI causing obesity rather than just an association (ie: the ultimate explanation of the insurance hypothesis)?

i) Experiments with humans - It is almost impossible to manipulate food availability for long periods of time as in the ideal experiment for ethical as well as practical reasons. But experiments manipulating specific variables hypothetically has been tried. For example, watching a video about future food scarcity, and then asking participants about their favourite foods (eg: Folwarczny et al 2021). Compared to a control group (who did not watch such a video), energy-dense foods are more likely to be chosen (Bateson and Pepper 2023).

Another type of experiment, which is indirect evidence, is where participants are kept on regular or irregular meal regimens (though total energy intake is equal) (eg: healthy lean women; Farshchi et al 2004). "The irregular condition caused a decrease in dietary thermogenesis. Although this did not cause significant

weight gain over the two weeks of the intervention, it would do, all else being equal, if sustained for longer. Thus, in the absence of increased total energy intake, variability in the temporal pattern of intake is sufficient to cause weight gain" (Bateson and Pepper 2023 p4).

Controlled environments with unlimited food find that FI participants consume more calories than food-secure ones (eg: 700 kcal per day more in a three-day study; Stinson et al 2018).

ii) Experiments with non-human animals - The insurance hypothesis was first proposed in birds, and so these have been studied in laboratory experiments. For example, Andrews et al (2021) randomised European starlings to unpredictable or predictable food conditions for five months, and found that the birds in the unpredictable condition had gained body weight by the end of the experiment.

iii) Observation of free-living humans - Food diary studies (eg: Hanson et al 2014) (ie: recall or record of all food eaten in a set period of time) show that "the nutritional quality of food-insecure diets is relatively poor. Food-insecure participants have less diverse intake, consuming a smaller number of distinct foods per consumption event. They consume fewer fruits, vegetables and dairy products and have lower intakes of vitamin A, vitamin B6, calcium, magnesium and zinc. In terms of relative macro-nutrient intake, food-insecure participants have lower intake of fibre and protein and higher intake of carbohydrate . They also consume more ultra-processed foods" (Bateson and Pepper 2023 p6).

In terms of proximate explanations for the food insecurity-obesity paradox, Bateson and Pepper (2023) outlined three factors - chronic stress around future food access, unpredictability in eating patterns, and poorer diet quality. The first is seen in the simple observation of worried people eating "comfort food" (high-energy dense). While unpredictability in meal times "will prevent the acquisition of anticipatory (cephalic) hormonal responses to food that contribute to homoeostasis" (Bateson and Pepper 2023 p8).

Bateson and Pepper (2023) concluded with two points. First: "Based on animal experiments showing that unpredictable food causes increased body fat, we argue that this association is likely to be causal. FI is

therefore a candidate cause of variation in adiposity seen in high-income countries" (Bateson and Pepper 2023 p9).

Second: "The mechanisms underlying FI-induced weight gain are currently poorly understood and may include both increases in energy intake and decreases in energy expenditure. Reductions in physical activity, dietary thermogenesis and basal energy expenditure could all contribute to reduced energy expenditure under FI" (Bateson and Pepper 2023 pp9-10).

3. PHYSIOLOGY

3.1. ENERGY HOMOEOSTASIS

A key term is "energy homoeostasis", which is "the active maintenance, or regulation, of appropriate levels of energy availability ('active' in this context refers to a system whose response involves dynamic reacting components)" (Geary 2023 p1). Geary (2023) continued: "It is important to recognise that the causal relationships among variables related to energy homoeostasis and the mechanisms through which they are regulated remain unclear. Body weight per se seems an unlikely candidate for regulation, although some evidence suggests that there is a gravitostat [Ohlsson and Jansson 2020]" (p1).

Understanding of the process of energy homoeostasis has changed over time, and Geary (2023) outlined four key concepts historically:

i) Physiological energetics - Antoine-Laurent de Lavoisier, in the mid-18th century, introduced the idea of the "law of conservation of mass", where "the sum of the weights of all products of a chemical reaction equals the sum of the weights of the materials entering the reaction" (Geary 2023 p2). This led to the concept of "energy balance" - ie: energy-in minus energy-out (appendix A).

ii) Homoeostasis - The idea of homoeostatic regulation within the body developed from work by Claude Bernard in the nineteenth century, and then by Walter Cannon in the early 20th century. He introduced and defined "homoeostasis": "The co-ordinated physiological processes which maintain most of the steady states in the organisms are so complex and peculiar to living beings... that I have suggested a special designation for these states, homoeostasis. The word does not imply, something set and immobile, a stagnation. It means a condition – a condition which may vary, but is relatively constant" (Cannon 1929 quoted in Geary 2023).

Curt Richter, later in the 20th century, showed that homoeostasis occurred in many aspects of the body (eg: thermoregulation) - "the maintenance of a constant internal environment" (Richter 1942-1943 quoted in Geary 2023).

iii) Adipose-tissue regulation - The idea that the body weight is regulated by homoeostasis (ie: body fat), and that obesity (or anorexia) are due to abnormalities

in the process came from animal studies mostly in the mid-20th century (eg: by John Brobeck; Gordon Kennedy).

iv) Control theory - The focus has moved in the second half of the 20th century to the control of homoeostatic regulation (eg: via negative-feedback or feed-forward controls). A simple negative feedback control would be that energy input continues until a mechanism feeds back that homoeostasis/balance is once more achieved. Some theories include a "set-point" weight or body fat level that the body returns to (Geary 2023).

There is evidence to support homoeostasis in humans. For example, Polidori et al (2016) found that obese individuals prescribed a drug to increase urinary glucose compensated with increased energy intake of an equivalent amount to the loss.

Applying the idea of homoeostasis to obesity is the "energy-balance model" (EBM) (eg: Hall et al 2022), for example. It "describes the generally held view that excess intake of palatable, energy-dense foods is the most important cause of increased adiposity. Negative feedback from the adipose tissue tends to inhibit eating and reduce the rate of bodyweight gain, but usually not strongly enough to prevent the development of obesity" (Geary 2023 p6).

A reverse causality to energy imbalance driving fat storage is proposed by the "carbohydrate-insulin model" (CIM) (Ludwig and Ebbeling 2018). "Under CIM, dietary carbohydrates shift energy use in favour of storage in adipose tissue" (Bernard and Spalding 2023 p1).

Metabolic fuels from food are partitioned in the body in three ways - expenditure vs storage, anatomical locations (lean vs fat tissue), and energy expenditure among tissues. Carbohydrates alter these processes (Bernard and Spalding 2023).

Support for the CIM comes from research on the insulin-to-glucagon ratio, and specifically that high-glycaemic load (GL) foods (eg: refined grains, potato products, added sugars) increase insulin and suppress glucagon. The upshot is increased hunger and food consumption.

Ludwig et al (1999) gave twelve adolescents meals varying in GL. The high-GL meal was carbohydrate 64%, fat 20%, and protein 16%, while the low-GL meal was 40, 30, and 30 respectively. Subsequently given free access to food, the high-GI group consumed 600-700 kcals more in one sitting (Ludwig 2023).

