Topoi
https://doi.org/10.1007/s11245-020-09722-1

From Obesity to Energy Metabolism: Ontological Perspectives on the Metrics of Human Bodies

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Accepted: 14 September 2020

Abstract
In this paper, we aim at rethinking the concept of obesity in a way that better captures the connection between underlying medical aspects, on the one hand, and an individual's developmental history, on the other. Our proposal rests on the idea that obesity is not to be understood as a phenotypic trait or character; rather, obesity represents one of the many possible states of a more complex phenotypic trait that we call 'energy metabolism.' We argue that this apparently simple conceptual shift can help solve important theoretical misconceptions regarding the genetics, epigenetics, and development of obesity. In addition, we show that our proposal can be fruitfully paired with the concept of developmental channeling of a trait, which connects to the study of the plasticity and canalization of complex traits. Finally, we discuss the potential impact of our approach on the assessment, treatment, and social narratives of obesity.

Keywords Obesity · Genetics of obesity · Epigenetics of obesity · Definition of obesity · Developmental canalization · Obesity and public health

1 Introduction

Obesity is a major issue on a global scale in contemporary societies. Since the 1990s (Hill and Peters 1998; James et al. 2001; Popkin and Doak 1998), it is customary for reports and documents to talk about obesity as an epidemic or even a pandemic that—in the words of Mozzaffarian—"will decimate population health, economic productivity and health-system capacity worldwide" (2020, p. 38). The potentially devastating impact, one may add, concerns not only societies and institutions, but also a reshaping of the ways in which people form life plans and socialize. In fact, the data leave little doubts about the urgency of the matter.

As of 2016, 650 million people in the world were considered obese and over 1.9 billion overweight.[1] Comparing figures between 1980 and 2016, it is remarkable that every single country worldwide has seen an increase in the number of obese and overweight people (Abarca-Gómez et al. 2017). A recent study regarding the US population suggests that nearly half of it will be obese by 2050 (Ward et al. 2019). The social significance of obesity is no less impressive than the medical. The category 'obese' is pivotal in public discourses concerning body image and plays a major role in shaping personal and group identities (Schwartz and Brownell 2004).

Obesity should not be thought of in isolation from other categories that are relevant to pinpoint human conditions that typically *precede* the development of chronic diseases and illnesses (e.g., type 2 diabetes or kwashiorkor disease) and that typically *follow from* certain dietary patterns (e.g., a diet with a great excess of fats or remarkably lacking in proteins). In fact, international organizations such as the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) consider obesity as one of the three forms of malnutrition existing, the other two being undernutrition and micronutrient malnutrition.

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[1] See *Ten Facts About Obesity*, fact 2 https://www.who.int/features/factfiles/obesity/en/.

Published online: 19 September 2020

Jointly taken, the three forms represent the so-called triple-burden of malnutrition. This is thought as an intermediate state typically linked to a prolonged unbalanced diet and potentially leading to chronic conditions (Rosenbloom et al. 2008; WHO 2018).

Research over the past two decades showed that these three forms of malnutrition are often correlated (for a recent study complexifying the concept of malnutrition, see Scrinis 2020). For instance, in some cases, the forms are associated to two distinct life phases—since the two conditions relate to similar dietary practices and approaches to food, a person is typically first undernourished and then obese (Caballero 2006; Popkin et al. 2012). Or, in other cases, the forms occur simultaneously (Gómez et al. 2013), as when a person has an excess or deficiency of micronutrients and is obese at once.

Despite its centrality to individual humans and to societies, the category of obesity remains conceptually fuzzy. Broadly speaking, obesity consists of a storage of excessive amounts of triglycerides in adipose tissue that may impair health (Herrera and Lindgren 2010), but most research on the biology of obesity focuses on proxy measures of overall body fat content, such as Body Mass Index (BMI), body weight, Waist Circumference (WC), and Waist to Hip Ratio (WHR). To calculate Body Mass Index (BMI), for example, a person's weight is divided by the square of the person's height (kg/m^2). Unfortunately, proxies of this sort have been proven to be not only inaccurate, but also insensitive to racial and sexual differences that are nonetheless of central importance as regards the many medical, psychological, and social facets of obesity. As Ahima and Lazar put it, "optimal weight that is predictive of health status and mortality is likely to be dependent on age, sex, genetics, cardiometabolic fitness, pre-existing diseases, and other factors" (2013, p. 858).[2]

What does 'obese' stand for? The term seems to trade in a sort of promiscuity between several understandings and their value-laden imports. In fact, it is declined within different narrative contexts and latched onto different conceptual frameworks (e.g., in terms of bodily measurements *vs* body appearance), parameters (e.g., health *vs* beauty *vs* group identity), and aims (e.g., efficiency *vs* appearance). These imports are often in tension with each other and may produce unwanted negative effects for both individuals and health care systems (Barnhill and Doggett 2018).

