 doi:10.20944/preprints202208.0309.v9

Review

Chronic Positive Mass Balance is the Actual Etiology of Obesity: A Living Review

Anssi H Manninen

Anssi H Manninen, Research & Development, Dominus Nutrition Oy, Ylipääntie 438, FIN-92220, Raahe, Finland
* Correspondence: anssi@dominusnutrition.fi

Abstract

According to known laws of physics, chronic positive mass balance is the actual etiology of obesity, not positive energy balance. The relevant physical law in terms of body mass regulation is the Law of Conservation of Mass, not the Law of Conservation of Energy. A recently proposed mass balance model (MBM) describes the temporal evolution of body weight and body composition under a wide variety of feeding experiments, and it seems to provide a highly accurate description of the very best experimental human feeding data. By shifting to a mass balance paradigm of obesity, a deeper understanding of this disease may follow in the near future. The purpose of this living review is to present the core issues of the upcoming paradigm shift as well as some practical applications related to the topic.

Keywords: obesity; body weight regulation; macronutrients; energy balance theory; mass balance model; paradigm shift; living review

Introduction

"*People are able to break any laws made by humans, but none made by physics.*" – Elon Musk

Recently, Arencibia-Albite published an exceptionally clever article entitled "The energy balance theory is an inconsistent paradigm" in the *Journal of Theoretical Biology* [1]. My own article deals with exactly the same topic, but focuses on *practical applications*. So, the purpose is to explain in plain language what this far-reaching paradigm shift

 doi:10.20944/preprints202208.0309.v9

will mean on a practical level. Therefore, in this article you will not find complex equations and formulas; rather, I have tried to summarize the core issues in such a way that every university-educated healthcare professional or natural scientist can reasonably understand them.

Since the upcoming paradigm shift has started to gather interest in the scientific community, I just changed the format of my article to a living review [18], and I will update this article as soon as there is a need. All feedback is gratefully received.

The energy balance theory is a flawed paradigm

It is widely assumed that the fundamental cause of obesity is an energy imbalance between calories consumed and calories expended (i.e., the energy balance theory; EBT: ”Calories In, Calories Out”). According to known laws of physics, however, this century-old obesity paradigm must be fallacious. **The relevant physical law in terms of body mass regulation is the Law of Conservation of Mass, not the Law of Conservation of Energy (i.e., the First Law of Thermodynamics).**

This is not a matter of opinion; rather, it is based on *exact* natural sciences. If matter (mass) can be exchanged between system and surroundings, then the system is an *open* one. So, all living organisms are open systems and such systems can be at mass balance while the system experiences a persistent energy imbalance. That is, energy balance may be positive ($\Delta E > 0$) or negative ($\Delta E < 0$) yet the *mass* change that may occur during energy flux is not required by the Law of Conservation of Energy to mirror the energy balance *direction* [1]. In practice, this means that an energy imbalance does not always lead to a change in body mass. It leads to a change in the body's mass only in the situation when one is simultaneously in a mass imbalance. *Body mass decreases in negative mass balance and increases in positive mass balance.*

Since there are widespread misconceptions about thermodynamics and body mass regulation, a brief recap follows.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 September 2022 doi:10.20944/preprints202208.0309.v9

OPEN SYSTEM: This is a type of thermodynamic system where the **energy and mass** can be exchanged with its surroundings. Consequently, the mass of the system will vary with time. An example is the human body.

CLOSED SYSTEM: This is a type of thermodynamic system where **only the energy** can be exchanged with its surroundings but not mass. Consequently, the mass of the system is constant. An example is the refrigerator.

The EBT falsely assumes that there is no difference between the two thermodynamic systems. It is important to understand that, contrary to what is often claimed, the EBT is not a consequence of the First Law of Thermodynamics.

The Law of Conservation of Mass

The Law of Conservation of Mass states that the mass can neither be created nor destroyed by chemical or physical changes. In other words, *total mass is always conserved*. This law dates from Antoine Lavoisier's 1789 discovery *par excellence* that **mass is neither created nor destroyed in any chemical reaction** [2]. Clever Frenchman heated mercuric oxide (HgO) and demonstrated that the amount the chemical's mass decreased was equal to the mass of the oxygen gas released in the chemical reaction. Lavoisier proved that mass must be conserved in chemical reactions, meaning the total amount of mass on each side of a chemical equation is always the same. That is, **the total number of atoms in the reactants must equal the amount in the products**, regardless of the nature of the chemical change. This forms the basis of *stoichiometry*, i.e., the accounting process by which chemical reactions and equations are mathematically balanced in terms of both mass and number of atoms on each side.

As an example, the oxidation of one generic triglyceride molecule:

$C_{55}H_{104}O + 78O_2 \rightarrow 55CO_2 + 52H_2O$ + HEAT 8,084 kcal

Reactants:		*Products:*	
$C_{55}H_{104}O$	860 g	$55CO_2$	2,420 g
$78O_2$	2,496 g	$52H_2O$	936 g

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 September 2022 doi:10.20944/preprints202208.0309.v9

+ _____ + _____

3,356 g 3,356 g

Note that there is mass only in reactants and products, but not in energy (calories).

The mass-energy equivalence principle

The mass-energy equivalence principle implies that when energy is lost in chemical reactions, the system will also lose a corresponding amount of mass. As far as the regulation of body mass is concerned, however, this equivalence principle has been misunderstood. This **global misconception** requires a detailed clarification.

Here is a very good question from one of my colleagues:

"How is energy intake and expenditure not the governing factors that determines if the body store the food we eat as fat or not? How could one change that? How can the mass of the food change that? If the eventual weight loss is from water, urea, or whatever [it] is still determined by if the body replace it or not, or even store more than was used. **Where is the gap where energy expenditure is not representative of substrate [i.e., mass] being used?**"

In order to see why nutrient mass, not nutritional energy, is the quantity that determines body mass fluctuations one has to unavoidably think in terms of arithmetic and analytical chemistry as shown next. The caloric values of macronutrients are rounded.

Weight gain is the result of mass accumulation, not the result of energy accumulation

Consider two individuals that gain 1 kg of non-water body mass as they accumulate within body cells 1000 g of absorbed macronutrients. The macronutrient distribution of the first subject is as follows:

- 200 g of protein = 200 g x 4 kcal/g = 800 kcal
- 300 g of carbohydrate = 300 g x 4 kcal/g = 1200 kcal
- 500 g of fat = 500 g x 9 kcal/g = 4500 kcal

 doi:10.20944/preprints202208.0309.v9

Thus, the total stored nutritional energy is 800 kcal + 1200 kcal + 4500 kcal = 6500 kcal.

Suppose, next, that the macronutrient distribution of the second subject is as follows:

- 400 g of protein = 400 g x 4 kcal/g =1600 kcal
- 400 g of carbohydrate = 400 g x 4 kcal/g =1600 kcal
- 200 g of fat = 200g x 9 kcal/g =1800 kcal

Thus, the total stored nutritional energy is 1600 kcal + 1600 kcal + 1800 kcal = 5000 kcal.

This example illustrates, therefore, that the property of food related to mass gain is its mass, not energy. The first subject, in effect, has accumulated substantially more nutritional energy than the second one yet both have experienced the same degree of weight gain.

Weight loss is the result of mass elimination, not the result of energy expenditure

Consider the oxidation of 100 g of glucose:

- $C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2 + HEAT$ (720 kcal/mol of $C_6H_{12}O_6$)

This requires the uptake of 107 g of O_2 as 100 g $C_6H_{12}O_6$ x (192 g O_2/180 g $C_6H_{12}O_6$) ≈ 107 g O_2. The Law of Conservation of Mass implies that mass of the products = mass of the reactants. The amount of water and carbon dioxide formed is 207 g as mass of the products = mass of the reactants = 100 g $C_6H_{12}O_6$ + 107 g O_2 = 207 g.

Now, assume that all the produced water and carbon dioxide are used in the following way:

1. Water becomes intracellular water in newborn cells

2. Hydrolysis reactions (i.e., the cleavage of a chemical bond by adding a water molecule which becomes part of the reaction products): for example, the release of thyroid hormones thyroxine (T4) and triiodothyronine (T3) requires a hydrolysis reaction.

 doi:10.20944/preprints202208.0309.v9

3. Carboxylation reactions (i.e., the addition of carbon dioxide to a molecule): for example, carboxylation of acetyl-CoA during fatty acid synthesis.

Notice that in the aforementioned situation 400 kcal has been expended by oxidizing 100 g of glucose yet body mass will not decrease when heat is dissipated but when the 207 g of reaction products are eliminated which in the described case are not since, as illustrated, oxidation products become part of the body mass.

The central message of this section is that energy balance and mass balance are separate balances in the human body.