Applied to weight management, Ebbeling et al (2018) assigned 164 adults to low, medium or high carbohydrate diets. Total energy expenditure (TEE) decreased on the high-carbohydrate diet, but increased on the low-carbohydrate diet to a difference of 200-250 kcals per day (Ludwig 2023).

"Virtually all long-term human trials have major methodological issues limiting generalisability, related to the difficulty of controlling all dietary and behavioural factors that might confound clinical outcomes. For this reason, laboratory animal research has been employed to examine predictions of obesity models" (Ludwig 2023 p4). For example, Pawlak et al (2004) fed rats high- or low-GI diets for seven weeks. Ludwig (2023) (who was one of the researchers) explained: "Initially, both groups of animals ate ad libitum and had similar weight gain. However, at seven weeks, the high-GI animals began to gain more weight than the low-GI group without an evident difference in food intake, suggestive of decreased TEE. Therefore, to maintain weight parity, we restricted food for the high-GI animals. At 18 weeks, the high- versus low-GI groups had virtually identical mean body weight (548 versus 549 g), but the former had a 71% increase in body fat, and a commensurate reduction in lean bodymass" (p4). This is viewed as clear evidence for the CIM.

Despite advocating for CIM, Ludwig (2023) accepted the following weaknesses of the approach: "(i) lacks critical evidentiary support in some areas; (ii) will require revision as new data accrue; (iii) cannot explain all of the variance in BMI observed during the obesity epidemic; and (iv) does not exclude other explanatory models that operate along different causal pathways" (p6).

Ludwig (2023) ended with a suggestion to combine the EBM and CIM. So, "hedonic and reward aspects of food could cause people to eat more than necessary to satisfy energy requirements, as postulated by the EBM (comprising a 'push' mechanism). Then, in the late post-prandial phase, anabolic hormonal responses to the meal might trap those extra calories into adipose tissue, and suppress their release, as specified in the CIM (a 'pull' mechanism) contributing to a vicious cycle of overeating and weight gain. The relative contributions of these mechanisms may vary between people, with differing physiology (eg: insulin secretion), metabolic health state, and for other reasons, explaining some of the heterogeneity in response to different weight loss diets" (p6).

3.1.1. Challenges

Stubbs et al (2023) argued that energy balance is regulated, but "that regulation is neither precise nor symmetric" (p2). They explained: "Unlike many physiological systems, which are regulated over periods of minutes, hours or days, body weight and composition are tolerant of considerable perturbations over weeks and months. Evidence suggests that in subsistence economies, seasonal body weight fluctuations of approximately 10% were commonplace. In many wild animals, seasonal fluctuations in body weight and composition are not unusual" (Stubbs et al 2023 p3). Most models of energy balance and homoeostasis are short-term (Stubbs et al 2023).

Negative feedback is key in models of energy balance regulation. Put simply, when too much energy is input a "stop" signal is sent. This signal is related to carbohydrate intake in some models (eg: Flatt 1987). But controlled studies that manipulate carbohydrate composition in the diet do not influence food intake (eg: Shetty et al 1994). This can be used as evidence against the CIM.

The are limits to the generalisability, however, of controlled feeding studies to real-life human behaviour, including that "people do not usually consume systematically manipulated diets. They tend to select and ingest foods from literally tens of thousands available in the food supply. Patterns of food intake tend to be habitual, but there is far more noise in the nutritional environment of the real world than that of diet manipulation studies" (Stubbs et al 2023 p10).

Stubbs et al (2023) preferred to focus on appetite (ie: the motivation to eat) rather than physiological homoeostasis mechanisms to explain weight gain in obesogenic environments. Actual eating motivation and behaviour are the product of variables including beliefs and attitudes, habits, liking, reward, and emotions. "Because a great deal of human behaviour is both reactive and learned, it is possible that the environment can produce prompts, cues and stimuli that influence learned patterns of motivation to eat" (Stubbs et al 2023 p9).

3.2. MECHANISMS OF HOMOEOSTASIS

The body's lean tissue (fat-free mass; FFM) and basal energy expenditure (resting metabolic rate; RMR) are now viewed as important in human appetite (Hopkins et al 2023).

In the mid-20th century the "lipostatis" hypothesis was proposed (eg: Mayer et al 1954). Originating in classic studies with rats (eg: Kennedy 1950) that selectively destroyed areas of the hypothalamus, the idea was that a blood borne signal released by body fat acted on the ventro-medial nucleus of the hypothalamus (VMH) to control food intake. This was an example of the classic homoeostatic model of appetite. Put simply, the motivation to eat is the product of energy input and output.

So, food consumption should be associated with fat mass (FM). But recent research has challenged this idea, and suggested that FFM and RMR correlate with food intake (Hopkins et al 2023). Studies keep individuals in controlled situations that record energy expended and energy input (EI). For example, Weise et al (2014) monitored a group of overweight and obese individuals in this way when food was freely available from an automated vending machine. FFM was positive associated with EI, and FM negatively correlated with EI. Regular measurements of hunger (eg: at 30-minute intervals) have shown a similar relationship in lean individuals (eg: Cugini et al 1998), and severely obese participants (eg: Grannell et al 2019) (Hopkins et al 2023).

RMR describes the energy demands of the body when not active, and includes a whole-body rate and for individual organs, and it varies between individuals. In terms of evolution, the individual will be motivated to provide energy for RMR. Hopkins et al (2023) explained: "While adipose tissue acts as an important energy reserve, it is quite plausible to propose that the purpose of the drive to eat is not to regulate body fat but to provide energy to meet the energetic demands of vital organs and to maintain life and growth. In achieving this goal, body weight will obviously be preserved but that is a consequence and not the primary target" (p4).

But, Hopkins et al (2023) continued: "The signals involved in sensing, integrating and translating the body's energy needs (arising from FFM) into eating behaviours are unknown" (p4). Whatever the signals, the idea that information is carried in the blood to the brain is accepted, as in the mid-20th century, but in a

more sophisticated way (Hopkins et al 2023).

Hopkins et al (2023) also accepted the complexity of the motivation to eat: "Although RMR may exert an effect on EI, the actual food consumed by an individual at any particular moment will be determined by a combination of FFM/RMR, FM and gastro-intestinal physiology, in addition to a wide range of sensory and cognitive variables, the nutritional composition of the foods and their accessibility, physical activity, time of day, environmental context and past history. Therefore, FFM/RMR alone cannot always predict the occurrence of an eating event nor what and how much is consumed. However, this explanation of the effect of energy demand can plausibly account for part of the individual variability between people in their drive to eat" (p5).

Hopkins et al (2023) applied these ideas to obesity: "During the development of obesity, as FM increases, FFM also increases with an inevitable increment in the drive to eat. At the same time, it can be deduced that the increase in FM will lead to a decrease in inhibition of appetite owing to the onset of leptin and insulin resistance. Consequently, as a person becomes fatter (and also accrues FFM) they will display a stronger drive to eat accompanied by a weakening inhibition, ie: a reduction in the strength of the signals that suppress eating. Therefore, people living with obesity do not receive any help from their increasing amounts of stored energy (as fat) to constrain their appetite. In fact the opposite is true; appetite self-control becomes more difficult" (pp6-7).