For the purposes of this paper, it is worth drawing a distinction between two possible conceptual understandings of obesity. The first one sees 'obese' as a tag for classifying those people who contribute to a certain *effect* over society, namely incurring in unprecedented health costs, e.g., in terms of economic expenditure, or medical consequences over individuals and groups. An illustration of this is the opening of Singer's well-known editorial on the ethical burdens of obesity: "We are getting fatter […] it has become commonplace to see people so fat that they waddle rather than walk […] Is a person's weight his or her own business? […] I don't think so. Obesity is an ethical issue, because an increase in weight by some imposes costs on others." Although this first understanding may be suitable for calculating economic and medical costs of obesity to society (those who matter, e.g., in a consequentialist spirit), it has modest explanatory ambitions as regards the processes that generate obesity, and it is probably unsuited for carefully assessing individual responsibilities.

The second understanding sees obesity as a condition of individual agents that *causes* certain consequences. Biological and medical research devoted to explaining how obesity is generated must be read as aiming (explicitly or not) at uncovering a plausible version of this second understanding. In the most simplistic version of this interpretation, all obese people would share a single characteristic (e.g., a high value of BMI) that, in isolation, account for *all* the phenomena associated with obesity from medical, psychological, social, and individual perspectives. If so, such characteristic should be the target of uniform socio-political and economic intervention.

In this paper, we focus on the second understanding of obesity, and we shall return briefly on the other one in our closing remarks. More precisely, we take on the task to conceptually reframe obesity in a way that would better capture the connection between biological and medical purposes, on the one hand, and the perspectives of individual agents and social effects, on the other. Can we devise an explanatory category of obesity without thereby overriding individual and social conceptual frameworks, values, and aims? As we shall discuss, this problem is especially pressing with respect to research on the genetics and epigenetics of obesity, which attempt to anchor the category to (apparently) clear-cut identity criteria.

In Sect. 2, we begin by reviewing genetic research on obesity. We then move, in Sect. 3, to pitch our proposal, which rests on the idea that obesity is not a phenotypic trait; rather, obesity is one of the many possible states of a phenotypic trait that we shall call *energy metabolism*—for a simple parallel, *having blue eyes* is not a phenotypic trait, but one of the ways that the phenotypic trait *having a certain eye color* can be realized. We argue that this apparently simple conceptual shift solves some important theoretical misconceptions regarding obesity, particularly the expectation that the biological aspects (i.e., genetic variation) involved in the development of obesity are consistent or sufficiently similar among different individuals. Finally, in Sect. 4, we show

[2] Note that the WHO regards BMI as the main index for tracking obese people. See *Ten Facts About Obesity*, fact 1 https://www.who.int/features/factfiles/obesity/en/.

that our proposal can be fruitfully paired with the concept of *developmental channeling* of a trait. In this view, energy metabolism is channeled through a person's life, so that an assessment of the obesity condition should be sensitive to the specific developmental story of the individual. Thus, our approach suggests a personalized medical assessments of obesity, which accounts not only for the specificities that Ahima and Lazar (2013) call for, but also for the framing of energy metabolism in individual terms and for temporally, geographically, and socially located dietary and life plans.

2 Genetics Research on the Proxies of Obesity

The genetic basis of obesity has been investigated through a variety of methodologies, including gene knockout experiments on animal models, heritability and family studies, linkage analyses, the candidate-gene approach, and, more recently, genome-wide association studies (GWAS). This plurality of approaches reflects the complex etiology and inter-individual variability of obesity, which can involve the effects of highly penetrant genes, the small effects of many single nucleotide polymorphisms (SNPs), and environmental effects such as nutrition and exercise.

In genetics, obesity is usually classified into types depending on the hypothesized etiology. For instance, forms of so-called monogenic or Mendelian obesity are associated with mutations in single genes affecting major biochemical pathways. By contrast, so-called common obesity is thought to be due to the combined effects of many genetic and environmental effects. Notably, common obesity phenotypes are *normally distributed*, meaning that individual values are distributed around a mean and the population's variance can be expressed in terms of standard deviations from the mean. In this sense, common obesity is represented by a range of values of a biometrical or quantitative trait (e.g., BMI).[3]

Between the 1970s and the 1990s, the genetics of obesity was extensively investigated in humans through family and twin studies, which estimated that the heritability of traits like BMI, WC, and WHR ranges between 0.3 and 0.8 (Herrera and Lindgren 2010; Maes et al. 1997).[4]

Since the late 1990s, with technological and methodological advancements, researchers started to seek specific alleles associated with obesity.