Energy balance cannot occur at body mass stability

The Law of Conservation of Mass guarantees that body mass stability (i.e., mass balance) can occur ONLY when the mean absorbed mass of each macronutrient equals its respective mean oxidized mass. Otherwise, body mass is increasing (i.e., absorbed mass > oxidized mass) or decreasing (i.e., absorbed mass < oxidized mass).

More specifically, energy balance can occur at body mass stability ONLY if the following three conditions are simultaneously satisfied:

1. Average absorbed fat mass = average oxidized fat mass

2. Average absorbed carbohydrate mass = average oxidized carbohydrate mass

3. Average absorbed protein mass = average oxidized protein mass

Obviously, this can never happen. If, for example, all the absorbed protein mass (amino acids) is oxidized, where would the body get building blocks? Thus, *energy balance is unattainable at body mass stability* [1,5]. This fact refutes the core idea of the EBT, i.e., that body mass remains constant in energy balance.

The regulation of body mass

By now it should be clear that the regulation of body *mass* is all about detailed *mass* balances (”Mass In, Mass Out”), not about energy conservation (”Calories In, Calories Out”). After all, we are talking about body *mass*. The Law of

 doi:10.20944/preprints202208.0309.v9

Conservation of Mass guarantees that *1)* the O_2 mass that enters cellular respiration plus *2)* the mass of macronutrients that served as energy fuel absolutely must equal the mass of the excreted oxidation products. This is not a matter of opinion. *Daily weight loss must, therefore, be the result of daily elimination of oxidation products (CO_2, water, urea, SO_3; "Mass Out"), not a consequence of the heat release upon nutrient combustion (i.e., daily energy expenditure)* [6]. *And it is macronutrient mass intake ("Mass In") that augments body mass; the absorption of 1 g of glucose, protein or fat increases body mass by exactly 1 g independent of the substrate's Calories*, as dictated by the Law of Conservation of Mass. The absorbed nutrient mass cannot be destroyed and, thus, it will contribute to total body mass as long as it remains within the body. Such a contribution ends, however, when the nutrients are eliminated from the body either as products of metabolic oxidation or in other forms (e.g., shedding of dead skin cells).

Animals, including humans, ingest food to get both energy and mass. While energy refers to capacity to do work, mass is used to build all bodily structures. Not a single gram of body mass is added through energy intake. Calories represent the *heat* release upon food oxidation, and as such, **calories have no impact on body mass** [1,5]. The term "calorie" comes from Latin *calor* (heat). Calorie is broadly defined as the amount of energy needed to increase the temperature of 1 g of water by 1 °C. *Heat certainly does not produce mass*; this is taught in an introductory kindergarten physics course.

Almost all of an atom's mass comes from the protons and neutrons (i.e., nucleons) that make it up; nuclei contain >99.9% of the mass of an atom. In the chemical reactions that take place in the human body, the nucleus of the atom remains intact. **Body mass can only change due to net mass flow** [1,5,16]; thus, the *only* food property that can augment body mass is its nutrient mass, not its energy content (i.e., calories). Like gravity, this is by no means a matter of opinion.

It follows that any anti-obesity intervention must

1) ***Decrease intake of energy-providing mass*** (EPM) ("Mass In"), i.e., satiating effect. EPM is the daily intake of carbohydrate, fat, protein, soluble fiber and alcohol.

 doi:10.20944/preprints202208.0309.v9

2) ***Increase elimination of oxidation products*** ("Mass Out"). Each day we experience a weight loss (i.e., body mass loss) given by the weight of the energy expenditure-dependent mass loss (EEDML) plus the weight of the energy expenditure-independent mass loss (EEIML) [5]. EEDML refers to the daily excretion of EPM oxidation byproducts (CO_2, water, urea, SO_3), whereas EEIML represents the daily weight loss that results from *i)* the daily elimination of non-metabolically produced water; *ii)* minerals lost in sweat and urine; *iii)* fecal matter elimination; and *iv)* mass lost from renewal of skin, hair and nails [5]. Or

3) ***Both***.

A recently proposed **mass balance model** (**MBM**) describes the temporal evolution of body weight and body composition under a wide variety of feeding experiments, and it seems to provide a highly accurate description of the very best experimental human feeding data [e.g., 1,3,4,5]. For example, we have compared head-to-head the predictions given by the MBM with the EBT-based model of Hall and coworkers [22] , and the MBM seems to be superior to the EBT-based model [3]. The difference in prediction accuracy is especially clear when the distribution of the macronutrient intake changes drastically, e.g., a low-carbohydrate diet *vs.* an isocaloric high-carbohydrate diet. And the ranking of such models is determined by their predictive accuracy; this is the reason why such models are developed in the first place. *I would like to emphasize that the MBM not only predicts the change in total body mass but also the change in fat mass.*

In **Figure 1**, adapted from reference [3], I present a comparative simulation between the EBT-based model [22] and the MBM [5]. All the details can be found in the original source [3], so there is no reason to repeat them here. But in my experience, many colleagues have had difficulty understanding what these simulation results mean, so I present the results here as easy to read as possible. In the simulations, we used the free-living feeding trial data of Kong and coworkers [21]. Their twenty young female subjects followed a "normal diet" (ND; carbohydrate 44.0 ± 7.6%, protein 15.4 ± 3.3%, fat 39.6 ± 5.8%) for four weeks as a baseline and then switched to a very-low-carbohydrate/high-fat diet (KD;

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 September 2022 doi:10.20944/preprints202208.0309.v9

carbohydrate 9.2 ± 4.8%, protein 21.9 ± 3.4%, fat 69.0 ± 5.4%) for another 4 weeks. This study showed that the 4-week KD intervention led to marked reductions in body mass (−2.9 kg) and body fat percentage (−2.0%). The results of the MBM-based simulations match the results of the feeding trial very closely, while the predictions of the EBT-based simulations go clearly wrong. *Pay special attention to how the incorrect formula (Daily Fat Loss) = (Daily Fat Intake) – (Daily Net Fat Oxidation) affects the prediction results provided by the EBT-based model*. The aforementioned formula would be valid only if the net fat oxidation is independent of diet´s macronutrient distribution. If the net fat oxidation increases as dietary fat intake increases (and *vice versa*), fat loss can be similar among isocaloric diets that vary greatly in fat content. Hall *et al.*´s respiratory quotient (RQ) data demonstrate that this is indeed the case, as their Figure 2C indicate that the oxidation of fatty acids increases as the proportion of fat in the diet increases [10]. For further details, see the figure legend.

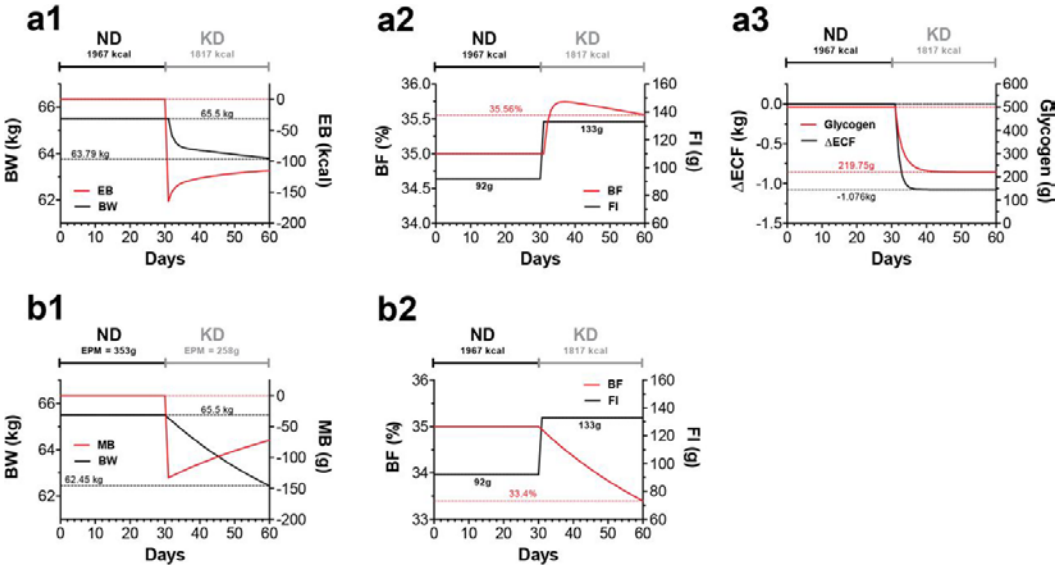

Figure 1. Simulations of Kong *et al.* feeding trial (EBT *vs.* MBM). *a1*. During the "normal diet" (ND; days 0-30) energy balance (EB; red curve) is zero. After day 30 EB becomes negative when following the very-low-carbohydrate/high-fat diet (KD) resulting in a 1.71 kg body weight (BW) loss at day 60. *a2*. The EBT-based model by Hall *et al.* (EBT; [22]) predicts that body fat (BF) percentage is *increased* during the KD, even though body weight is decreased. This completely incorrect prediction is due to the 41 g increase in fat intake during the KD; EBT incorrectly assumes that (Daily Fat Loss)