The theory of the role of FFM and RMR on appetite is known as the "Leeds Model" (based on the location of the researchers) (Hopkins et al 2023).

3.3. LEPTIN VS GRAVITY

Leptin appears key in homoeostasis after its discovery in mice in the 1990s (Zhang et al 1994). It is "a hormone produced in fat tissue and then released to the bloodstream in relation to fat mass to exert anti-obesity effects. Animals and humans that lack leptin become very obese, with severely increased food intake and also decreased energy expenditure" (Jansson et al 2023 p2).

It is a form of "off-switch" for energy intake, though the leptin system is more complex than just that. "Leptin seems to be the main homoeostatic regulator of body weight at the lower end of the body weight spectrum,

while the nature of the homoeostatic regulator at the upper end of the body weight spectrum is unclear. It is possible that the nature of the homoeostatic mechanisms regulating body weight at the upper end of the body weight spectrum is leptin-independent" (Jansson et al 2023 p2).

Jansson et al (2023) suggested that "there might be a homoeostatic system that uses gravity for regulation of body weight in land-living species, and we denoted it the gravitostat" (p2). Rodent studies that induce hypergravity lead to reduced body mass (Jansson et al 2023). One method used is to surgically implant weight capsules under the skin (eg: Jansson et al 2018).

A chance observation supported this idea with homing pigeons (Portugal and White 2021). Birds fitted with biologgers (in effect extra weight as in the weight capsules) had a compensatory reduction in body weight, while removal of the load produced increased body weight (Jansson et al 2023).

Jansson et al (2023) proposed two components to the gravitostat - sensor-independent and sensor-dependent mechanisms. The former involves increased energy consumption in relation to body weight when "working against gravity on land" (Jansson et al 2023 p2). The sensor-dependent component involves "sensing of the body weight by osteocytes in the weight-bearing bones, resulting in a feed-back regulation of global energy metabolism and body weight" (Jansson et al 2023 p3). These components register deviations in body weight outside the normal range.

Putting the ideas together, Jansson et al (2023) proposed the "dual hypothesis of body weight regulation", where leptin regulates the body at the lower end of the weight range, and the gravitostat at the top end.

3.4. OESTROGENS

Bardhi et al (2023) reviewed the evidence on oestrogens and the storing of fat, particularly by women. They stated: "Women store fat in a healthy way because they are programmed to gain weight 'healthfully' during pregnancy. Additionally, women need to mobilise stored fat and calories during breastfeeding to provide nutrition to their young" (Bardhi et al 2023 p1). Speakman (2018) emphasised the selective advantage of this process.

Oestrogens are hormones that not only control reproduction, but they act directly on the adipocyte (fat

cell), "as well as influence different regions of the brain providing a mechanism for neural communication to the fat tissue and different cells within adipose tissue" (Bardhi et al 2023 p1). Sex differences exist in adipose, or more specifically, white adipose tissue (WAT) [3], which is divided into sub-cutaneous adipose tissue (SAT) (located below the skin), and visceral adipose tissue (VAT) (inside the abdominal wall) (Bardhi et al 2023). "In general, females, have more SAT, typically creating a 'pear-shape' adipose tissue distribution, referred to as a gynoid body fat distribution... Males and post-menopausal women have a higher ratio of VAT to SAT creating an 'apple-shape' body habitus, also called android body fat distribution" (Bardhi et al 2023 p2).

In rodent studies, the surgical removal of ovaries (ovariectomy) increased overall adiposity, and VAT specifically (Bardhi et al 2023).

Oestrogens also influence the capacity of the adipocyte in terms of lipid - ie: making the fat cell more "expandable" (able to store more calories) (Bardhi et al 2023).

[3] Adipose tissue is divided into WAT, brown (BAT), and biege (BET) (Bardhi et al 2023). "The colour of the adipose tissue differs by the amount of lipid content within a lipid droplet. WAT has a large amount of stored lipid and few mitochondria. Contrarily, BAT has an increased number of mitochondria and a smaller amount of lipid stores when compared to WAT" (Bardhi et al 2023 p7).

4. EARLY LIFE

Twin and family studies suggest the heritability of BMI to be between 40% and 75%. "However interpretation of such studies are complicated by the complexities of accounting for shared fetal environment—70% of monozygotic twins share a placenta — and current environment (and the interaction of both with genotype). The incomplete explanation of BMI by genetics shows that there is a strong impact of the environment on obesity susceptibility" (Dearden and Ozanne 2023 p1).

Specifically, the early life environment (from conception to two years old), embodied by the "Developmental Origins of Health and Disease" (DOHaD). This approach was first observed in a link between reduced birth weight and cardio-metabolic disease in adulthood (Hales et al 1991). Subsequently, data on individuals in the womb during the "Dutch Hunger Winter" (1944-1945) (Schulz 2010) established a causative relationship between in utero under-nutrition and adult metabolic disease (Dearden and Ozanne 2023).

The DOHaD approach includes "the more common situation nowadays" (p2) of the mother being overweight or obese during pregnancy (eg: over 50% of mothers in developed countries) (Dearden and Ozanne 2023).

One means of study is of women who underwent gastric bypass surgery between pregnancies (eg: Smith et al 2009). Such studies "show children born from the pregnancy when the mother was lean have reduced adiposity and improvements in insulin sensitivity compared to their siblings who were born from a pregnancy when the mother had obesity" (Dearden and Ozanne 2023 p2).

Dearden and Ozanne (2023) reviewed the evidence on maternal obesity and the impact on the offspring. Three main areas of impact were distinguished:

i) Birth weight and adiposity - Maternal BMI and offspring birth weight is not a simple linear relationship as offspring of obese mothers can be both large for gestational age (LGA; birth weight greater than 4000 g) and small for gestational age (SGA; less than 2500 g). For the latter group, rapid post-natal catch-up growth is a risk factor for adult adiposity and obesity (eg: Widdowson et al 1962; rodent study).

ii) Food intake pathways in the brain - "Animal models have shown that a common cause of the increased body weight observed in offspring of obese mothers is hyperphagia, implicating altered regulation of food

intake as an underlying cause of obesity" (Dearden and Ozanne 2023 p3). The hypothalamus is the area of the brain that regulates food intake, and, put crudely, it is set too high. Again rodent studies have been undertaken, also showing other changes in the brain (eg: response to leptin; reward systems).

iii) Heart - Studies with animals have shown maternal obesity and impaired glucose tolerance during pregnancy causes problems in foetal heart development.

There is also evidence that genes inherited by the offspring may behave differently with obese mothers (due to epigenetics) (eg: Sharp et al 2015).

A public health solution to maternal obesity would be to ensure all mothers enter pregnancy with a healthy BMI through exercise and diet. Alternatively, intervening during pregnancy with pharmacological treatments. Limited successful evidence on both approaches (Dearden and Ozanne 2023).