Early studies focused on extreme or rare forms of obesity characterized by Mendelian inheritance patterns. Identifying genetic variants associated with these forms of obesity is easier, at least in theory, due to the strong penetrance of genes on the phenotype. By 2005, hundreds of candidate genes across the whole human genome were investigated. Unfortunately, most results of candidate-gene studies were not successfully replicated, and only about twenty obesity susceptibility loci were identified by five different studies (Herrera and Lindgren 2010; Qi and Cho 2008; Rankinen et al. 2006).[5]

Mutations more strongly associated with monogenic obesity were in genes encoding leptin and leptin receptors (*LEP* and *LEPR*), proopiomelanocortin (*POMC*), and melanocortin receptor 4 (*MCR4*), which all play a role in the regulation of food intake and energy balance (Farooqi and O'Rahilly 2006; O'Rahilly 2009; Xia and Grant 2013).

As we mentioned above, common forms of obesity are probably not due to single, rare, and highly penetrant alleles. Rather, they are thought to be due to many common genetic variants (allele frequency in the population > 1%) with small individual effects that are normally distributed in the general population. In this view, severe obesity would represent an extreme tail of the variation in BMI reflecting genetic factors shared by all individuals as well as environmental factors (Rohde et al. 2019; Xia and Grant 2013). Together with the limitations of the candidate-gene approach, the focus on common obesity eventually determined a shift towards more systematic investigation of the human genome. Within this trend, GWAS came to represent the most promising methodology for seeking genetic variants associated with obesity.[6]

Early GWAS allowed researchers to identify some new potential candidate genes operating both through adipose tissue and through the central nervous system and affecting appetite, satiety, energy expenditure, and feeding behavior (Herrera and Lindgren 2010; Locke et al. 2015). Unfortunately, as it is often the case with GWAS, such findings have

[3] For a critical analysis of the distinction between qualitative (Mendelian) and quantitative (biometrical) traits, see Serpico (2020).

[4] Heritability (h^2) is a statistical index, varying between 0 and 1, that represents the portion of variance in a trait that is accounted for by genetic variance (in a specific population, in a specific environment). Note that the relationship between heritability and genetic causality has been debated since the 1970s (Downes and Matthews 2019; Serpico 2018).

[5] It is important to notice that the candidate-gene approach relies on specific research hypotheses on the pathogenesis of a condition formulated through the study of animal models. Moreover, candidate-gene studies usually entail small sample sizes, decreasing the reliability of the results.

[6] In GWAS several hundred thousand to more than a million SNPs can be assayed in thousands of individuals. In the case of traits that vary discontinuously in populations, like monogenic obesity, GWAS compare allelic frequencies for groups of affected individuals versus controls. In the case of quantitative traits, like BMI, they compare low-scoring versus high-scoring individuals. Variants that consistently show up among obese individuals, but not among lean ones, are thought to increase the risk of obesity (Willyard 2014).

not paved the way for the discovery of satisfying mechanistic explanations. It is worth noting that GWA is a hypothesis-free method where no specific prior knowledge of genes' function is required. Thus, a SNP can be statistically associated with a trait's variation for a number of reasons (not necessarily because it *causes* variation in such trait; see Eley and Rijsdijk 2005; Rohde et al. 2019). For instance, the *FTO* (fat-mass and obesity) gene is widely considered the most robust common obesity-susceptibility locus, but it only accounts for a small portion of variance in BMI and its role in the regulation of energy homeostasis remains unclear (Frayling et al. 2007; Xia and Grant 2013; Willyard 2014; for some explanatory attempts, see Claussnitzer et al. 2015; Karra et al. 2013; Smemo et al. 2014).

Another problem affecting GWAS on obesity is that currently identified SNPs (~97) together accounted for a small part of the variability of BMI (~3–5%) and are thus poor predictors of obesity (Bogardus 2009; Herrera and Lindgren 2010; Locke et al. 2015; Rohde et al. 2019).[7] The gap between the heritability estimated through family studies and the heritability accounted for by the SNPs identified by GWAS is called 'missing heritability.'

Within the long-lasting debate on the missing heritability problem, researchers have pointed at a variety of potential explanations for the phenomenon, including the necessity of technical or methodological improvements (e.g., larger sample sizes and datasets) but also theoretical issues. For instance, many have pointed out that GWAS are unsuited to identify rare genetic variants and non-additive genetic effects. In this view, part of the missing heritability would depend on epistatic gene–gene interactions and epigenetic regulation of genetic expression; others have argued that heritability of BMI might be much lower than originally believed (Hebebrand et al. 2010; Li and Qi 2019; Rohde et al. 2019; Yang et al. 2015; Willyard 2014; Xia and Grant 2013).[8]

Some scholars have suggested that part of the problem might also depend on how obesity is operationalized. For instance, Hebebrand et al. (2010) identified shortcomings in the adoption of proxies like BMI. First, BMI depends on two different sub-traits, i.e., body weight and height, which have different heritability and are measured independently from each other. This could increase the chance of measurement errors. Second, BMI cannot differentiate the various *components* of body weight (i.e., fat and lean mass, which both contribute to body weight) and cannot account for the *relative contribution* of bones, muscles, and other tissues to body weight, which differs inter-individually. This might decrease our ability to detect reliable causal effects. Relatedly, Li and Qi (2019) noted that BMI cannot account for the *distribution* of body fat. This is significant because different types of body fat distribution (independent of overall adiposity as measured by BMI) are associated with different diseases, e.g., type 2 diabetes, cardiometabolic disorders, coronary heart disease, and hypertension.

