



# **How interdisciplinary research at the crossroad between socio-cultural anthropology, nutritional and physical activity physiology can help addressing the obesity epidemic**

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### **Abstract in English (1297/1300 characters)**

Despite large global initiatives to manage obesity, its prevalence reaches pandemic levels. A potential reason is that the complex interactions between biological, behavioral, and socio-ecological factors and their respective role in the regulation of body weight (BW) and fat mass are still not well understood. Our view is that as long as physical activity (PA) is above a certain level, diet, genes and other factors play a role, but their contribution is less pronounced. However, PA levels below a certain threshold uncouple energy intake and energy needs, and impair metabolic control, thus promoting long term excessive BW and fat mass gain. Technological advances of the past centuries have most likely decreased PA below this threshold in our societies. The epidemiological transition model summarizes the changes in lifestyle, diet and PA that initiated the onset of obesity in Westernized countries. We believe that to identify which factors pose the greatest risk for excessive BW gain, scientists need to study lifestyles, diet, PA and the metabolism of pre-industrial populations, who are undergoing this transition, in a comprehensive metabolic, behavioral and socio-anthropological approach. Here we are presenting the related state-of-the-arts, current gaps in knowledge and future directions.

**3-5 key words :** Epidemiological transition, metabolism, anthropology, body weight, physical activity, pre-industrial populations

### **Résumé en français**

Malgré les programmes de santé publique mis en place à travers le monde, la prévalence de l'obésité atteint des niveaux pandémiques. Une des raisons possibles est que les interactions complexes entre les facteurs biologiques, comportementaux et socio-écologiques, ainsi que leur rôle respectif dans la régulation du poids corporel et de la masse grasse ne sont toujours pas bien compris. Notre groupe de recherche souscrit à l'hypothèse selon laquelle tant que l'activité physique est supérieure à un certain niveau, le rôle de l'alimentation, des gènes et des autres facteurs reste. En revanche, dès que le niveau d'activité physique passe en dessous d'une certaine valeur seuil, les apports énergétiques et les besoins énergétiques sont découplés, et le contrôle métabolique altéré. L'ensemble de ces changements favorise une prise de poids et de masse grasse excessive à long terme. Les progrès technologiques de ces derniers siècles ont très probablement fait baisser l'activité physique en dessous de ce seuil dans nos sociétés occidentales. Le modèle de la transition épidémiologique résume les changements de l'alimentation, de l'activité physique et de la culture ou modes de vie qui ont déclenché l'apparition de l'obésité. Nous pensons que pour identifier les facteurs qui présentent le plus grand risque pour une prise de poids excessive, les scientifiques doivent étudier le métabolisme, l'alimentation, l'activité physique et le mode de vie des populations préindustrielles. Nous présentons ici un modèle de travail expliquant comment les facteurs proximaux et distaux contribuent à une prise de poids, les lacunes actuelles dans les connaissances et les orientations futures.

**3-5 mots-clés:** Transition épidémiologique, métabolisme, anthropologie, Poids corporel, activité physique, populations pré-industrielles

**Box of Key points (articles main conclusions):**

**between 3 and 5 bullet points (85 characters maximum, including spaces, per bullet point).**

- Biological, behavioral and eco-anthropological factors contribute to weight gain
- Interdisciplinary research is needed to assess the respective role of these factors
- Pre-industrial populations who are ongoing transitions are an excellent study model
- Longitudinal studies tracking these populations are therefore needed.

**Introduction**

The pandemic of obesity places tremendous burdens on societies and health care systems [1]. Despite intensive efforts developed across the globe to reduce the prevalence of obesity, all attempted strategies have failed [2]. This may be explained by the fact that how excessive weight gain is affected by biological, environmental, and social factors remains one of the most debated research topics [3, 4]. This may be due to the fact that past socio-ecological transitions that initiated excess weight gain related to an excess of fat mass, in our modern industrial societies ended decades ago, and long-term studies in relevant populations are lacking.

The diet, demography, health and physical activity transitions are often reunited in the concept of epidemiological transition, i.e. the change in the pattern of mortality and disease from high children mortality and infectious diseases to chronic diseases. How these transitions impact the social, ecological, biological, behavioral and cultural factors associated with diet and physical activity, and ultimately weight and fat mass regulation, are part of the debate on the etiology of obesity. Rather than being independent we believe the effects of those transitions are progressive and synergistic.

*Understanding the respective contribution and synergistic effects of the biological, behavioral and socio-eco-anthropological factors to the global obesity epidemic requires novel approaches.* Our interdisciplinary group of research believes that studying pre-industrial populations who are currently facing major socio-ecological transitions will help addressing these challenges. In this viewpoint, we will present the limitations of past traditional research, the gaps in knowledge that need to be addressed and the arguments that support the use of pre-industrial populations for future research.