 doi:10.20944/preprints202208.0309.v9

= (Daily Fat Intake) – (Daily Net Fat Oxidation) [14]. *a3*. During the ND the amount of glycogen stored was 500 g, but during the KD its amount decreases to 280.25 g. Extracellular fluid (ECF) has also decreased by 1.076 kg. Thus, glycogen + ECF = 1.35625 kg. Of the 1.71 kg weight loss in a1, 0.35375 kg (1.71 kg – 1.35625 kg) are from other mass sources: 0.2436 kg fat mass + 0.11015 kg fat-free mass. According to EBT, this indicates that the total weight loss is distributed as 0.2436 kg of fat mass plus 1.4664 kg of fat-free mass. As the decline in fat-free mass is much larger than that of fat mass, EBT completely falsely predicts that BF % will *increase* as illustrated in a2. *b1*. During the ND period (days 0-30) mass balance (MB; red curve) is zero. After day 30 MB becomes negative when following the KD resulting in a 3.05 kg weight loss at day 60. *b2*. According to the MBM, of the 3.05 kg of weight loss 2.07 kg came from fat mass and 0.98 kg from fat-free mass. Even though fat intake has increased the decline in fat-free mass is much smaller than that of fat mass and thus BF decreases as shown. This figure can be found larger in reference [3].

Although free-living feeding trials are always a mixture of effectiveness and compliance, there is every reason to believe that Kong *et al.*'s study was as well controlled as such a study can be. To assure subjects' adherence to the KD, Kong and coworkers required that:

- The subjects measure urinary ketones every day (early morning or after dinner) and record 3-day food diaries (2 weekdays and 1 weekend day) during the experimental period;
- 3-day food diaries were kept by all subjects for 8 weeks;
- All subjects were given in advance "thorough instructions" on how to estimate portion sizes and record food/beverages intake on food composition tables;
- Subjects were asked to report to the laboratory every week to assess changes in body weight and hand in the logbook with dietary records;

 doi:10.20944/preprints202208.0309.v9

- Energy intake and macronutrient distribution were calculated by the same dietician using the nutrition analysis and management system;
- Diet compliance was evaluated based on the results of the urinary ketones and food diaries, and subjects received follow-up dietary advice and counseling individually from the dietician.

In summary, it can be stated that the feeding data produced by Kong *et al*. provides reliable information on the effects of macronutrient distribution on body mass and composition. Thus, *the simulation comparison would seem to show "beyond reasonable doubt"* [24] *that the MBM-based simulation provides clearly more accurate predictions than the EBT-based simulation*. As mentioned earlier, Hall and colleagues' EBT-based model assumes that body fat fluctuations are the consequence of the imbalance between dietary fat consumption and net fat oxidation. This formula would be valid if the distribution of macronutrients in the diet did not affect the oxidation of fatty acids, but this assumption does not correspond to reality. Hall *et al*. estimate the reduction in body fat indirectly according to the following equations (in grams):

(Daily Fat Loss) = (Daily Fat Intake) – (Daily Net Fat Oxidation) (1)

where Daily Net Fat Oxidation is another estimate calculated by

(Daily Net Fat Oxidation) = $1.63VO_2 – 1.64VCO_2 – 1.84N$ (2)

where VO_2 and VCO_2 are the liters of consumed O_2 and produced CO_2, respectively, while N is the urinary nitrogen excretion per 24 h. In these equations, the only precise numeric input is Daily Fat Intake, whereas Daily Net Fat Oxidation is an *estimate* obtained from *estimates* which unavoidably increases the measurement inaccuracy. As recently discussed by Arencibia-Albite [1], the aforementioned equations ignore, among other things, the fact that body fat can also decrease through the excretion of fatty acid derivatives.

A low-carbohydrate diet provides less nutrient mass than an isocaloric high-carbohydrate diet

 doi:10.20944/preprints202208.0309.v9

A low-carbohydrate/high-fat diet leads to a greater body mass and fat mass loss than an isocaloric high-carbohydrate/low-fat diet because it provides less nutrient mass [1,3,4,5]. When the energy fraction from dietary fat increases, while energy intake is clamped (i.e., fixed), mass intake decreases due to the significantly higher energy density of fat compared with other energy substrates. Such a difference in mass intake translates into greater body mass and fat loss in a low-carbohydrate diet *vs.* an isocaloric high-carbohydrate diet. If such a feeding response is not observed, then it is simply not a well-controlled study, as alternative results would indicate a violation of the Law of Conversation of Mass.

If two persons eliminate body mass at the same daily rate, then the one ingesting less nutrient mass will express a greater daily body mass and fat loss. For example, daily energy intake of 2,500 kcal distributed as 30% fat (9.4 kcal/g), 55% carbohydrate (4.2 kcal/g) and 15% protein (4.7 kcal/g) corresponds to a mass intake of ~487 g, whereas the same energy intake sorted as 60% fat, 30% carbohydrate, and 10% protein reduces mass ingestion by ~96 g. This is not a small difference in the long run.

It has been suggested that a low-carbohydrate diet is more effective in losing body mass and fat mass than an isocaloric high-carbohydrate diet because the former lowers insulin levels [9]. However, it is worth noting that insulin – or any other hormone – cannot create any kind of mass out of thin air. Only ingested nutrient mass can increase body mass. Insulin just makes sure that this mass can be stored. Similarly, a lowered insulin level cannot magically destroy any mass. Although insulin levels decrease with a low-carbohydrate diet, it is not a causal factor in body mass and fat mass loss. It just happens simultaneously with a decrease in nutrient mass intake. What about de novo lipogenesis (DNL), i.e., the process of synthesizing fatty acids from acetyl-CoA subunits? Hyperinsulinemia caused by consuming a large amount of carbohydrates can increase DNL, but it is only relevant in extreme overfeeding situations. DNL seems to

 doi:10.20944/preprints202208.0309.v9

play a central role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD; e.g., [30]), but this topic is beyond the scope of this article.

However, the insulin level can be important in terms of *where* body fat is reduced. It seems reasonable that during a high-carbohydrate diet, the reduction of body fat occurs mainly through a reduction in dietary fat intake, since high insulin levels favor fat synthesis and inhibit lipolysis. In contrast, a low-carbohydrate diet lowers insulin levels, reducing fat synthesis and stimulating lipolysis, which nullifies the effects of high dietary fat intake. These factors may explain why low-carbohydrate diets tend to work well for visceral fat reduction [e.g., 15,17].

Recently, Goss *et al*. reported that in their eight-week study the very-low-carbohydrate/high-fat diet group experienced 3-fold greater loss of visceral adipose tissue (VAT) and intermuscular adipose tissue (IMAT) when compared to the high-carbohydrate/low-fat diet group [17]. Following the very-low-carbohydrate/high-fat diet, there was a drastically greater decrease in fasting insulin compared to the high-carbohydrate/low-fat diet (13.7 ± 5.6 → 9.4 ± 4.0 *vs.* 15.6 ± 6.5 → 16.0 ± 8.2). It should be noted, however, that the very-low-carbohydrate/high-fat group reported consuming significantly fewer total calories – and thus nutrient mass – per day than the high-carbohydrate/low-fat group. Nevertheless, it seems that the very-low-carbohydrate/high-fat diet works particularly well on these metabolically harmful fat depots.

In **Figure 2**, I present two hypothetical overweight individuals whose body composition and total energy intake are identical, but the distribution of macronutrients is clearly different.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 September 2022 doi:10.20944/preprints202208.0309.v9