To summarize, two major factors have been identified as potential explanations of shortcomings in genetic research on obesity: first, currently available methodologies could be unable to account for some aspects involved in the etiology of obesity (e.g., gene-environment interactions); second, coarse-grained proxies of body fat content (like BMI) cannot account for the actual biological complexity of obesity-related traits. In the rest of the paper, we will expand on both points by exploring the possibility that inconsistencies in empirical findings do also stem from conceptualizing obesity (and the related traits) in terms of certain phenotypic traits or characters.

3 Reconceptualizing Obesity

A phenotypic trait is usually defined as an observable or measurable characteristic of an organism that is due to the interaction between its genotype and the environment (Hartl and Jones 1998; Lawrence 2008).[9] Given this definition, it would be reasonable to think that obesity is, in fact, a trait: not only is obesity observable, but it is also measurable or operationalized through, e.g., BMI and, no doubt, it is due to G-E interactions.

As we mentioned in Sect. 2, attempts to identify the genetic causes of obesity reflect a view of monogenic obesity as a qualitative or Mendelian trait caused by single genes that can be identified through the candidate-gene approach. In the same vein, common obesity can be understood as a complex trait that is due to the interaction between genetic and environmental effects, and quantitative proxies like BMI, in turn, could be understood as quantitative traits. In this view, the multiple genetic effects involved in both common obesity and BMI could be identified through GWAS.

In our understanding, the conceptualization of monogenic obesity, common obesity, and BMI as phenotypic traits is one important source of inconsistencies in genetic research and is also likely to hinder personalized treatment. In the following, we shall propose that obesity (as well as other

[7] In a recent meta-analysis including ~700.000 individuals, Yengo et al. (2018) revised the genome-wide significance threshold and identified 941 SNPs associated with BMI, which together explain ~6% of the BMI variance.

[8] For general discussions on the missing heritability problem, see Downes and Matthews (2019), Eichler et al. (2010), and Matthews and Turkheimer (2019).

[9] See also the *Encyclopaedia Britannica* https://www.britannica.com/science/phenotype.

observable characteristics like leanness, normal weight, and any BMI value) should be regarded as a specific *value* or *form* that a trait can have, rather than a trait (no matter whether monogenic or quantitative).[10]

To clarify this point, we need to introduce the distinction between *characters* and *character states*.[11] *Characters* represent general—often species- or lineage-specific—phenotypic characteristics, such as the shape of pea seeds, eye color in fruit flies, and height in humans. *Character states*, instead, are values or forms of the *characters* that further detail individual organisms. Instances include wrinkled pea seeds, the scarlet-eye phenotype in flies, and a given height value.

The distinction between the two concepts has a central theoretical relevance. Thus, it is worth illustrating it in more details through two case studies. First, flies' eyes. These can be of different colors depending on how different genes transport pigment precursors into the eye cells: scarlet phenotypes are due to the presence of red pigment only; brown phenotypes to brown pigment only; white phenotypes to the absence of any pigments (Guilfoile 1997; Pollock 1989). Each of such alternative phenotypes represents a possible form or *state* that the eye-color *character* can take.

Second, to consider a subtler case, let us take wrinkledness in pea seeds. At the molecular level, the shape and texture of seeds depend on the functioning of the starch-branching enzyme 1 (SBE1), which converts sugar into starch. Different quantities of starch affect the seeds' water absorption capability during embryonic development, which, in turn, results in different seed shapes (Bhattacharyya et al. 1990; Guilfoile 1997).[12] One might be tempted to think that wrinkledness itself is a *character*. However, according to our definition, wrinkledness should be regarded as a *character state*, that is, a specific, determinate form that pea seeds can have. The *character*, instead, would be the pea shape, which involves *starch metabolism* and thus depends on the quantity of available sugar and on the functioning of the SBE1.