**The obesity pandemic, a complex problem**

According to the law of energy conservation, body weight gain can only result from a positive energy balance, i.e. an excess of calories intake over calories expended. If the theoretical principle of energy balance seems trivial [5], its regulation is complex. It involves intertwined genetic, epigenetic,

physiological, ecological, social and cultural dimensions [6]. Because the epidemic has mainly occurred over the past 50 years, blaming genetics alone is inappropriate. The regulation of energy stores is a complex and dynamic process influenced by proximal factors, including sex, age, genes, aerobic fitness and others, that modify both intake and expenditure. It is also influenced by distal environmental factors at the societal, cultural and global levels which modify lifestyles and behaviors [6]. The influence of these combined factors triggering weight gain is recapitulated in the notion of diet, demographic and physical activity transitions, all somehow reunited in the epidemiological transition model. This transition includes changes in diet (high-fat and energy dense food), energy expenditure (low physical activity levels), lifestyle (sedentary behaviors, feeding behaviors and job occupations) and culture, which are the primary socio-ecological drivers of the obesity pandemic [7-11].

### **The key role of physical activity in the regulation of body weight**

The role of exercise and physical activity in the regulation of body weight has recently been the topic of animated debates in both the scientific community and the media. Diet-centric research groups argue that the diet transition is essentially responsible for the onset of the obesity epidemic. By contrast, our view is that as long as physical activity is above a certain level, diet, genes and other factors play a role, but their contribution is less preponderant.

In the 1950s, Jean Mayer, a French American nutritionist, suggested that beyond being the most variable component of total energy expenditure (TEE), physical activity is a major determinant of energy intake (see [12]). In addition, below a certain physical activity level ( $PAL = TEE/RMR$ , where RMR is resting metabolic rate) threshold (likely around 1.7-1.8) that we have most certainly reached in our modern societies, energy intake, no longer TEE, drives weight regulation. These early findings were later supported by observational and intervention studies [13, 14]. More recently, we showed that physical activity energy expenditure (PAEE), but not TEE, predicts nutrient partitioning between oxidation and storage [15]. The effect of physical activity on food intake and metabolism is likely the result of its action on metabolic flexibility, i.e. ability of the body to adjust substrate use to changes in substrate availability and energy demand. The concept of metabolic flexibility implies that health is determined by the ability to adapt to conditions of temporary stress, such as overfeeding, and thus maintain or regain homeostasis. Chronic stress conditions may induce adaptation processes that go beyond the limits of normal metabolic flexibility leading to progressive inflexibility, which in turn contributes to a disease onset. Our view is that inability to maintain this flexibility in an organism as a phenotype appears with insufficient levels of physical activity; this is the metabolically inflexible phenotype.

In support, we showed that physical activity predicts metabolic flexibility [16-18], and that physical inactivity induces an inability to adjust fuel use to match the changing fuel availability and energy

demand (i.e. metabolic inflexibility). Metabolic inflexibility precedes the development of glucose intolerance in the pathophysiology of insulin resistance [19]. Importantly, these associations between PAEE and nutrient partitioning and metabolic flexibility were observed independent of changes in energy balance, and even in absence of an increase in TEE [20]. This suggests an independent role of physical activity and PAEE in the regulation of metabolism. In support of this, we recently showed that the inability to both decrease time spent sedentary and adjust fuel use (metabolic inflexibility) in response to an acute overfeeding episode is correlated with long-term weight gain [21, 22]. Because of the high occurrence of overfeeding events over a lifetime, these findings are highly relevant. Finally, we believe that the effects of physical activity on metabolic flexibility may contribute to the mismatch between excess body weight and adiposity and the absence of metabolic disorders that is commonly observed in metabolically healthy obese individuals. This is supported by a meta-analysis conducted by Barry et al. [23] showing that regardless of BMI, normal weight unfit individuals have a risk of mortality twice higher than their normal-weight fit counterparts. Furthermore, fit individuals with overweight or obesity had similar mortality risks as normal weight fit individuals.