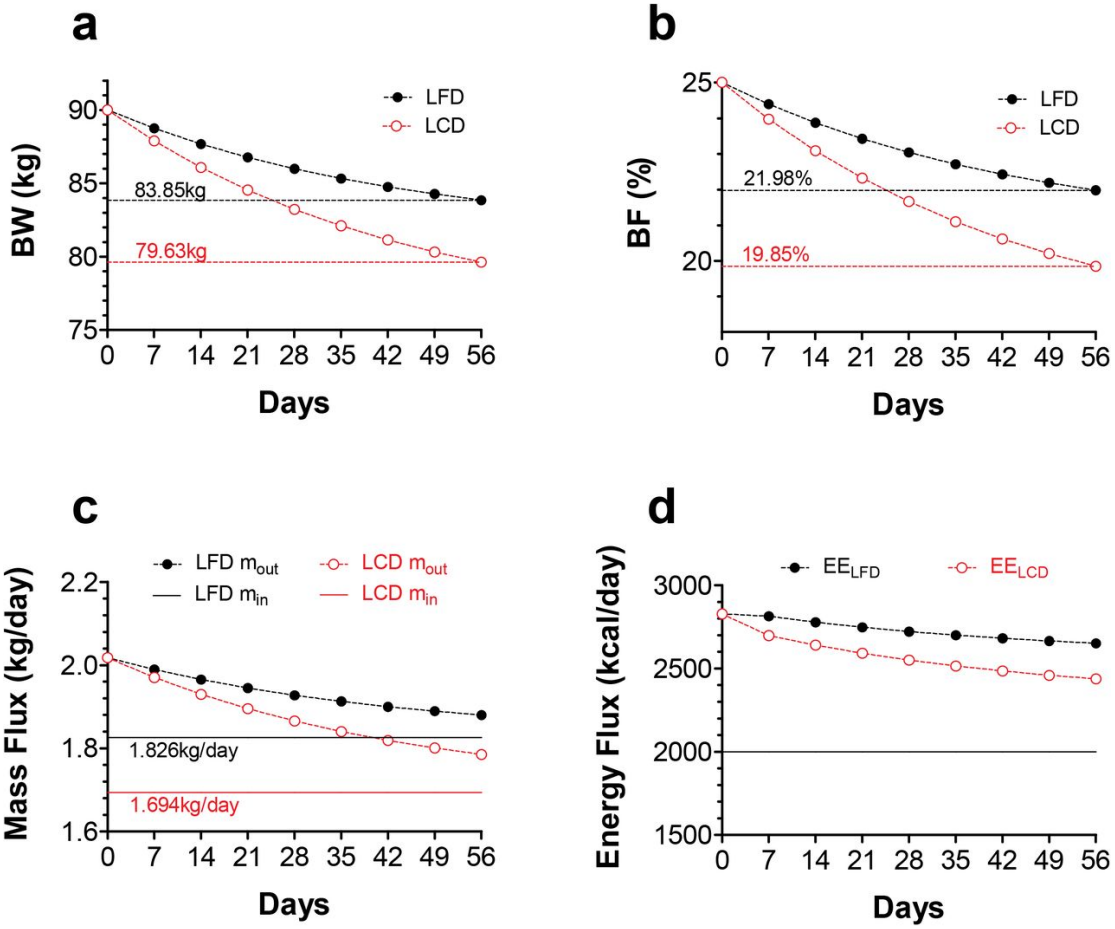

Figure 2. **MBM-based simulation of two hypothetical overweight (90 kg) individuals whose body composition and total energy intake are identical, but macronutrient distribution is clearly different**. In the initial situation, the nutrient intake is as follows: energy intake 2 750 kcal/day; 35% fat (F), 50% carbohydrate (C), 15% protein (P). Next, these individuals start following either a 2 000 kcal high-carbohydrate/low-fat diet (LFD) or a 2 000 kcal low-carbohydrate/high-fat diet (LCD), whose macronutrient distribution is as follows: LFD = 20% F, 65% C, 15% P or LCD = 70% F, 15% C, 15% P. According to the EBT, these diets should lead to almost identical effects in terms of body mass and fat mass. However, the MBM predicts that the LCD results in greater body mass and fat mass loss compared with the LFD. As demonstrated, the nutrient mass intake (m_{in}) is smaller compared with the eliminated mass (m_{out}); and, thus, the net daily mass loss is larger (i.e., $m_{in} - m_{out}$). BW = body weight; BF = body fat.

 doi:10.20944/preprints202208.0309.v9

A highly controlled metabolic ward feeding trial supporting the mass balance approach

When it comes to proving causality in this type of matter, metabolic ward studies are rightly considered the most authoritative. Unfortunately, such trials are very expensive to implement, so new ones are hardly in sight in the near future [37]. Perhaps the best controlled experiment performed in a metabolic ward is that of Hall and co-workers [10]. The results of this study are also in full agreement with the mass balance approach; two separate articles have been published on the subject, i.e., [4] and [14], so it will not be discussed further in this article.

Recent meta-analyses of randomized and controlled free-living feeding trials supporting the mass balance approach

Feeding trials performed on free-living subjects are always a mixture of effectiveness and compliance. When subjects are randomized to a certain diet, it often happens that many subjects are not very committed to following the prescribed diet. Usually, at the latest at one year, the macronutrient distribution of the compared diets starts to converge. Nevertheless, I will briefly review a couple of recent meta-analyses on the topic.

A meta-analysis by Choi *et al.* included eight feeding trials reporting changes in weight-related parameters [19]. Their results indicated that the very-low-carbohydrate/high-fat diet diets were significantly more effective in reducing body mass than higher carbohydrate control diets. Such results are completely in accordance with the mass balance approach. Let me remind you that when the energy fraction from dietary fat increases, while energy intake is fixed, mass intake decreases due to the significantly higher energy density of fat compared with other energy substrates.

A recent meta-analysis by Zaki *et al*. compared the effectiveness between very-low-carbohydrate diets and low-carbohydrate diets [20]. In this comparison, there is not such a significant difference in nutrient mass intake as in the aforementioned meta-analysis. As can be assumed based on the mass balance approach, those who followed a very-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 September 2022 doi:10.20944/preprints202208.0309.v9

low-carbohydrate diet lost, generally speaking, slightly more body mass than those who followed a low-carbohydrate diet. There was some variation in the results, which must be due to poor compliance.

An "old" well-controlled feeding experiment supporting the mass balance approach

In the early seventies Young *et al*. compared 3 diets that contained the same amounts of calories (1800 kcal/d) and protein (115 g/d) but that differed in carbohydrate content [25]. After 9 weeks on the 30 g, 60 g, and 104 g carbohydrate diets, weight loss was 16.2 kg, 12.8 kg, and 11.9 kg and fat accounted for 95%, 84%, and 75% of the weight loss, respectively. Thus, the authors concluded, "[w]eight loss, fat loss, and percent of weight loss as fat appeared to be inversely related to the level of carbohydrate in the isocaloric, isoprotein diets", consistent with the mass balance approach. And because these diligent researchers naturally followed the EBT paradigm, "[n]o adequate explanation can be given for weight loss differences." To my knowledge, no one has seriously criticized Young *et al*.'s study. It is worth noting that they utilized underwater weighing (i.e., hydrodensitometry) to determine body composition, which is more accurate than other widely available methods of body composition testing. When performed properly, underwater weighing can be accurate to 1.8 to 2.8% compared to the state-of-the-art methods (e.g., magnetic resonance imaging [MRI], computed tomography [CT]).

Epidemiological data supporting the mass balance approach

As recently pointed out by Mozaffarian [8], **the National Health and Nutrition Examination Survey (NHANES) data do NOT show any increase in energy consumption or availability over ≥20 years,** a time period when obesity has steadily risen (See Figure 1 in [8]). In fact, NHANES data suggest small but statistically significant *declines* in energy intake over this period [8]. What about the other side of the coin, i.e., energy expenditure? According to my understanding, similar epidemiological data on the matter is not available; however, high-quality studies utilizing

 doi:10.20944/preprints202208.0309.v9

double-labeled water (DLW) method indicate that **modern day total energy expenditure do not differ from modern-day hunter-gatherers** [12]. Despite of high physical activity level, the total energy expenditure of Hadza hunter-gatherers was similar to Westerners and others in market economies [12]. Thus, it seems clear that the main factor causing the obesity epidemic is increased food intake rather than declined expenditure.

If there has been no change in energy intake and energy consumption, what on earth is causing the obesity epidemic? If we follow the EBT paradigm, this seems paradoxical, but from the point of view of the mass balance approach, there is nothing surprising about it. According to nutritional recommendations, citizens should increase their intake of carbohydrates at the expense of fat. If such recommendations are followed (i.e., carbohydrates ↑; fats ↓), the intake of nutrient mass increases while the calorie intake remains the same. NHANES data indicates that, for men, the percentage of calories from carbohydrates increased between 1971 - 1974 and 1999 - 2000, from 42.4% to 49.0%, and for women, from 45.4% to 51.6% [13]. The percentage of calories from fats decreased from 36.9% to 32.8% for men and from 36.1% to 32.8% for women [13]. Although self-reported dietary intake is subject to recall bias, there is every reason to assume that strongly marketed nutritional recommendations produced results in line with the goals at the population level.

In the Women's Health Initiative Observational Study (WHI/OS), the relationship between four common diet patterns and weight gain was examined [27]: *1)* a low-fat diet; *2)* a reduced-carbohydrate diet; *3)* a Mediterranean-style diet; and *4)* a diet consistent with the US Department of Agriculture's (USDA) Dietary Guidelines for Americans (DGA). The WHI/OS was a longitudinal study of postmenopausal women aged 49–81 years (n = 93 676) who were enrolled between 1994 and 1998, and followed for up to 8 years. The researchers' conclusion tells all that is needed: "Our findings therefore challenge prevailing dietary recommendations, suggesting instead that a low-fat may *promote* rather than *prevent* weight gain after menopause." So, the results were the opposite of what could have been assumed based on the EBT.