According to the definitions provided so far, neither obesity nor any BMI value can be considered as a *character*. In fact, they do not single out a generic phenotypic characteristic, which would be more plausibly connected to body shapes, height to weight ratios, and alike connotations of a person's body. For the sake of simplicity, we will call this general feature 'energy metabolism' or 'energy homeostasis,' a far more general and complex phenotypic feature that involves species-specific developmental mechanisms related to bodily functions. Such a *character* represents a higher-level feature of an organism involving neuroendocrine and metabolic regulatory networks related to energy intake and expenditure, body shape, growth, and weight.[13] Obesity and BMI, on the other hand, seem to be different *states* of a *character*, that is, specific forms of the more general *character* 'energy metabolism.'

Conceptualizing obesity as a *character* reflects a simplified view of phenotypic development and, in particular, of the genetic and environmental factors involved in obese phenotypes. This misleading view of obesity, we contend, can generate important misunderstandings in public health efforts to mitigate obesity. To best explain this point, let us consider how different the development of *characters* and *character states*, respectively, can be.

The development of *characters* like energy metabolism, seed shape, eye color, and height, is usually due to many interacting genetic and environmental influences. For instance, the development of pea seeds shape depends on both genotypic and environmental factors (e.g., sugar and water availability). Likewise, the development of energy homeostasis is due to the interaction between a variety of factors, including genetic factors, neuroendocrine and metabolic regulatory networks, epigenetic mechanisms, long- and short-terms psychological factors, and life experience.

Sometimes, *character states* can causally depend on single-gene mutations, as in the case of scarlet eye color in flies and wrinkledness in pea seeds (see above). This applies to obesity, too. For instance, single gene-mutations in the *LEP* gene are associated with severe forms of obesity

[10] It is worth noting that conceptual issues involving the definition of phenotype are seldom discussed within empirical research; in this sense, the conceptualizations here discussed are often implicit, and it is possible that recent research trends endorse a view of obesity like our own (we thank an anonymous reviewer for suggesting this). For instance, this might be the case for GWAS, where obese versus lean groups are compared. It is likely that the problem is more significant for classical research programs, such as those involved in the study of so-called qualitative traits like monogenic obesity. For a discussion on the theoretical and historical connection between the study of qualitative/monogenic traits and Mendelian methods, on the one hand, and of quantitative/polygenic traits and biometrical methods, on the other, see Serpico (2020).

[11] Note that the two terms have a variety of meanings in biology. Here, we shall refer to the definition discussed in Serpico (2020).

[12] Bhattacharyya et al. (1990) identified the molecular cause of wrinkledness into the insertion of a transposon in SBE1, leading to the inactivation of the gene and absence of the enzyme.

[13] Focusing on a very general and systemic feature like energy metabolism seems to us the best conceptual strategy (at least as a first approximation) due to the physiological complexity of obesity-related traits as well as their inter-individual variability. In mechanistic terms, two major neuroendocrine networks involved in energy homeostasis have been identified, involving leptin resistance and ghrelin resistance, respectively (Cui et al. 2017). So, one may want to consider two characters (e.g., *leptin metabolism* and *ghrelin metabolism*) instead of just energy metabolism more generally. However, it is unlikely that all forms of obesity (and all the individual forms that energy homeostasis can take) could be reduced to the functioning of just two endocrine regulatory networks: not only both leptin and ghrelin are involved in many biological functions beyond energy homeostasis, but about 500 molecules are probably implicated in obese states (Jagannadham et al. 2016).

(see Sect. 2), leading to the view that a single gene alone can cause obesity. However, if we look at this from a wider perspective and consider the general functional role of the *LEP* gene, we can see that it encodes genetic products that enter complex developmental and regulatory networks of energy homeostasis.[14] Some *LEP* mutations just 'drive' an organism's development towards the *character state* that we usually call 'overweight' or 'obesity.'

Importantly, in genetics research, genes involved in the development of different *states* of energy metabolism are usually expected to be highly consistent or sufficiently similar among individuals with similar phenotypes (e.g., similar BMI indexes). However, the *character/character states* distinction allows us to predict that etiological factors involved in different *states* of energy metabolism (or even in apparently similar states) can differ greatly from an individual to another, making each examined population highly heterogeneous in biological terms. Indeed, obese people in a sample can be very different from each other in terms of what genetic and environmental influences have driven energy metabolism towards the obese *state*—though they can be very similar as regards some phenotypic parameter like BMI. Thus, for instance, people in the sample can have similar weight or BMI value, despite having achieved it through quite different avenues; to name just a few sorts of avenues, individuals within the same category may have reached it *because* they were differently able, lead a sedentary lifestyle, overeating, through specific medical history, socio-economic conditions, and so on. This heterogeneity might impair our ability to identify reliable associations between genotypic and phenotypic variation.