Taken altogether, this data suggest that physical activity plays a key role in the regulation of energy expenditure, energy intake and metabolic control, which are the main tenants of body weight regulation. ***Physical activity levels below a certain threshold are associated with a metabolically inflexible phenotype that impairs appetite regulation, energy intake, and metabolic control promoting weight and fat mass gain over the long term.*** We hypothesize that environmental changes lead to changes in physical activity, diet and lifestyle/culture (Figure 1). ❶ During the first phase of the nutrition transition, improvement in food intake, i.e. increase in protein, micro-nutrients and energy intakes, decreases the prevalence of under-nutrition and malnutrition. Healthier food intake improves the ability of the body to adapt to physiological stresses and increases body weight to healthy values, mainly due to increase in fat-free mass. However, sugar, high fat content and salt start to appear in the diet. ❷ During the physical activity transition, physical activity decreases leading to drops in PAEE (when normalized per kg of body weight) and PAL that reaches a threshold corresponding to a metabolic tipping point. This is associated with an alteration of the regulatory mechanisms of food intake leading to an uncoupling between energy intake and expenditure, and a metabolically inflexible state, which are favoring body weight gain and excessive fat mass accumulation. Metabolically inflexible phenotypes are then more vulnerable to the impact of poor diet but also to the adverse health effects associated with social and cultural changes, which increase the overall disease burden associated with obesity [24]. Other factors influencing body weight and composition regulation such as poor diet (high-fat, high saturated fatty acid, high fructose), increased stress, altered social structures and interactions are therefore appearing. ❸ With more advanced technology as those present in most developed countries, additional factors such as poor sleep hygiene, endocrine disruptors, high levels of CO<sub>2</sub>, etc. will come at play and influence the regulation of metabolism and energy balance.

In summary, as long as sufficient levels of physical activity are maintained, the prevalence of overweight is kept low even in presence of dietary changes. However as soon as physical activity levels drop under a certain threshold and meet the metabolic tipping point, the “perfect storm” is in place to trigger and boost the obesity epidemic. We believe that to understand which factors are contributing to the epidemic of obesity, we need to investigate this overall phenomenon. The challenge resides in the available approaches to test this global hypothesis.

### **What have we learnt so far?**

The low prevalence of obesity in most developing countries and pre-industrial populations compared to the high prevalence in Western countries supported the hypothesis that energy expenditure and diet differs between populations at different stages of epidemiological transitions[25]. If the shifts in diet (diet transition) have been well documented, the changes in physical activity (physical activity transition) remains a major gap in our knowledge<sup>[4, 13]</sup>. A commonly shared view is that populations in developing countries must have higher PAEE than industrial societies[26]. Recent meta-analysis compiled studies during which free-living total energy expenditure (TEE) was measured with the gold standard doubly labelled water (DLW) method (see figure 2 and insert 1). Unexpectedly, the meta-analysis did not show differences in TEE adjusted for body weight or PAL between low and middle human development index countries[27]. One of the meta-analysis even suggested that PAEE slightly increased in industrial countries whereas PAL remained stable [28] in the 1980s-1990s, a time period during which obesity prevalence increased. While informative, these studies cannot replace longitudinal data. To our knowledge, only the elegant METs study provided longitudinal data on body weight gain and physical activity in five populations spanning different degrees of the epidemiological transition (rural Ghana, USA, urban South Africa, Seychelles, urban Jamaica)[29]. No associations between accelerometry-derived activity at baseline and 2-year BW change were observed [30]. Altogether these findings questioned the role of reduced TEE and physical activity in the onset of body weight gain and have generated animated debates. However, the paucity of data in traditional populations have precluded clear conclusions and fed the debate.

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### **Answers to promises and pitfalls of current data depends on methodological issues and interdisciplinary science**

A lack of field data. Most previous reports are compilations of existing literature [27, 28, 31]. In the 1980s, when the DLW method was developed in humans, most industrial countries had already been subjected for multiple decades to the epidemiological transition. Changes in TEE had therefore plateaued and DLW studies were measuring TEE at a new and lower steady state. Similarly, most studies in developing countries compared populations who were already sedentary in a mix of sub-urban/sub-rural environments. Although these data are important, they did not allow to fully detect the changes in the determinants. To address this challenging question, the appropriate scientific approach

is to conduct longitudinal studies in populations who have not transitioned from a pre-industrial lifestyle to an urban/modern lifestyle yet.

*The regulation of TEE is debated in Westernized populations.* Because physical activity is the most variable component of TEE, it is thought that the greater moderate-to-vigorous intensity activity (MVPA) is, the higher is TEE. Pontzer et al. [32, 33] recently challenged this simple relationship. Although hunter-gatherers engage in large volume of MVPA, no relationship was found between time spent in MVPA and TEE. They hypothesized that high activity levels are offset by decreases in the other components of TEE, i.e. RMR, thermic effect of food (TEF) or light intensity physical activity (any body movement of daily life including walking, gardening, taking the stairs, doing dish washing, etc.). They proposed the concept of constrained TEE [34], in which TEE increases with physical activity at low levels but plateaus at higher activity levels as the body adapts to maintain TEE within a narrow range. This hypothesis challenges our current knowledge of the regulation of energy balance and warrants further studies. However, Westernized populations are not suited for such studies as they have engineered activity out of daily life. Traditional populations are ideal to test this hypothesis.