Extremely obese individuals have very high total energy expenditure

 doi:10.20944/preprints202208.0309.v9

Based on the EBT, it has been suggested that low total energy expenditure (TEE) is a risk factor for obesity [31], but the evidence does not support this assumption. For example, Das *et al*. tested the hypothesis that both TEE and resting energy expenditure (REE) are low in extremely obese individuals, but the results showed the exact opposite, i.e., TEE of their extremely obese subjects was *very* high [32]. If the EBT were a valid paradigm, high TEE should protect against obesity. Similarly, Rimbach *et al.* concluded, "TEE is not a risk factor for, and high TEE is not protective against, weight or body fat gain over the time intervals tested." [33] These findings cause more gray hairs for the proponents of the EBT.

Diet writers' favorite hormones

Leptin

Leptin, a peptide hormone predominantly made by adipose cells, helps to regulate energy balance by inhibiting hunger [34]. According to the EBT, the macronutrient distribution of the diet has only a minimal effect on body mass and fat mass; and, accordingly, should have only a minimal effect on leptin levels. Hormonal responses were also determined in the previously mentioned feeding experiment by Kong and colleagues and their data (Table 1 in [21]) show the complete opposite of what could be assumed based on the EBT. Data indicates that switching from a "normal diet" (carbohydrate 44.0 ± 7.6%, protein 15.4 ± 3.3%, fat 39.6 ± 5.8%) to a very-low-carbohydrate/high-fat diet (carbohydrate 9.2 ± 4.8%, protein 21.9 ± 3.4%, fat 69.0 ± 5.4%) significantly lowers leptin levels, consistent with the mass balance approach. The less body fat, the less leptin you have.

Insulin (with special reference to the carbohydrate-insulin model)

Insulin, a peptide hormone produced by beta cells of the pancreatic islets, is considered to be the main anabolic hormone of the body. This is probably the reason why this hormone has become a favorite of diet writers. One obesity-related model, called the carbohydrate-insulin model (CIM), proposes a reversal of causal direction [8]. According to proponents of the CIM, "increasing fat deposition in the body – resulting from the hormonal responses to a high-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 September 2022 doi:10.20944/preprints202208.0309.v9

glycemic-load diet – drives positive energy balance." [8] It is worth emphasizing that the CIM operates within the EBT; that is, it also assumes that a positive energy balance is the cause of obesity. So, it is actually not a competing paradigm. The direction of causality in this matter does not affect the laws of physics in any way. The physical basis of both the EBT and the CIM operating within it is flawed, as has already been demonstrated. One of the central claims of the CIM is that high insulin levels promote weight gain, but as already mentioned, insulin cannot create mass from nothing. Although insulin levels decrease with a low-carbohydrate diet, it is not a causal factor in body mass and fat mass loss. It just happens simultaneously with a decrease in nutrient mass intake. Proponents of the CIM suggest that high insulin levels slow down the metabolism*, promoting weight gain [8]. Ludwig *et al*. claim that their meta-analysis [35] supports this assumption, but the conclusions do not stand up to critical scrutiny [36].

In summary, although at a cursory glance it might appear that the CIM is in agreement with the insulin response data, in reality it is a free passenger traveling on the wing of mass change. The decrease in the insulin level and the decrease in the intake of nutrient mass happen at the same time, but only the mass can be a causal factor in mass changes. In the mass balance model, it is assumed that the changes in body mass and composition are independent of the physiological effects of the diet. Rather, the differences are due to different amounts of nutrient mass intake. As already discussed, however, the insulin level can be important in terms of *where* body fat is reduced. In addition, there are other reasons to keep insulin levels low, as individuals with hyperinsulinemia are at high risk of developing obesity, type 2 diabetes, cardiovascular disease, cancer and premature mortality [39].

(*Let it be mentioned that the universal assumption that metabolism is synonymous with energy expenditure is misleading, as *metabolism is actually mass expenditure*).

The timing of nutrient mass ingestion cannot modify the Law of Conservation of Mass

 doi:10.20944/preprints202208.0309.v9

The timing of nutrient mass ingestion is guaranteed not to be able to modify the Law of Conservation of Mass; it can have an effect on body mass and fat mass only if the timing affects mass expenditure. A well-controlled feeding trial by Ruddick-Collins *et al*. demonstrates this fact in an excellent way [38]. They performed a 4-week crossover isocaloric and eucaloric feeding trial, comparing "morning loaded" (45%:35%:20% calories at breakfast:lunch:dinner) *vs.* "evening loaded" (20%:35%:45% calories at breakfast:lunch:dinner) calorie intake. This was a free-living study, but all food and beverages were provided, making it "the most rigorously controlled study to assess timing of eating in humans to date" [38]. As can be assumed based on the mass balance approach, the results indicate no differences in body mass loss, total daily energy expenditure or resting metabolic rate related to the timing of calorie distribution.

The Nutrition Facts label

The Nutrition Facts label on packaged foods was updated in 2016 "to reflect updated scientific information, including information about the link between diet and chronic diseases, such as obesity and heart disease." [7] One of the most prominent updates of the new food labeling regulations released by the Food and Drug Administration (FDA) is found on the calorie line; the font for calories has been significantly enlarged as well as emboldened for first-glance reference. The idea behind this well-meaning update was that Caloric values can be very simply understood without having to look very deeply into the food label. Humans need, of course, energy (i.e., the capacity to do work) but Calories have no impact on body mass. Thus, **the calorie line should be replaced, or complemented, with the mass line** (e.g., "Nutrient Mass" or just "Mass").

It is also worth noting that the concept of "light product" is very misleading. In reality, these products are often "heavy products". When the energy fraction from dietary fat increases, while energy content remains the same, mass intake decreases due to the significantly higher energy density of fat compared with other energy substrates. Thus, **a high-**

 doi:10.20944/preprints202208.0309.v9

carbohydrate "light product" containing 200 kcal provides more mass than a high-fat product containing 200 kcal.

This fact should have a significant impact on the prevailing legislation and the operation of the food industry.

A flawed paradigm leads to misinterpretation of research data

In the research literature, it is easy to find plenty of feeding trial reports that seem to support the EBT. A flawed paradigm, however, almost always leads to incorrect interpretations and conclusions. There are many research reports in which the more effective weight loss effect of a low-carbohydrate diet compared to an isocaloric high-carbohydrate diet is attributed to a methodological error (e.g., underreporting of food consumption, low sensitivity of research equipment). The assumption is that such results would violate the Law of Conservation of Energy (i.e., the First Law of Thermodynamics). As has been shown before, this is not the case (See **The energy balance theory is a flawed paradigm**). In studies where a low-carbohydrate diet has not been more effective in terms of fat loss, EBT-based calculation formulas have been used, which give incorrect results (e.g., 10; see reanalysis in [14]). Such points are very important to consider when reading these reports.

The real "acid test" of every theory is how good results can be obtained in practice based on it. How effective have EBT-based obesity treatment interventions been? According to 2017–2018 data from the NHANES, nearly 1 in 3 adults (30.7%) are overweight [11]. Thus, it is clearly not possible to talk about effective interventions.

Other applications of the mass balance approach

Although this review has focused on the macronutrient distribution of the diet, the mass balance approach also has many other practical applications. For example, anti-obesity drugs or dietary supplements that affect satiety should mainly reduce the consumption of carbohydrates, not fat. I will cover other applications in updates to this article.

The mass balance approach has nothing to do with metabolic advantage hypothesis

 doi:10.20944/preprints202208.0309.v9

Contrary to what some have thought, the mass balance approach has nothing to do with the metabolic advantage hypothesis [28]. Proponents of this hypothesis postulate that a low-carbohydrate diet leads to faster body mass and fat mass loss than an isocaloric high-carbohydrate diet because "[e]nergetic inefficiency, substrate cycling and demands of gluconeogenesis support observed advantages for weight [and fat] loss." [29] *Unlike energy, mass has no efficiency*. The amount of mass that is taken in always comes out in exactly the same amount. It is worth noting that the metabolic advantage hypothesis operates within the EBT.

It would seem that the proponents of the metabolic advantage hypothesis do not notice that efficiency is not related to incomplete substrate oxidation, but to how the body uses the available fuel resources. Consider the following simple example. You start to run 5 km every day and soon you will find out that you can complete the same distance in same time (let say 0.5 h) but with a smaller amount of heartbeats. Your body has adapted to this cardiovascular stress physiologically, biochemically and – in the long run – anatomically – and thus has become more efficient fuel utilizer. That is, your body can achieve the same running average speed (5km/0.5 h=10km/h) utilizing less fuel. However, every time the body oxidizes 1 g of glucose while running the heat released by the body continues to be ~4 kcals, which will not change as you age or as a function of your genome, epigenome, or proteome.