It is also worth emphasizing that the adoption of coarse-grained measures like BMI exacerbated the theoretical misunderstandings. BMI is expressed as a single quantitative dimension on which individuals can be placed. This has misled and still misleads those who make use of the concept in thinking that BMI is a quantitative character. Taking obesity as a *character* has prompted the view that it was possible to identify well-defined genetic factors involved in the development of obese states, and it was expected that such factors were uniformly distribute among obese individuals. On the contrary, BMI is the outcome of a cluster of different sub-traits, and the etiological factors that drive development towards obese *states* can vary widely also in apparently similar individuals.

This subtle and seemingly innocuous misconception has fueled inconsistencies in the study of statistical associations between phenotypic and genotypic variation in large samples of individuals, where the same *character state* can be the end point of multiple developmental trajectories. Let us clarify that the problem is not just that different forms of obesity (e.g., monogenic or common) can have different etiologies (such as being related to single or many genes, respectively). What we would like to stress is that different forms of the energy metabolism *character* can have drastically different developmental bases in different individuals regardless of their phenotypic similarities.

Moreover, conceptualizing obesity as a *character state* does work conceptually better with respect to the study of *how* genes and the environment interact to generate obesity *states*. Indeed, the distinction implies a shift in focus *from how etiological factors generate an observable characteristic like obesity to how they drive an organism towards a specific developmental pathway*, that is, a possible *state* of energy metabolism.

In the next section, we aim to exemplify the impactful role of the *characters/character states* distinction for the study of the epigenetics of obesity, particularly as regards what aspects of the development of obesity future personalized medicine should target.

4 Perspectives on the Intervention on Obesity States

As we explained in Sect. 3, the *characters/character states* distinction construes obesity as one possible *state* of the energy metabolism *character*. This allows us to better frame the role of genes in the development of body fat content: rather than *causing* the 'obesity trait,' genes drive individuals towards one of the many possible metabolic *states*, each of which is associated with forms of obesity, leanness, and 'normality.'

The exposure to an obesogenic environment is widely recognized as necessary for the development of obesity, but a renewed focus on the environment in biomedical research was favored by the 'failure' of GWAS (see Sect. 2). Thus, in the last decade, the study of the epigenetics of obesity have attracted much attention, leading to the view that the effects of genetic factors on health depend on the effects of environmental factors and vice versa. For instance, dietary preferences have turned out to have long-term effects on behavior by affecting epigenetic programming of genetic expression and, in turn, epigenetic programming of genetic expression can affect dietary preferences (McGowan et al. 2008). As another example, physical activity and dietary changes have been shown to modify the action of genes like *FTO* (see Li and Qi 2019; Qi 2014; Qi and Cho 2008; Rohde et al. 2019).

Understanding the role of the environment in the development of obesity would surely have profound implications for its prevention and treatment. Bogardus and Swinburn, for instance, assert that "if our goal is to reduce obesity, then the

[14] Note, moreover, that the function of leptin is not limited to energy homeostasis or metabolism (see Cui et al. 2017).

environment should be the predominant focus for research and action because that is where the pathology lies" (2017, p. 1861). Notably, epigenetic modifications induced by gene-environment interactions are dynamic and thus potentially reversible (Rodhe et al. 2019). However, the limitations of environmental intervention on obesity are yet to be assessed. How should we think of the gene-environment interaction when it comes to obesity? And in what ways the conceptualization of obesity as a *character state*, rather than a *character*, can help us in this task?

Our contention is that the *character/character states* distinction allows us to reframe the public health efforts targeting obesity at an individualized level in new terms. If obesity is one *state*, among many, of a *character*, then the question becomes: under which circumstances is it possible to revert the *character state* obesity into another desired state (viz., a 'healthy' one)? Designing effective interventions on obesity requires considering this question carefully. In this section, we suggest that the answer will depend on how much the *character state* under analysis is *canalized* against environmental variations.

The concept of canalization was originally introduced by Edwin Holt to denote prenatal conditions as factors that narrow down the initially random nature of motor activity in the embryo or fetus (see Gottlieb 1991) and then by Conrad Waddington to denote "the property of a developmental process of being to some extent modifiable [plastic], but to some extent resistant to modification [robust]" (1961, p. 270).[15]

For clarifying the notion of canalization, Waddington depicted the developmental process as a ball rolling through valleys (which he called *chreods*) that represent branching paths: "the steeper the valley and the larger the ridges separating the valleys, the stronger the tendency of the ball, when it is pushed from its course along the valley bottom by internal or external disturbances, to go back to its original course" (Scharloo 1991, p. 65; see Waddington 1942). Canalization is thus defined as a preferred path that the development will follow against disturbances in the internal or external environment.

Although canalization is often presented as a property of genotypes,[16] Waddington's epigenetics involves a belief in the power of the environment in shaping the developmental path: "the environment can act either as a switch, or as a factor involved in the system of mutually interacting processes to which the buffering of the paths is due" (Waddington 1942, p. 564).