5. PSYCHOLOGY

5.1. HIGHER COGNITIVE FUNCTION

One area of interest in terms of psychology is "higher cognitive functions" (HCFs), which are "mental processes that allow the organisation, control and flexible adaptation of behaviour. These functions include processes that come under the umbrella of executive function: inhibitory control, working memory and cognitive flexibility, as well as episodic memory (memory for specific personal events)" (Higgs 2023 p1). These are important because human eating behaviour is complex, and includes decisions about when and what to eat that are not related to biological drives for food.

"Flexible eating" refers to the decision to eat one food item (eg: cake) over another (eg: salad). Key is self-control (or will-power). The dual-process theories (eg: Hofmann et al 2009) propose that "enacting self-control relies on a reflective/flexible system in the brain that encodes long-term goals suppressing an impulsive/automatic system that encodes immediate rewards" (higgs 2023 p2). The dorso-lateral prefrontal cortex is a key area of the brain here, and repetitive transcranial magnetic stimulation of this area leads to increased intake of palatable foods (Higgs 2009).

An alternative to these inhibition-based ideas is value-based choice models (eg: Berkman et al 2017), which sees decisions as based on cost and benefit evaluation. Higgs (2023) used this example: "you decide to get a coffee with a friend and your friend takes a cake with their drink. In this situation you may forgo having the cake, not because you are resisting a temptation, but because in that moment the cake is not an attractive option. There may be several factors that weigh into this decision such as the fact that you have not long had your lunch, the cake is expensive, and it is not your favourite flavour" (p2).

Higgs (2023) explained that "food choices leading to weight gain would not be viewed as failures of self-control but merely the outcome of the process of integrating multiple factors that influence the attractiveness of the choice" (p2).

HCFs are involved in such decision-making, but these processes can be disrupted leading to biased choice (ie: not including all costs and benefits in an evaluation). For example, "delayed discounting", which undervalues the future in comparison to the now (eg: the pleasure of the cake now over the long-term health costs) (Higgs 2023).

HCFs may be disrupted by weight gain and obesity. Cross-sectional studies that compare individuals of different BMIs on the same cognitive tasks find poorer performance as an average by obese participants (Higgs 2023). For example, Cheke et al (2016) asked participants to recall the identity, location, and timing of objects hidden during a computer game. "Participants with obesity performed less well on spatial, temporal and item memory and made more errors when combining these elements into a 'what–where–when' memory. Other aspects of task performance were unaffected (eg: reaction time), which is consistent with the suggestion that obesity is associated with reduced higher cognitive function specifically rather than a general decline in ability to perform a task" (Higgs 2023 p2).

Differences in brain activity have been reported in neuroimaging studies. For example, participants with higher BMI have lower activity in some areas related to cognition and increased activity in reward processing areas (eg: meta-analysis of 29 studies; Parsons et al 2021).

Cross-sectional and neuroimaging studies do not provide evidence of causal direction (ie: differences in HCFs cause obesity). "In fact, it is possible that no causal relationship exists, and that the association is explained by a common third factor exerting an independent effect on both cognition and obesity. There could be causal pathway from cognition to obesity, but the cross-sectional association could equally be explained by the reverse causal pathway: an impact of adiposity on cognitive function. Indeed, there is evidence that prolonged consumption of a high fat diet, accumulation of excess adipose tissue and development of the metabolic syndrome is associated with reduced cognitive function via several mechanisms including oxidative stress, inflammation, insulin resistance and altered neurochemical signalling" (Higgs 2023 p3).

Longitudinal studies allow researchers to establish the direction of causality. For example, low inhibitory control in childhood and subsequent weight gain (eg: Anzman and Birch 2009). But there is evidence of a more complex relationship. "Indeed, there is evidence to support a reciprocal relationship from longitudinal studies whereby obesity predicts cognitive function which in turn predicts greater adiposity. For example, a study of a large cohort of children found that greater adiposity at the age of 9 predicted poorer working memory at the age of 10 but also that poorer working memory at the age of 10 predicted greater adiposity at the age of

15.5 [Shields et al 2021]" (Higgs 2023 p4). Other longitudinal studies have found an opposite relationship in children, and it depends when the study began (ie: "where measurement occurs after there has already been a chance for obesity to develop"; Higgs 2023 p4).

Another way to establish causality is via cognitive training interventions that lead to weight reductions. There are a limited number of studies that use digital based skills to improve specific cognitive functions. "The findings from two reviews suggest that cognitive training of working memory, episodic future thinking and food-specific inhibitory control, results in a decrease short-term food intake. However, at present there is not sufficient evidence to suggest that these effects are translated into a reduction body weight either in adults or children" (Higgs 2023 p4).

A further line of evidence is weight loss intervention and cognitive function. For example, one meta-analysis (Siervo et al 2011) found that weight loss was associated with improved attention and memory. "However, there is large variability across studies and the underlying mechanisms are unclear. Weight loss is associated with an improvement in metabolic indicators related to cognitive function but there are also changes in emotional functioning and mental health outcomes that accompany weight loss that could also explain improvements in cognition" (Higgs 2023 p5).

Finally, there are non-human animal experiments which control and manipulation of variables. For example, deliberately over-feeding of rats to produce obesity impairs memory performance (eg: Greenwood and Winocur 1990) (appendix B). "It is notable that the effects of diet on cognitive processes in non-human animal models are much more profound than the more subtle cognitive impairments associated with obesity in humans. Such differences in the magnitude of the effects in non-human relative to human animal models may reflect differences in the sensitivity of the measures of the processes, differences in the types of cognitive processes that are being assessed in the two species, and/or the magnitude of the exposure" (Higgs 2023 p5).

Higgs (2023) concluded that disruption to HCFs increases food intake, and that there is an association between high levels of adiposity and lower cognitive performance, but data on causality "have not yet established cognition as a primary cause of obesity in humans" (p6).

5.2. PSYCHOLOGICAL DISTRESS

"For much of human history, a large body size and heavier weight has been regarded as a symbol of affluence, prosperity and high social status, making it likely that obesity was associated with good mental and physical health" (Steptoe and Frank 2023 p1). However, today the negative physical health consequences of obesity are known. But what about mental health and heavier weight? The results of research "have not been entirely clear-cut, because while some studies find that obesity is associated with depression and anxiety, others argued that people living with obesity have notably good psychological well-being, coining the unfortunate term 'jolly fat' [Crisp and McGuinness 1976 [4]]" (Steptoe and Frank 2023 p1).

Steptoe and Frank (2023) outlined five relevant points in their review of the subject:

i) The correlation between high body weight and psychological state - Steptoe and Frank (2023) stated that "the overwhelming evidence is that greater body weight is correlated with heightened distress and depressive symptoms in high-income countries in the present day, although the pattern may be different historically and in lower income countries" (p2).

Six meta-analyses (eg: Frank et al 2022) covering over eighty studies (mostly in the West) have confirmed a relationship between obesity (measured in different ways) and depression, while some data (eg: Yu et al 2022) from South-East Asia found the opposite in older adults (Steptoe and Frank 2023).

ii) The direction of causation appears to be that higher body weight leads to increased psychological distress, "although distress associated with living with overweight and obesity may subsequently help maintain greater body weight" (Steptoe and Frank 2023 p2).