The Coca-Cola Company and their insidious marketing arms

The Global Energy Balance Network (GEBN) was a US-based marketing arm of The Coca-Cola Company (hereinafter referred to as Coke) claiming to fund research into causes of obesity [40]. GEBN's core message was that the main cause of obesity is physical inactivity, not a bad diet [41,42,43]. So, in plain language, the message was that you can also enjoy high-carbohydrate junk food, including Coke's drinks, as long as you exercise enough to stay in "energy balance". With around 1.4 billion inhabitants, China is the world's most populous country, so Coke has naturally been very interested

 doi:10.20944/preprints202208.0309.v9

in the market of that country. In her excellent article Greenhalgh covered this topic [43]; the following is a brief summary of her findings:

- Coke's main vehicle for influencing obesity science in China was the International Life Sciences Institute (ILSI), a Coke-sponsored marketing organization masquerading as a scientific organization. The organization's founding president Alex Malaspina was concurrently vice president of Coke. So, a few years ago, the ILSI and Coke were practically synonymous.
- ILSI's website [49] emphatically spotlights their long commitment to scientific integrity, but, as pointed by Greenhalgh, "close examination of how the organization [ILSI] works in practice reveals a different picture." [43] Simply put, the fox watches over the chicken cage.
- Coke, working through ILSI-Global and ILSI-China, succeeded in redirecting China's obesity science and policy to emphasize physical activity over dietary modifications.

In addition to GEBN and ILSI, Coke leveraged the authority of countless health organizations to spread its delusional message. In Spain, for example, at least 74 health organizations were sponsored by Coke during the period 2010 - 2016, with a total investment above 6 million euros [44]. The main message was the same as with GEBN: "The most prevalent strategy was to focus on physical activity and sedentary behaviours [sic] as key obesogenic risk factors." [44] Rey-López *et al.*'s article [44] has an excellent discussion of Coke's main marketing strategies.

Coke has also utilized governmental organizations in spreading its propaganda. For example, the Centers for Disease Control and Prevention (CDC) has had longstanding ties to Coke [46]. Barbara Bowman, then director of the CDC's Division for Heart Disease and Stroke Prevention, resigned after emails between her and a former Coke executive were disclosed [46]. These emails proved that Bowman had advised the former Coke and industry association executive on how to influence the Director-General of the World Health Organization (WHO) to stop promoting taxes on sugar.

 doi:10.20944/preprints202208.0309.v9

Perhaps prompted by this incident, the CDC website currently states the following: "Frequently drinking sugar-sweetened beverages is associated with weight gain, obesity, type 2 diabetes, heart disease, kidney diseases, non-alcoholic liver disease, tooth decay and cavities, and gout, a type of arthritis… Limiting sugary drink intake can help individuals maintain a healthy weight and have healthy dietary patterns." [47] However, with regard to individual cases, there is absolutely no reason to assume systematic abuses on the part of the CDC. In my opinion, the CDC website and other bulletins currently have reliable information on the subject.

Although not everyone necessarily likes this view, I dare say, on the basis of the *best* available evidence, that the *International Journal of Obesity (IJO)* [50] is a marketing journal mostly operated by Coke and other companies that live on sugar (e.g., Mars). In this context there is no reason to go through all the evidence, but I will present a couple of facts, which is why *IJO* cannot be considered a reliable source of information.

- *IJO*'s former editor-in-chief, Ian Macdonald, is proven to be a sugar industry mannequin [51]. This phony metabolic physiology "professor" still has not figured out that energy balance and mass balance are separate balances.
- *IJO* published most of the manuscripts related to Coke's fake research project, called International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE). As always, the purpose of this project was to "prove" that physical inactivity is the main cause of obesity.
- At the point when the mannequin Macdonald of the sugar industry had to be fired from his position [52], it was of course natural that a similar propagandist spreading Coke's delusional message was appointed to the position. Indeed, they found a very suitable person for this task, named David Stensel. This person has a long history of spreading Coke-like nonsense about the effects of physical activity on weight management [53].

 doi:10.20944/preprints202208.0309.v9

Although it is clear that *IJO* is a marketing publication for the sugar industry, this does not in any way mean that all the researchers who publish in it are corrupt. A fake publication would not be able to operate without honest publications. Nevertheless, an update to this article will show incontrovertible evidence that many of the journals published by Nature Springer, including – but certainly not limited to – *IJO*, *European Journal of Nutrition* and *European Journal of Clinical Nutrition* are actually advertising publications for the sugar industry. **There is sufficient evidence that these misguided publications have had a considerable detrimental effect on humanity and thus require very careful legal scrutiny.** And when people's lives and health are threatened with misinformation, it is a very serious crime. While waiting for the next update, I recommend reading Noakes' recent work *Real Food On Trial: How the diet dictators tried to destroy a top scientist* [54]. This book presents in an excellent way the large-scale quackery in nutrition-related publications.

In summary, contrary to what Coke-sponsored "researchers" try to claim, you cannot outrun a bad diet [45].

Concluding remarks

I would like to propose a new paradigm that paints a more accurate picture of the evolution of body weight: **Chronic positive mass balance is the actual etiology of obesity, not positive energy balance**, opening up a completely new era in obesity research. By shifting to a mass balance paradigm of obesity, a deeper understanding of this disease may follow in the near future. The immediate consequence of such a shift is that feeding studies will become much more accurate and significantly less expensive as mass measurements are cheaper and do not suffer from all the problems that energy measurements do.

It must be clear as day that the paradigm shift must finally begin. The researchers' own honor cannot go above the importance of treating and preventing obesity. Sometimes it happens that the fundamental knowledge structure turns out to be incorrect and thus it has to be abandoned. The whole game needs to be changed. "That is what fundamental

 doi:10.20944/preprints202208.0309.v9

novelties of fact and theory do. Produced inadvertently by a game played under one set of rules, their assimilation requires the elaboration of another set", as Thomas S. Kuhn stated in his classic work *The Structure of Scientific Revolutions* [23].

The rational mind's ability to bias, exaggerate and cover up is fundamental [48]. Rationality *per se* does not cause problems, but the rational mind is attracted to the greatest of sins; namely, the tendency to think of the things one knows as absolute, "ultimate truths". Researchers celebrate their own theories, claiming that better ones – or ones outside of them – do not even have to exist. They usually start from the basic assumption that all the most fundamental facts have already been proven beyond doubt; that is, nothing important has been left unexplored. This is sometimes the case, but from time to time even the "ultimate truths" change.

A paradigm shift is an intellectual revolution, accompanied by the chaos and fear inherent in revolution. Sacrifice is always required to correct a mistake – and if the mistake has been significant, so must the sacrifice. When the new truth has been rejected for a long time, a large amount of sacrificial debt may have already accumulated. Some leading researchers in the field seem to have already accumulated enough debt that they treat the mass balance approach like a plague; what reminded me of Nietzsche's statement in his classic work *The Gay Science* (1882):

"There is a stupid humility that is not at all rare, and those afflicted with it are altogether unfit to become devotees of knowledge. As soon as a person of this type perceives something striking, he turns on his heel, as it were, and says to himself: "You have made a mistake. What is the matter with your senses? This cannot, may not, be the truth." And then, instead of looking and listening again, more carefully, he runs away from the striking thing, as if he had been intimidated, and tries to remove it from his mind as fast as he can. For his inner canon says: "I do not want to see anything that contradicts the prevalent opinion. Am I called to discover new truths? There are too many old ones, as it is."

 doi:10.20944/preprints202208.0309.v9

Nietzsche described above the phenomenon that later came to be called cognitive dissonance. The theory of cognitive dissonance proposes that people are averse to inconsistencies within their own minds [26]. More specifically, cognitive dissonance refers to the perception of contradictory information. If a person has been teaching things related to energy balance at a university for decades, the magnitude of dissociation can be at a very massive level.

Finally, Occam's razor (*novacula Occami*) is also on the side of the mass balance approach. This principle states that entities should not be multiplied unnecessarily. By definition, all assumptions introduce possibilities for error. If an assumption does not improve the accuracy of a theory or model, its only effect is to increase the probability that the overall theory or model is wrong. What do you measure when you stand on the bathroom scale? Your body mass or your energy? Obviously, you determine the amount of mass in your body. So why do you want to look at body mass changes in light of energy changes? Such a perspective only offers a rough second-hand estimate at best. The right starting point is to measure the mass *directly*, because that is what it is all about. As already mentioned before, *energy balance and mass balance are separate balances in the human body*.

For further details, please see the key publications mentioned in the reference list. I intentionally kept the reference list short, as other references can be found in these key publications. I especially recommend reading the recent paper by Arencibia-Albite [1], which should – at least in my humble opinion – stop the press.

Conflict of interest

The author declared no conflict of interest.

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

The sole author was responsible for all aspects of this manuscript.

 doi:10.20944/preprints202208.0309.v9

Acknowledgements

I would like to thank my family for support and care and numerous colleagues for stimulating discussions.