The *characters/character states* distinction does nicely fit Waddington's depiction of development: on the one hand, canalization explains why a species-specific *character* will tend to develop against perturbations in most (if not all) the members of a species; on the other hand, understanding a *character*'s variation within a species involves asking how much the *character* is plastic or robust.

Framing phenotypic development this way allows us to return to the question above about the power of the environment in treating obesity, which, as we mentioned, depends on how much such *character state* is plastic or robust. In Waddington's view, "an alteration in the course of a developmental path will, if it occurs early in development, shift the whole set of paths which afterwards branch from it" (1941, p. 147). In this sense, the range of developmental potentials narrows down over time.[17] This suggests that, depending on the developmental stage, environmental interventions might be more or less effective, because we cannot just 'revert' development or 'replay the developmental tape.' It is plausible, however, that different *character states* can be more or less canalized.

Let us consider two examples, namely, phenylketonuria (PKU) and intelligence (assessed through IQ tests).

PKU is a metabolic disease due to mutations in a single gene (*PAH*). In individuals with two mutated *PAH* copies, the enzyme phenylalanine hydroxylase is unable to properly metabolize phenylalanine, and this leads to the stacking up of the amino acid in the body, causing clinical symptoms including cognitive disability.[18] Notably, environmental intervention can prevent the manifestation of clinical symptoms: by assuming a diet poor of phenylalanine early in development, it is possible to prevent the pathological *state* and favor a healthy one. However, if this specific diet is not assumed on time, individuals carrying two mutated *PAH* alleles will develop PKU and, eventually, it will become

[15] Phenotypic plasticity concerns the ability of environmental influences to alter genetic expression (Bradshaw 1965). Robustness, instead, represents the ability of an organism to bypass minor perturbations from the genotype and the environment and develop as a typical individual of its species under a normal set of conditions (Palmer 1994).

[16] For instance, Ariew (1996) argued that Waddington's idea of canalization represents a developmental interpretation of the vernacular concept of innateness. However, as Griffiths (2002) noticed, species typicality does not imply developmental fixity: the former reflects what traits an organism *of that kind* will have; the latter means that a trait is 'hard to change' or insensitive to environmental inputs.

[17] Notably, as Scharloo noticed, "this occurs not only in the development of distinct types of tissue, but also on the organismic level in the realization of morphological patterns, in size and shape of organs and in matters of growth and determination of size of whole organisms" (1991, p. 65).

[18] According to the *characters/character states* distinction, PKU would represent a specific variant of liver metabolism: in normal conditions, liver is capable of metabolize phenylalanine; in other cases, liver is unable to do so, leading to PKU. Thus, both normal liver metabolism and PKU are *states* of the *character* liver metabolism (on this interpretation of PKU, see Serpico 2020).

impossible to revert the *character state* into a healthy one. In other words, at some point of the developmental trajectory, liver metabolism will become insensitive to perturbations and its pathological *state* highly canalized.

Human intelligence represents a slightly different exemplification of canalization. Intended as a species-specific *character*, intelligence is strongly canalized: most human beings develop (or have the developmental potential for) that sort of higher-level cognition.[19] In terms of individual variation (i.e., in terms of the possible *states* that intelligence can take), intelligence is usually very plastic due to the sensitivity to environmental influences characterizing the human neurocognitive system (see Sauce and Matzel 2018). However, there are probably some limitations to how much the cognitive capacities of an individual can change at various developmental stages. There are also some extreme developmental scenarios where genetic or environmental influences can drive an individual's intellectual development towards highly canalized paths. For instance, some single-gene mutations, early-life experience, or injuries can disrupt the whole neurodevelopmental process and drive an individual's development towards a path that will lead to low IQ performance. In these extreme scenarios, intelligence will become 'hard to change' or highly canalized, like in the case of PKU analyzed above.

To return to our main topic, energy metabolism and obesity seems to abide by patterns of organization similar to intelligence and intelligence *states*. The human neuroendocrine system and metabolism are highly sensitive to environmental influences and plastic. At the same time, they are robust to a certain extent. This robustness was defined by Walter Cannon as 'physiological homeostasis,' that is, the production of constant metabolic states despite disturbances (see Debat and David 2001). Thus, it is plausible that, in some developmental scenarios, the range of the *accessible states given the previous developmental history* is reduced, and energy metabolism becomes canalized into one state (*chreod*) or another.

This is consistent with the observation that "most of the monogenic causes of human obesity seem to operate through increasing the 'set point' at which body adipose stores stabilize in the individual. Individuals with mutations in leptin, the leptin receptor and MC4R, for example, become obese at a very young age and remain severely, but not necessarily increasingly, obese throughout their lives. Other individuals, included among which are some of the most massively obese, gradually and progressively become more severely obese over time" (O'Rahilly 2009, p. 311).