The direction of causation is established using longitudinal studies. For example, two meta-analyses of such studies (eg: Luppino et al 2010) show that higher body weight at baseline predicts future risk of depression (Steptoe and Frank 2023).

iii) The specific symptoms of depression with high

[4] Crisp and McGuinness (1976) surveyed over 700 middle-aged adults at a general practice in London. The measures of obesity and mental health were not standardised, however, and there was no adjustment for confounders like other health problems, and socio-demographic factors (Steptoe and Frank 2023).

body weight - For example, Frank et al's (2022) meta-analysis found that "in cross-sectional analyses, obesity status, but not overweight, was robustly associated with lack of energy, the anhedonia-related symptom little interest in doing things, feelings of inadequacy and feeling depressed. Notably, individuals living with obesity were two times more likely to experience three or four of these symptoms than to experience overall depression" (Steptoe and Frank 2023 p4).

iv) The mechanisms of the relationship - Emotional (eg: stigma and discrimination, especially for women), and biological (eg: hypothalamic-pituitary-adrenocortical (HPA) axis dysregulation; systemic inflammation).

v) The relevance to weight management programmes - "It has sometimes been argued (implicitly or even explicitly) that negative attitudes to adiposity will somehow shame individuals with high body weight into making greater efforts to regulate food intake and increase physical activity, so should be encouraged. However, any such marginal benefit of 'fat shaming' must be set against the strong evidence for adverse effects on psychological well-being. Far from promoting weight loss, such attitudes may lead to weight gain" (Steptoe and Frank 2023 p7).

6. ENVIRONMENT EXTERNAL TO THE BODY

An "obesogenic environment" refers to aspects of the external world to the body (including the physical, social and food environment) that "influence the production of obesity" (Ulijaszek 2023 p2) (ie: the input (food eaten) and output (physical activity)) [5].

i) The built environment, which is "distinguished from the natural environment by its human-made materiality — its vehicular and pedestrian infra-structure, its buildings, its public places — as well as being the locale of domestic life, work and leisure" (Ulijaszek 2023 p2).

For example, compact urban conurbations in the USA have lower rates of obesity than sprawling ones, "mostly due to differences in walkability and other possibilities for engaging in physical activity" (Ulijaszek 2023 p3). Likewise for polycentric urban conurbations with "multiple independent centres with similar degrees of importance" (Ulijaszek 2023 p3) (eg: Yang and Zhou 2020).

ii) The food environment includes the physical proximity of food stores, the number of stores, and food services (eg: fast-food outlets), as well as food advertising (specific to particular foods, and generally).

Ulijaszek (2023) pointed out: "Sensory cues that can stimulate people to over-eat in the built environment, including ubiquitous exposure to food and the omnipresence of food advertising, are also important, but usually not considered by epidemiologists" (p3).

iii) The social environment - eg: social interactions and networks; social media and online activity.

"Obesity travels through social networks, and social media promote its travel. Three inter-related processes are viewed to drive this process: social contagion (whereby the network in which a person is embedded influences their weight or weight-influencing behaviours); social capital (whereby a sense of belonging and of having social support influences weight or weight influencing behaviours); and social selection (whereby a person's network might develop according to their

[5] The term "Global Syndemic" (Swinburn et al 2019) has been used to describe the epidemics of obesity, under-nutrition, and climate change, which is "affecting most people across the world now, co-occurring in time and place with complex outcomes and sharing common underlying societal drivers" (Ulijaszek 2023 p1).

weight)" (Ulijaszek 2023 pp4-5).

The three aspects of environment interact, and are mediated be factors like socio-economic status, and life stressors. Also the aspects are changing in influence - for example, the issue of walking or driving to get food is being replaced by home delivery, which is promoted by social media.

High-energy dense food only increases body weight if there is no compensation (ie: smaller meal sizes or volumes). Short-to-medium term laboratory studies (two weeks - several months) suggest no compensation, whereas real-world food diary studies find some compensation (Stubbs et al 2023). But there needs to be caution around self reports of diets as in the latter studies, while many controlled studies involve the situation where "the diet is manipulated in a way that subjects can only change the quantity consumed while the composition of the foods remains fixed" (Stubbs et al 2023 p6).

6.1. FOOD ADDITIVES

Corkey (2023) commented: "World-wide obesity has nearly tripled since 1975, according to the World Health Organisation. This is unlikely to be caused by genetic changes since they do not occur on such a short time scale. Furthermore, a recent study found that average body weights have risen among primates and rodents living in research environments, as well as among domestic dogs and cats. Thus, animals that share our environment are also becoming obese" (p1). This author argued, therefore, the focus must be upon changes in the environment in the last fifty years. She proposed food additives (as in ultra-processed food; UPF; appendix C), which have produced false information in the body about energy stores.

Individual cells in the body maintain energy balance, and reactive oxygen species (ROS) are "produced as signals in response to fuel excess" (Corkey 2023 p1). Corkey (2023) hypothesised that food additives generate false and misleading signals here. "Such misleading signals of fuel excess stimulate insulin secretion and lipid storage, inappropriately. This would transiently lower blood glucose, thereby inducing hunger, followed by food consumption, insulin secretion and increased fat storage" (Corkey 2023 pp1-2).

Corkey (2023) summed up her view: "It is unlikely

that macro-nutrients such as carbohydrates or fats cause obesity since these have long been constituents of the human diet. High carbohydrate diets have been common in warm to moderate climates where agriculture thrives, and high fat diets have been consumed in cold climates where dairy is a major source of nutrients. Furthermore, food consumption and body weight have been stable and well-regulated in all species until recent times. In addition, the notion that increased saturated fat or red meat consumption could cause obesity is inconsistent with the most recent public health data since consumption of these foods has decreased. The increasing incidence of obesity correlates with increasing consumption of UPF along with thousands of potential environmental toxins including some derived from fertilisers, insecticides, plastics and air pollutants" (p5).

7. MISCELLANEOUS - PEOPLE LIVING WITH HIV

As obesity is increasing globally, so is the case with people living with HIV (PWH). For example, in the "US Military HIV Natural History Study" (Crum-Cianflone et al 2010), 25% of PWH at the point of diagnosis were classed as overweight and 3% as obese in the late 1980s compared to 41% and 12% respectively a decade later. This sample was over 90% male. Nearly two-thirds of PWH gained weight after diagnosis. Anti-retroviral therapy (ART), the main treatment for HIV, has the side effect of weight gain, though this varies depending upon the type of ART (Talathi et al 2024). "Weight gain is also apparent among women switching ART regimen" (Millman et al 2024 p31).

While in a mostly female cohort in northern Tanzania (Hertz et al 2022), for instance, one-fifth of the PWH were obese (Talathi et al 2024). Table 1 gives some examples of obesity prevalence among women with HIV.

Particular risk of obesity is associated with being female [6], older, and having longer duration of ART (and being Black in the USA). Studies also show that "analogous to the general population, vulnerable patient populations living with HIV, such as uninsured minorities, female minorities, and food insecure individuals, may be at especially high risk for obesity" (Talathi et al 2024 p4).