List of abbreviations

MBM = mass balance model; EBT = energy balance theory; CIM = carbohydrate-insulin model; EPM = energy-providing mass; EEDML = energy expenditure-dependent mass loss; EEIML = energy expenditure-independent mass loss; EB = energy balance; MB = mass balance; TEE = total energy expenditure; REE = resting energy expenditure; BW = body weight; BF = body fat; ECF = extracellular fluid; DNL = de novo lipogenesis; NHANES = National Health and Nutrition Examination Survey; WHI/OS = Women's Health Initiative Observational Study; DLW = double-labeled water; FDA = Food and Drug Administration; VAT = visceral adipose tissue; IMAT = intermuscular adipose tissue; RQ = respiratory quotient; GEBN = Global Energy Balance Network; CDC = Centers for Disease Control and Prevention; ILSI = International Life Sciences Institute (ILSI); ISCOLE = International Study of Childhood Obesity, Lifestyle and the Environment; IJO = International Journal of Obesity.

References

1. Arencibia-Albite F. The energy balance theory is an inconsistent paradigm. *J Theor Biol*. 2022 Aug 6:111240. doi: 10.1016/j.jtbi.2022.111240. Epub ahead of print. PMID: 35944592.
2. Sterner RW, Small GE, Hood JM. The Conservation of Mass. *Nature Education Knowledge*. 2011:3(10):20
3. Arencibia-Albite F, Manninen AH. The energy balance theory: an unsatisfactory model of body composition fluctuations. *medRxiv* 2020.10.27.20220202; doi: https://doi.org/10.1101/2020.10.27.20220202

4. Arencibia-Albite F, Manninen AH. The mass balance model perfectly fits both Hall et al. underfeeding data and Horton et al. overfeeding data. *medRxiv* 2021.02.22.21252026; doi: https://doi.org/10.1101/2021.02.22.21252026

5. Arencibia-Albite F. Serious analytical inconsistencies challenge the validity of the energy balance theory. *Heliyon*. 2020 Jul 10;6(7):e04204. doi: 10.1016/j.heliyon.2020.e04204. Erratum in: *Heliyon*. 2020 Sep 14;6(9):e04609. PMID: 32685707; PMCID: PMC7355950.

6. Meerman R, Brown AJ. When somebody loses weight, where does the fat go? *BMJ*. 2014 Dec 16;349:g7257. doi: 10.1136/bmj.g7257. Erratum in: *BMJ*. 2014;349:g7782. PMID: 25516540.

7. Food and Drug Administration (FDA). Changes to the Nutrition Facts Label. https://www.fda.gov/food/food-labeling-nutrition/changes-nutrition-facts-label (accessed 7.8.2022)

8. Mozaffarian D. Perspective: Obesity-an unexplained epidemic. *Am J Clin Nutr*. 2022 Jun 7;115(6):1445-1450. doi: 10.1093/ajcn/nqac075. PMID: 35460220; PMCID: PMC9170462.

9. Ludwig DS, Aronne LJ, Astrup A, de Cabo R, Cantley LC, Friedman MI, Heymsfield SB, Johnson JD, King JC, Krauss RM, Lieberman DE, Taubes G, Volek JS, Westman EC, Willett WC, Yancy WS, Ebbeling CB. The carbohydrate-insulin model: a physiological perspective on the obesity pandemic. *Am J Clin Nutr*. 2021 Sep 13;114(6):1873–85. doi: 10.1093/ajcn/nqab270. Epub ahead of print. PMID: 34515299; PMCID: PMC8634575.

10. Hall KD, Bemis T, Brychta R, Chen KY, Courville A, Crayner EJ, Goodwin S, Guo J, Howard L, Knuth ND, Miller BV 3rd, Prado CM, Siervo M, Skarulis MC, Walter M, Walter PJ, Yannai L. Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss than Carbohydrate Restriction in People with

Obesity. *Cell Metab*. 2015 Sep 1;22(3):427-36. doi: 10.1016/j.cmet.2015.07.021. Epub 2015 Aug 13. PMID: 26278052; PMCID: PMC4603544.

11. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats, Centers for Disease Control and Prevention. 2020. Updated February 8, 2021. www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm (accessed 22.8.2022)
12. Pontzer H, Raichlen DA, Wood BM, Mabulla AZ, Racette SB, Marlowe FW. Hunter-gatherer energetics and human obesity. *PLoS One*. 2012;7(7):e40503. doi: 10.1371/journal.pone.0040503. Epub 2012 Jul 25. PMID: 22848382; PMCID: PMC3405064.
13. Centers for Disease Control and Prevention (CDC). Trends in intake of energy and macronutrients--United States, 1971-2000. *MMWR Morb Mortal Wkly Rep*. 2004 Feb 6;53(4):80-2. PMID: 14762332.
14. Manninen AH. A reanalysis of the highly important metabolic ward feeding data of Hall and colleagues: a brief report. *Authorea*. August 24, 2022. doi: 10.22541/au.166134987.70569518/v1
15. Volek J, Sharman M, Gómez A, Judelson D, Rubin M, Watson G, Sokmen B, Silvestre R, French D, Kraemer W. Comparison of energy-restricted very low-carbohydrate and low-fat diets on weight loss and body composition in overweight men and women. *Nutr Metab (Lond).* 2004 Nov 8;1(1):13. doi: 10.1186/1743-7075-1-13. PMID: 15533250; PMCID: PMC538279.
16. Kooijman SA, Kooi BW, Hallam TG. The application of mass and energy conservation laws in physiologically structured population models of heterotrophic organisms. *J Theor Biol*. 1999 Apr 7;197(3):371-92. doi: 10.1006/jtbi.1998.0881. PMID: 10089148.

17. Goss AM, Gower B, Soleymani T, Stewart M, Pendergrass M, Lockhart M, Krantz O, Dowla S, Bush N, Garr Barry V, Fontaine KR. Effects of weight loss during a very low carbohydrate diet on specific adipose tissue depots and insulin sensitivity in older adults with obesity: a randomized clinical trial. *Nutr Metab (Lond)*. 2020 Aug 12;17:64. doi: 10.1186/s12986-020-00481-9. PMID: 32817749; PMCID: PMC7425171.

18. Wikipedia. Living review. https://en.wikipedia.org/wiki/Living_review (accessed 27.8.2022)

19. Choi YJ, Jeon SM, Shin S. Impact of a Ketogenic Diet on Metabolic Parameters in Patients with Obesity or Overweight and with or without Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2020 Jul 6;12(7):2005. doi: 10.3390/nu12072005. PMID: 32640608; PMCID: PMC7400909.

20. Zaki HA, Iftikhar H, Bashir K, Gad H, Samir Fahmy A, Elmoheen A. A Comparative Study Evaluating the Effectiveness Between Ketogenic and Low-Carbohydrate Diets on Glycemic and Weight Control in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Cureus*. 2022 May 31;14(5):e25528. doi: 10.7759/cureus.25528. PMID: 35800806; PMCID: PMC9246466.

21. Kong Z, Sun S, Shi Q, Zhang H, Tong TK, Nie J. Short-Term Ketogenic Diet Improves Abdominal Obesity in Overweight/Obese Chinese Young Females. *Front Physiol*. 2020 Jul 28;11:856. doi: 10.3389/fphys.2020.00856. PMID: 32848830; PMCID: PMC7399204.

22. Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, Swinburn BA. Quantification of the effect of energy imbalance on bodyweight. *Lancet*. 2011 Aug 27;378(9793):826-37. doi: 10.1016/S0140-6736(11)60812-X. PMID: 21872751; PMCID: PMC3880593.

23. Kuhn TS. *The Structure of Scientific Revolutions*. Second Edition, Enlarged. The University of Chicago Press, 1970.

24. Diamond HA. Reasonable Doubt: To Define, or Not to Define. *Columbia Law Review* 90, no. 6 (1990): 1716–36. https://doi.org/10.2307/1122751.

25. Young CM, Scanlan SS, Im HS, Lutwak L. Effect of body composition and other parameters in obese young men of carbohydrate level of reduction diet. *Am J Clin Nutr*. 1971 Mar;24(3):290-6. doi: 10.1093/ajcn/24.3.290. PMID: 5548734.

26. Vaidis DC, Bran A. Respectable Challenges to Respectable Theory: Cognitive Dissonance Theory Requires Conceptualization Clarification and Operational Tools. *Front Psychol*. 2019 May 29;10:1189. doi: 10.3389/fpsyg.2019.01189. PMID: 31191395; PMCID: PMC6549475.

27. Ford C, Chang S, Vitolins MZ, Fenton JI, Howard BV, Rhee JJ, Stefanick M, Chen B, Snetselaar L, Urrutia R, Frazier-Wood AC. Evaluation of diet pattern and weight gain in postmenopausal women enrolled in the Women's Health Initiative Observational Study. *Br J Nutr*. 2017 Apr;117(8):1189-1197. doi: 10.1017/S0007114517000952. Epub 2017 May 16. PMID: 28509665; PMCID: PMC5728369.