[19] It should be noted that most *characters* are highly canalised, being them related to species-specific developmental and evolutionary mechanisms.

5 Concluding Remarks

Two main ideas emerge from our analysis, which focused primarily on the biological basis of obesity. First, obesity should not be regarded as a trait of an individual; rather, it is a specific realization of a more general trait of an individual—which we suggest identifying with energy metabolism. Second, individual states of energy metabolism are canalized in a way that is specific to each individual, depending on a combination of aspects including gender, age, genetics, environment, historical development, and education. Therefore, two individuals may realize similar forms of the more general trait energy metabolism, but their cones of future possibilities may diverge deeply. These two ideas have important consequences that we urge should be considered by the different communities of researchers and practitioners addressing obesity. We outline three of them.

The most immediate and striking implication regards *how we measure obesity*. The assessment of an energy metabolism *state*—e.g., whether a person is obese and to what extent—should take place at the individual level, rather than involving the statistical inter-individual comparison of some parameters, in order to account for the range of potential future possibilities and trajectories that are actually accessible to a given individual. People with the same BMI, or with strikingly similar genetic characteristic, may turn out to instantiate the trait energy metabolism in very different ways, so that one is regarded as obese and another as having a normal weight. Thus, we come out with a subverted picture of the matter, according to which obesity is far from being a 'shared trait' and an equalizing condition for a subpopulation of people. In this sense, our framework does not offer ready-made metrics to assess obesity at an individual level. Rather, it aims to render the concept of obesity temporally dynamic, sensitive to individual specificities, and theoretically flexible to accommodate varying medical, psychological, and social variables—and, hence, different understandings of the category.

The second consequence regards *how we cure obesity*. Therapeutic efforts should not attempt to go back or recover a normal *state* of energy metabolism that an individual had (or could have had) at a previous developmental stage. The idea of epigenetic landscape suggests that organisms cannot move backwards through the developmental trajectory, because the time arrow is monodirectional, and development too. In treating obesity, we cannot subsume a narrative framework under which a patient is supposed to 'replay the developmental tape.' Rather, a patient may see themselves in a developmental path that is channeled and may choose to target specific 'future' directions and points within the channel. In this view, we need to identify therapeutic strategies capable of generating or making available new *chreods*, to

speak metaphorically, through which 'the ball can roll down' and, with them, effective as well as ethically suitable ways to communicate them. Considering the strikingly low success rate of dieting programs (Puhl and Heuer 2010), it seems to us promising to suggest reasonable and attainable steps that a patient would (under the best conditions) agree upon realizing at a future stage in life starting from the present state.

The third consequence regards the *way we talk about obesity*. Thinking of obesity in terms of canalization reframes the narratives within which media as well as public health interventions conceive and communicate about it. In this sense, the metaphor of obesity as a *sui generis* epidemic or pandemic that has been in use since the 1990s is particularly misleading. Apart from very superficial characteristics (e.g., being within a certain range of values on the BMI scale) there seems to be no single common trait that, like a virus, all people who end up being regarded as obese in some contexts do share. The parallel with our minds may be handy here. Each of us has their own personal conscious life, rooted in a personal history of embodied experiences, sensitive to social and environmental conditions as well as to the individual developmental stage, and linked to a host of potential future conscious states; in a parallel fashion, we contend, each of us has their own energy metabolism, emerging from a specific dietary history, sensitive to social and environmental conditions as well as to the individual developmental stage, and linked to a host of potential future energy metabolism *states*.

An important corollary of our proposal is that it undercuts certain grounds for ethical prejudices against obesity (see Puhl and Heuer 2010). To elaborate on this point, we should come back to the first understanding of 'obese' we introduced in Sect. 1, according to which the term applies to all those people who contribute to certain effects over society (remaining silent with respect to underlying causal mechanisms that may explain these effects). Of course, in this first sense, obese people may often contribute to a burden to themselves or to others. And, in this sense, we can conclude that all obese people partake in a moral problem. But the reasons why that is the case vary on an individual basis, and the specific course of action that may help each individual with the burden varies, too. It serves little explanatory purposes to divide people into subgroups—such as obese *vs* lean, or obese *vs* overweight—and, on the basis of such divisions, derive medical and ethical consequences. Rather, we should start from the assumption that all humans share the energy metabolism *character*, in some form or another, and cultivate ethically meaningful ways to live with specific realizations of that character.

Acknowledgements This research was funded by the Department of Philosophy "Piero Martinetti" of the University of Milan under the Project "Department of Excellence 2018-2022" (awarded by MIUR, the Italian Ministry for Higher Education and Research) as well as by the Department of Classics, Philosophy and History of the University of Genoa.

Funding Open access funding provided by Università degli Studi di Milano within the CRUI-CARE Agreement.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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