STUDY	DETAILS
"Positive Transitions through the Menopause" (PRIME) Study (Ashraf et al 2022)	UK; 396 women aged 45-60 years; 32.1% overweight and 40.2% obesity (based on body mass index)
"North American AIDS Cohort Collaboration on Research and Design" (NA-ACCORD) (Koethe et al 2016)	3 years of ART; 21% of overweight non-White females at treatment initiation became obese
South Africa (Hanley et al 2021)	Two-thirds of 372 women on ART for at least one year were overweight
Ethiopia (Abebe et al 2023)	15 683 women with HIV; 29% living in urban areas classed as overweight compared to 3% in rural areas

Table 1 - Four studies from different parts of the world on women with HIV and obesity.

"Obesity among PWH is also associated with adverse

[6] Two additional considerations for women living with HIV are the menopause, and pregnancy, which can impact weight (Millman et al 2024).

complications" (Talathi et al 2024 p4) (eg: type 2 diabetes; hypertension; high cholesterol). This is also manifest in lower health-related quality of life (eg: "US National Health and Wellness Survey"; Ken-Opurum et al 2023).

8. CONCLUSIONS

Heeran et al (2023) talked of the "multi-faceted nature" of obesity with complex interactions between causal drivers. Nearly one hundred potential contributors to excess energy storage have been reported, and these can be divided into two levels - individual, and environmental. "Individual-level contributors refer to those occurring within a person and range from examples such as genetic and epigenetic variability, metabolic and physiological conditions such as chronic inflammation, disturbances to the gut microbiome, mood disorders and endocrine dysregulation (eg: thyroid dysfunction, polycystic ovarian syndrome and Cushing's syndrome). Environmental-level determinants refer to those originating outside the body and range from food insecurity, disproportionate access to and affordability of energy dense foods and the vast food environment (which dates back to the 1970s), the obesogenic built environment, socio-economic status or weight bias and stigma" (Heeran et al 2023 p2).

Put simply: "Physiology can drive behaviour; however, it is critical to recognise that the manifestation of that behaviour is limited by an individual's available options — the decisions that people make are based on the choices that they have" (Heeran et al 2023 p2).

Based on this position, Heeran et al (2023) ended with this conclusion: "To address the high prevalence of obesity the following actions are required: (i) enhance access to affordable evidence-based medical interventions (eg: anti-obesity medications and metabolic and bariatric surgery) and lifestyle modification programmes (eg: dietary, physical activity, sleep and stress management), and (ii) investigate effective environmental changes (eg: food environment; socioeconomic support to minimise psycho-social stress) to address determinants of obesity and to support existing treatment modalities. One way to implement these requirements is through a layered, approach adapted from targeted universalism which sets universal goals that benefit the health of all individuals within a population, with tailored approaches to meet the needs of broadly defined sub-groups based on, for example, demographics, socio-economic status and weight status" (p6).

Raubenheimer and Simpson (2023) took a similar position as Heeran et al (2023), and commented that a problem is the "tendency to regard existing perspectives

on obesity as separate, unrelated or even competing explanations, rather than potentially inter-related co-contributors to the problem in a complex ecosystem of interacting biological, behavioural, cultural and societal factors" (p1). They argued for more integrated perspectives.

"For example, it is equally true that obesity is 'caused' by energy imbalance and the aggressive marketing of ultra-processed foods (UPF) and it would be futile to argue that one or the other is 'responsible'. However, it would not be futile to consider which cause is most relevant to the rise of the obesity epidemic, or to inter-individual variation in susceptibility to obesity" (Raubenheimer and Simpson 2023 p2).

Central to their "nutritional ecology framework" is "protein leverage" (Simpson and Raubenheimer 2005), "in which the strong human appetite for protein drives increased intake when dietary protein is diluted" (Raubenheimer and Simpson 2023 p2). If a diet is low in protein, there is a motivation to increase intake, and if this increased intake includes fat and carbohydrate with the protein, obesity is the result, put simply.

Zoh et al (2023) focused on the idea of causation itself in science generally, and specifically in relation to obesity. Concerning the latter, many different terms have been used in the literature, including "major cause", "primary cause", "principal cause", "more important cause", and "predominant cause", all of which Zoh et al (2023) did not know the precise meaning (nor did the users of the terms it was suggested): "How then can we evaluate whether, in fact, any research questions or hypotheses involving those terms have been answered or answered adequately?" (p2).

Zoh et al (2023) further observed: "Too often, our thinking about causes is cluttered with glossing, smoothing over, or transitioning from one thing to another without much clarity in the approach. For example, when thinking about the cause of obesity, are we asking what the cause of the secular increase in obesity is? Does this cause the obesity pandemic? Could this have contributed to the obesity epidemic? Equivalently, research findings are often presented as 'in the population, people who do more of this have less of that' or 'this gene seems to be associated with that trait/phenotype within the population'. Nevertheless, the question remains: why does one person (or some people) become obese and others remain lean? Also, do those questions tell us necessarily what caused the obesity

pandemic or the secular increase in obesity or what change occurs when people consume a particular diet or take a specific drug or treatment? There are yet other questions one could ask" (p2).

Any causal model involves assumptions about the world, and the method used to provide supporting data will have methodological issues, like randomisation, and controls. Other issues include whether to average a number of outcomes or not, how to interpret the effect size/significance level, and the generalising of the findings to other situations than the original research environment (Zoh et al 2023).

Zoh et al (2023) ended with a general and a specific point. Firstly, the general point: "In science, there is both deductive reasoning about cause and inductive reasoning. The latter generally refers to drawing inferences from empirical observations. A problem with induction is, as the philosophers of science say, that the data underdetermine the hypotheses or theories. In other words, for any given set of data, there can be more than one hypothesis or theory that may be consistent with the data. Therefore, it is generally accepted that no single explanation can be unequivocally proven to be the only explanation consistent with a set of evidence. How, then, does one decide among competing explanations? In the long run, one tries to prove some of them, or as Feynman& and Sackett [1985] put it, oneself, wrong. This is very much in the spirit of Popper's falsificationism, although most modern philosophers of science no longer find Popper's framework useful or de rigueur. However, until some explanations can be ruled out, competing explanations can be compared in numerous ways" (Zoh et al 2023 p12).

The specific point was that "too much research around obesity does not use the best design, measurement, or analytic and interpretive techniques to test and estimate causal effects optimally and to report on what we know separately from what we conjecture in straightforward, objective, transparent and honest ways" (Zoh et al 2023 p13).

The conclusion that can be drawn from Zoh et al's (2023) discussion, which may be positive or negative depending how you look at it, is that there is no simple (single) cause of obesity.

9. APPENDICES

APPENDIX A - ENERGY AVAILABILITY CHANGES

Halsey et al (2023) presented the hypothetical scenario of identical twins Jill and Jane who want to lose weight. Jill reduces her intake (dieting), while Jane increases her exercise by the same reduction in energy availability. "However, the physiological challenges presented to the body as a result of dieting versus being active are by no means entirely the same. Thus, the following question arises as to whether the physiological response to the disruption of energy balance is truly independent of whether an energy deficit of the same magnitude is created by dietary restriction or by increased activity" (Halsey et al 2023 p1).