28. Feinman RD, Fine EJ. Nonequilibrium thermodynamics and energy efficiency in weight loss diets. *Theor Biol Med Model*. 2007 Jul 30;4:27. doi: 10.1186/1742-4682-4-27. PMID: 17663761; PMCID: PMC1947950.

29. Feinman RD. Beyond “a Calorie is a Calorie”: An Introduction to Thermodynamics. In: *Nutrition in Crisis: Flawed Studies, Misleading Advice, and the Real Science of Human Metabolism*. Chelsea Green Publishing, 2019.

30. Watanabe M, Tozzi R, Risi R, Tuccinardi D, Mariani S, Basciani S, Spera G, Lubrano C, Gnessi L. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature. *Obes Rev*. 2020 Aug;21(8):e13024. doi: 10.1111/obr.13024. Epub 2020 Mar 24. PMID: 32207237; PMCID: PMC7379247.

31. Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, Boyce V, Howard BV, Bogardus C. Reduced rate of energy expenditure as a risk factor for body-weight gain. *N Engl J Med*. 1988 Feb 25;318(8):467-72. doi: 10.1056/NEJM198802253180802. PMID: 3340128.

32. Das SK, Saltzman E, McCrory MA, Hsu LK, Shikora SA, Dolnikowski G, Kehayias JJ, Roberts SB. Energy expenditure is very high in extremely obese women. *J Nutr*. 2004 Jun;134(6):1412-6. doi: 10.1093/jn/134.6.1412. PMID: 15173405.

33. Rimbach R, Yamada Y, Sagayama H, Ainslie PN, Anderson LF, Anderson LJ, Arab L, Baddou I, Bedu-Addo K, Blaak EE, Blanc S, Bonomi AG, Bouten CVC, Bovet P, Buchowski MS, Butte NF, Camps SGJA, Close GL, Cooper JA, Das SK, Dugas LR, Ekelund U, Entringer S, Forrester T, Fudge BW, Goris AH, Gurven M, Hambly C, El Hamdouchi A, Hoos MB, Hu S, Joonas N, Joosen AM, Katzmarzyk P, Kempen KP, Kimura M, Kraus WE, Kushner RF, Lambert EV, Leonard WR, Lessan N, Martin CK, Medin AC, Meijer EP, Morehen JC, Morton JP, Neuhouser ML, Nicklas TA, Ojiambo RM, Pietiläinen KH, Pitsiladis YP, Plange-Rhule J, Plasqui G, Prentice RL, Rabinovich RA, Racette SB, Raichlen DA, Ravussin E, Reynolds RM, Roberts SB, Schuit AJ, Sjödin AM, Stice E, Urlacher SS, Valenti G, Van Etten LM, Van Mil EA, Wells JCK, Wilson G, Wood BM, Yanovski J, Yoshida T, Zhang X, Murphy-Alford AJ, Loechl CU, Luke AH, Rood J, Schoeller DA, Westerterp KR, Wong WW, Speakman JR, Pontzer H; IAEA DLW Database Consortium. Total energy expenditure is repeatable in adults but not associated with short-term changes in body composition. *Nat Commun*. 2022 Jan 10;13(1):99. doi: 10.1038/s41467-021-27246-z. PMID: 35013190; PMCID: PMC8748652.

34. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, Gojobori T, Isenovic ER. Leptin and Obesity: Role and Clinical Implication. *Front Endocrinol* (Lausanne). 2021 May 18;12:585887. doi: 10.3389/fendo.2021.585887. PMID: 34084149; PMCID: PMC816704

35. Ludwig DS, Dickinson SL, Henschel B, Ebbeling CB, Allison DB. Do Lower-Carbohydrate Diets Increase Total Energy Expenditure? An Updated and Reanalyzed Meta-Analysis of 29 Controlled-Feeding Studies. *J Nutr*. 2021 Mar 11;151(3):482-490. doi: 10.1093/jn/nxaa350. PMID: 33274750; PMCID: PMC7948201.

36. Guyenet SJ, Hall KD. Overestimated Impact of Lower-Carbohydrate Diets on Total Energy Expenditure. *J Nutr*. 2021 Aug 7;151(8):2496-2497. doi: 10.1093/jn/nxab213. PMID: 34363484; PMCID: PMC8491863.

37. Hall KD. Challenges of human nutrition research. *Science*. 2020 Mar 20;367(6484):1298-1300. doi: 10.1126/science.aba3807. PMID: 32193306.

38. Ruddick-Collins LC, Morgan PJ, Fyfe CL, Filipe JAN, Horgan GW, Westerterp KR, Johnston JD, Johnstone AM. Timing of daily calorie loading affects appetite and hunger responses without changes in energy metabolism in healthy subjects with obesity. *Cell Metab*. 2022 Aug 30:S1550-4131(22)00344-8. doi: 10.1016/j.cmet.2022.08.001. Epub ahead of print. PMID: 36087576.

39. Janssen JAMJL. Hyperinsulinemia and Its Pivotal Role in Aging, Obesity, Type 2 Diabetes, Cardiovascular Disease and Cancer. *Int J Mol Sci*. 2021 Jul 21;22(15):7797. doi: 10.3390/ijms22157797. PMID: 34360563; PMCID: PMC8345990.

40. Kmietowicz Z. Coca-Cola funded group set up to promote "energy balance" is disbanded. *BMJ*. 2015 Dec 4;351:h6590. doi: 10.1136/bmj.h6590. PMID: 26637498.

41. Barlow P, Serôdio P, Ruskin G, McKee M, Stuckler D. Science organisations and Coca-Cola's 'war' with the public health community: insights from an internal industry document. *J Epidemiol Community Health*. 2018 Sep;72(9):761-763. doi: 10.1136/jech-2017-210375. Epub 2018 Mar 14. PMID: 29540465; PMCID: PMC6109246.

42. Serodio P, Ruskin G, McKee M, Stuckler D. Evaluating Coca-Cola's attempts to influence public health 'in their own words': analysis of Coca-Cola emails with public health academics leading the Global Energy Balance Network. *Public Health Nutr*. 2020 Oct;23(14):2647-2653. doi: 10.1017/S1368980020002098. Epub 2020 Aug 3. PMID: 32744984.

43. Greenhalgh S. Inside ILSI: How Coca-Cola, Working through Its Scientific Nonprofit, Created a Global Science of Exercise for Obesity and Got It Embedded in Chinese Policy (1995-2015). *J Health Polit Policy Law*. 2021 Apr 1;46(2):235-276. doi: 10.1215/03616878-8802174. PMID: 32955566.

44. Rey-López JP, Gonzalez CA. Research partnerships between Coca-Cola and health organizations in Spain. *Eur J Public Health*. 2019 Oct 1;29(5):810-815. doi: 10.1093/eurpub/cky175. PMID: 30169613.

45. Malhotra A, Noakes T, Phinney S. It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. *Br J Sports Med*. 2015 Aug;49(15):967-8. doi: 10.1136/bjsports-2015-094911. Epub 2015 Apr 22. PMID: 25904145.

46. Maani Hessari N, Ruskin G, McKEE M, Stuckler D. Public Meets Private: Conversations Between Coca-Cola and the CDC. *Milbank Q*. 2019 Mar;97(1):74-90. doi: 10.1111/1468-0009.12368. Epub 2019 Jan 29. PMID: 30693564; PMCID: PMC6422605.

47. Centers for Disease Control and Prevention (CDC). Get the Facts: Sugar-Sweetened Beverages and Consumption. https://www.cdc.gov/nutrition/data-statistics/sugar-sweetened-beverages-intake.html (accessed 11.9.2022)

48. Peterson JB. *12 Rules for Life: An Antidote to Chaos*. Random House Canada, 2018.

49. The International Life Sciences Institute (ILSI). https://ilsi.org/ (accessed 13.9.2022)

50. https://www.nature.com/ijo/

51. Harrison-Dunn AR. Conflict of interest? On the sugar payroll. https://www.foodnavigator.com/Article/2014/01/20/Conflict-of-interest-On-the-sugar-payroll# (accessed on 13.9.2022)

52. Stensel DJ, Dhurandhar NV, Atkinson RL. Ian Macdonald retires as Editor-In-Chief. *Int J Obes* (Lond). 2022 Sep;46(9):1567-1568. doi: 10.1038/s41366-022-01166-4. Epub 2022 Jun 29. PMID: 35768566.

53. Harman AE, Stensel DJ. *Physical Activity and Health: The Evidence Explained*. Routlegde, 2009.

54. Noakes T, Sboros M. *Real Food On Trial: How the diet dictators tried to destroy a top scientist*. Columbus Publishing, 2019.