These researchers reviewed the evidence. The first point to note is that the body compensates for a larger gap between energy in and out. "This compensation could occur in the form of behavioural adaptations, such as reductions in non-exercise activity (eg: walking, pottering, fidgeting), or in the form of metabolic adaptations, ie: a reduction in basal energy requirements measured at the cellular level. Mechanisms that could underlie putative metabolic adaptations include improved energy efficiency, and down-regulation of energy-expensive processes such as immune defence, the sympathetic nervous system, reproduction, growth, maintenance of body core temperature and the function of vital organs such as the heart and kidneys" (Halsey et al 2023 p2). The evidence comes from three main sources - experiments with humans, and non-humans (table 2), and real-life situations (eg: patients with anorexia nervosa).

Firstly, metabolic adaptation to reduced calorie intake. Resting metabolic rate (RMR) change is a key measure. Both methods of human study show reductions in RMR as the sign of metabolic adaptation, while animal experiments suggest a reduction in organ size (Halsey et al 2023).

In terms of metabolic adaptation in response to increased exercise, Halsey et al (2023), combining the data from eleven studies, found some reduction in RMR. But there were methodological issues with estimates of RMR changes after exercising (eg: resistance training exercise "likely result in gains in muscle mass, which may obscure the depletion of body energy stores..."; Halsey et al 2023 p3). There were studies showing no

evidence of metabolic adaptation also (Halsey et al 2023).

Halsey et al (2023) summed up: "In terms of the effect on whole-body energy expenditure, the available data suggest that a calorie deficit is a calorie deficit; that is, regardless of how that deficit is induced, the greater the decrease in weight the greater the decrease in RMR, and the more likely are metabolic adaptations. However, the analysis of studies involving an exercise intervention is limited, first because the nominal energy deficit created by exercise is often rather small and second because unless food intake is restricted the deficit is attenuated by a compensatory increase in energy intake" (p7).

In trying to quantify the change the "absolute magnitude of these metabolic adaptations — even as a result of a chronically low energy availability — appears modest at well below 100 kcal per day" (Halsey et al 2023 p7).

Returning to the hypothetical scenario of Jill and Jane, Halsey et al (2023) stated: "While both of them will likely present with similar, small differences in metabolic adaptation and similar systemic endocrine responses, Jill will possibly see a reduction of her skeletal muscle mass and strength, while Jane will become leaner, preserve or increase her skeletal muscle mass and improve her strength and cardio-respiratory capacity" (p8).

- Humans with parasitic worm infections show lower rates of certain diseases, specifically metabolic disease (Cortes-Selva et al 2021). It seems that the parasite can modify the immune system (Wade 2023).
- Cortes-Selva et al (2021) infected ten male mice with a water-borne parasite in a ten-week study. The immune cells showed changes that protected against obesity, type 2 diabetes, and heart disease.
- "Mammals immune systems have evolved in the presence of these worms... and there is an advantage for worms if their hosts are healthier" (Wade 2023 p10). But there was no effect for female mice (Wade 2023).

Table 2 - Parasitic Worm Infection.

APPENDIX B - OVER-FEEDING STUDIES

Homoeostasis is seen both in under- and over-

feeding. In the latter case, experiments have been performed with humans and non-humans.

With humans, "voluntary over-feeding" or "conscious over-feeding" has varied from single energy-rich meals to months of up to 50% caloric surplus, while animal studies are "involuntary and executed via controlled intra-gastric nutrient infusion or forced gavage of food" (Lund and Clemmensen 2023 p2).

There is variability in the weight gained with the extra calories, and in the subsequent weight loss when over-feeding ceases. The weight gain in human studies range from 1.4 kg to 15 kg, and 60-70% increase in body fat mass and 30-40% in lean mass (Lund and Clemmensen 2023). In one example (Bouchard et al 1990), twelve identical twins underwent a 100 days of over-feeding with the weight gained ranging from 4.3 kg to 13.3 kg, and "the majority of this variation was attributed to genetic factors" (Lund and Clemmensen 2023 p2).

Mice and rats on 150% over-feeding (ie: 1.5 times more intake) for a few weeks gain 20-40% of body weight, and "the weight gain variability is much less than in the human studies. The homogeneous over-feeding-induced weight gain in rodents is likely the result of eg: low genetic variability (inbreeding), single-housing of animals in a highly controlled environment, and the experimental conditions in which the intra-gastric infusion of liquid food through a tube not only enables high-energetic over-feeding accuracy, but likely also minimises variation in spontaneous physical activity between animals" (Lund and Clemmensen 2023 p2).

There is less research on the weight recovery after human over-feeding experiments. "Most studies have focused on the weight gain that occurs during the over-feeding period [Bray and Bouchard 2020]. This might reflect that it is challenging to quantify energy intake once subjects are released to ad libitum eating in the recovery phase. Nonetheless, the available data in human studies point to a relatively rapid initial weight loss. For some individuals, the entire weight gain is lost within weeks of stopping the over-feeding, yet for others, the initial rapid weight loss seems to be followed by a more slow and gradual return towards the pre-over-feeding body weight. While some people seem to fully recover their body weight within a few months, others fail to do so" (Lund and Clemmensen 2023 pp2-3).

Lund and Clemmensen (2023) considered three questions in relation to a "physiological defence mechanism against weight gain" (p3):

i) Does over-feeding lower appetite?

Rats, for example, show a short term of suppression of food intake straight after over-feeding ceases (eg: for two weeks after three months of 200% over-feeding). Similar results have been noted in dogs and rhesus monkeys (Lund and Clemmensen 2023).

In the case of humans, one study found suppressed appetite after three weeks of over-feeding, while another study saw a return to baseline intake after two weeks of over-feeding (Lund and Clemmensen 2023).

ii) Is weight gain counteracted by adaptive thermogenesis?

This is the idea that the body increases the resting metabolic rate and so uses increased energy. In part due to problems in measuring the resting metabolic rate, "whether an adaptive increase in energy expenditure that is greater than what is gauged from a larger body mass (so-called 'Luxuskonsumption') contributes to offset overfeeding-induced weight gain remains uncertain" (Lund and Clemmensen 2023 p4).

Another problem is distinguishing between "diet-induced thermogenesis" (DIT), and "non-exercise activity thermogenesis" (NEAT). "While DIT refers to an increase in energy expenditure above basal metabolic rate after a test meal, NEAT refers to the energy expenditure that is derived from both unconscious movements, such as fidgeting and other restless behaviours and 'spontaneous' physical activity outside of formal exercise programmes, such as walking and standing" (Lund and Clemmensen 2023 p4). DIT is influenced by factors like the greater energetic cost of ingesting protein than carbohydrate or fat (Lund and Clemmensen 2023) [7].

"Parallel to the human literature, animal studies are also relatively inconclusive when it comes to over-feeding-induced effects on energy expenditure" (Lund and Clemmensen 2023 p4).

iii) What about energy excretion?

As well as energy intake and expenditure, there is energy lost through excretion (eg: macro-nutrients in faeces). Figures vary from 1% to 11% of ingested energy

[7] The idea that "a calorie is a calorie is a calorie" has been challenged. For example, in the case of drinking orange juice or eating an orange, the former with lead to the absorption of the sugar as no digestion is involved while the latter requires energy to digest the fibre and extract the sugar. "Physiologically, your body does completely different things with it, with exactly the same calorie hit" (Giles Yeo quoted in de Lange 2023).

Simple measures of calories as in food labelling is also challenged by changes due to cooking, and how much nutrition the body can extract (eg: 70% of a protein calorie). Add to this individual differences in digestion (de Lange 2023).

in faeces, while in one study, the variation between individuals was 80 to 500 kcals per day (Lund and Clemmensen 2023).

The idea of homoeostasis for weight gain fits with the "set-point theory" or the "dual intervention point model". The latter suggests the body maintains a weight range rather than a specific weight of the former theory (Lund and Clemmensen 2023).

What about the mechanisms for maintaining the weight point or range? Hormones, like leptin, are a key candidate, but also sympathetic nervous system activity (eg: non-shivering thermogenesis), and genetic variations play a role (Lund and Clemmensen 2023).

B.1. Brown Adipose Tissue

BAT keeps mammals warm by using energy from food or stored in the body. "If this occurs under conditions where the heat is not needed for thermoregulatory purposes, we have a situation of 'diet-induced thermogenesis'. This was principally what was formulated by Rothwell and Stock in 1979, including that this thermogenesis probably originated in brown adipose tissue. Thus, diet-induced thermogenesis would protect against obesity" (Nedergaard et al 2023 p1). But if the process was less effective, it would lead to obesity.

Much of the research involves mice and genetic modification (eg: UCP1 gene) [8]. Nedergaard et al (2023) commented that "there is reason to assume that the phenomenon of diet-induced thermogenesis can be observed in mice under certain conditions, that it then is mediated via UCP1, and that a genetic reduction of UCP1 may promote obesity in mice" (pp7-8) (table 3). There is inconsistent evidence of the UCP1 gene in genome-wide association studies of humans (Nedergaard et al 2023).

Human studies tend to find correlations between BAT and obesity through analysis of fluro-deoxyglucose positron emission tomography (PET) scans, for instance, which measure (radioactive) glucose uptake into tissues. Nedergaard et al (2023) described two main problems with this method. Firstly, "the radioactive glucose will, particularly after a meal, also be taken up into the muscles, and this disturbs the interpretation" (Nedergaard et al 2023 p8). Secondly, the interaction

[8] The "Uncoupling Protein 1" gene is involved in the oxidation of fat to produce energy in cells (https://www.sciencedirect.com/topics/medicine-and-dentistry/uncoupling-protein-1; accessed 8th January 2024).

between obese and glucose uptake. "There is good reason to think that the glucose uptake observed during PET scans is mediated to a large extent by insulin stimulation. This means that insulin resistance caused by the obesity may lead to lower glucose uptake into brown adipose tissue, and this will thus create a false negative correlation between brown adipose tissue activity and obesity" (Nedergaard et al 2023 p9).

Nedergaard et al (2023) concluded, tentatively, that "meal-induced brown-fat-derived thermogenesis does seem to occur in humans, and its presence and absence could therefore — everything else being equal — affect the propensity to obesity in humans. The total thermogenesis from brown adipose tissue in adult man has been estimated to correspond to a change in bodyweight of somewhere from about 1 (most estimates) up to 10 kg per year. Thus, brown adipose tissue may, even in humans, to some extent protect us against obesity, and a reduced brown adipose tissue activity may — again everything else being equal — aggravate the development of obesity in humans" (p9).

- Duration of experiment - standard is 12 weeks
- Age of mice - eg: "young adults"
- Ambient temperature - normally around 30 °C
- Microbiota
- Prehistory of mice - ie: early experiences before experiment
- Strain of mice - eg: inbred C57BL/6 strain

Table 3 - Variables in mice experiments which could influence findings (Nedergaard et al 2023).

APPENDIX C - ULTRA-PROCESSED FOOD

"Producing enough food has challenged humans for millennia" (Hall et al 2023 p1). Yet today the issue is that "more people around the world now have obesity than suffer from hunger" (Hall et al 2023 p1). Technological developments in agriculture, and "food science" in the last approximate 300 years (in the West) has increased food production, and specifically processed foods (and then UPFs).

Monteiro et al (2010) introduced a food classification system called "NOVA" based on the amount of processing (Hall et al 2023):

- Category 1 - unprocessed or minimally processed foods that have been washed, frozen, or dried, for

example.

- Category 2 - food processed with culinary ingredients like sugar, and salt.

- Category 3 - Combinations of categories 1 and 2 to increase preservation and/or palatability.

- Category 4 - "ultra-processed foods". They can be defined as "industrial formulations manufactured by deconstructing foods into their component parts, modifying them and recombining them with a myriad of additives and little, if any, whole foods. Importantly, ultra-processed foods are distinct not only in terms of their ingredient composition but also in terms of the purpose for which they are produced. The purpose underlying the manufacture of ultra-processed foods is to create convenient (durable, ready-to-consume), tasteful (often hyper-palatable) and highly profitable (cheap ingredients, value adding) products that are liable to displace all other NOVA food groups" (Scrinis and Monteiro 2022 quoted in Hall et al 2023).

UPFs are new to the food environment in recent years, and their role in obesity is linked to their high energy density, and high palatability. Hall et al (2019), in a controlled study, found that "a diet high in ultra-processed foods caused an increase in ad libitum energy intake of approximately 500 kcal [per day] and weight gain in adults as compared to an unprocessed diet matched for overall presented calories, carbohydrate, sugar, fat, sodium, energy density, glycaemic load and fibre that resulted in spontaneous weight loss" (Hall et al 2023 p3).

Two other potential mechanisms of UPFs leading to obesity are (i) highly processed carbohydrates in the food that causes the rapid increase in glucose followed by a rapid decline and feelings of hunger, or (ii) the low protein content which the body compensates for with increased intake (Hall et al 2023).

C.1. Food Addiction

"Food addiction" is a developing concept in the 21st century. The "Yale Food Addiction Scale" (YFAS) (Gearhardt et al 2016) was created to measure it using eleven symptoms of substance use disorder (eg: cravings;

withdrawal) (Gearhardt et al 2023). Using the YFAS, recent reviews (eg: Praxedes et al 2022) estimate a prevalence of 14% of adults and 12% of children with food addiction.

"Not all foods have addictive potential. The YFAS asks people to report on intake of foods with high levels of refined carbohydrates or added fats, such as sweets and salty snacks. These types of foods are most strongly implicated in the behavioural indicators of addiction, such as excessive intake, loss of control over consumption, intense cravings, and continued use despite negative consequences" (Gearhardt et al 2023 p1). UPFs contain these ingredients in larger amounts. "The combination of refined carbohydrates and fats often found in UPFs seems to have a supra-additive effect on brain reward systems, above either macro-nutrient alone, which may increase the addictive potential of these foods" (Gearhardt et al 2023 p1). UPFs also include additives which enhance the potential for addiction.

Gearhardt et al (2023) argued for "UPF addiction" as a sub-category of food addiction: "UPF addiction is not currently an official diagnosis, but such recognition would be likely to promote research into its clinical management" (p3).

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