*The precision of existing data on energetics is disputable.* Previous comparative studies measured TEE and its components with relatively low precision and accuracy. DLW-derived TEE requires experimental and analytical precisions to reach 1-2% accuracy and 5-6% precision as obtained in our lab; however large variability existed and still exists across laboratories[35]. Because of the constraints inherent to field conditions, most past studies have estimated, rather than measured, RMR using equations known to have low precisions [36]; and TEF has been assumed to be constant (10% of TEE). With the propagation of errors, the estimation of PAEE ( $PAEE = TEE - RMR - TEF$ ) has necessarily low precision. This is critical given that a daily energy gap (difference between energy expenditure and intake) not higher than 50-100 kcal/d[37] is thought to be sufficient to induce unhealthy weight gain and excessive fat mass at the population level. Normalization of metabolic rates is another debated topic. For example, Gallagher et al.[38] reported that lower RMR among African-American adults was likely due to lower volume of high metabolically active organs contributing to RMR, which was not accounted for by statistical adjustments. Long-term studies in pre-industrial populations using state-of-the-art techniques are needed to assess TEE and its components with precision achieved in clinical trials. Metabolic rates need to be properly adjusted by including body size, as measured via body surface and volume, and a dissociation between low and high metabolically active organs contributing to RMR.

*Physical activity is not a homogenous component.* Most past studies assumed that PAEE is a homogeneous compartment of TEE. However, PAEE represents energy expended during the complete 24h-nycthemeral cycle, from sleep and sedentary activities to vigorous exercise. Activities differing in intensity and in bouts duration might not have the same effect on energy balance [39]. We and others have also questioned the impact of daily light-intensity activities[20] and sedentary behavior patterns

on weight regulation, independent of MVPA [40]. We further showed that a comprehensive view of the activity/sedentary components is needed to prevent excess weight gain during adolescence, another transition situation[41]. Moreover, although the more recent studies used 3D-accelerometry [42, 43], the commonly used algorithms overestimate MVPA and do not give precise information on sedentary behaviors, light-intensity activities and posture. Understanding activity behavior in relation with the environmental context also needs information on the location and context where the activity is performed. The phenology of the complete 24h activity cycle needs to be precisely assessed to understand the effects of the physical activity transition on weight regulation and health[44].

*Diet patterns and quality, an unavoidable determinant of energy balance and metabolic health.*

Improved dietary profile has been associated with reduced BW and healthier metabolic profile[45]. Moreover, beyond its energy and macronutrient composition, a better nutritional quality of the diet has been associated with a lower mortality risk [46, 47]. Because food is rarely consumed in isolation, food profile analysis allows to analyze how different food components aggregate together and integrate the synergistic effects of diet as a whole, compared to food items taken in isolation. For this purpose integrative methodologies that consider the whole diet by deriving dietary patterns, data-driven methods such as principal component analysis (PCA) or clustering [48] are needed.

*The socio-anthropological dimension, a parameter influencing health.* During epidemiological transitions in rural populations, the modernization/urbanization processes impact living conditions and lifestyles that include eating patterns, transhumance patterns and professional/social activities, needing a sociocultural approach to better understand the impact of social background and cultural identities. This complementary approach will allow to detect changes at smaller scales and better understand the socio-cultural dynamics involved in behavioral changes [49]. For instance, the rapid evolution from a traditional rural pastoralist to an urban lifestyle, as observed in other rural populations exposed to urbanization process[50] can disrupt the social structure affecting lifestyle and quality of life, and involving higher social stress level. Precisely, the urban transition affects local dietary and physical activity habits and their associated representations as well as body weight norms [51, 52]. Social representations of a population correspond to a form of knowledge, socially elaborated and shared, contributing to the construction of a common reality [52]. They consist as much of knowledge and opinions as of beliefs intended to legitimize behaviors and practices. Rapid changes in the social representations and practices of diet and physical activity are inseparable with structural changes of the society. Clearly, feeding and physical activity must be considered in their complex interactions with the environment, biology, and local socio-cultural norms as developed by Poulain et al. [53] and Drenowski & Poulain [54].

Both poor social relationships[55] and stress[56] caused by a degraded sociocultural environment have been associated with adverse health outcomes. Stress has also been linked to unhealthy behaviors such as poor diet[56]. Given the rapid urbanization process in different rural populations, future research

will therefore need to employ a bio-socio-anthropological approach to assess changes in the social representations of body weight and lifestyles related to body weight within the context of rapid sociocultural changes potentially associated with social stress levels and quality of life, and their interactions with energy balance-related determinants will need to be assessed.

### **Answers reside in populations who have not completed their epidemiological transition**

Systemic and holistic studies of pre-industrial populations are needed. In the above reported meta-analyses, data from pre-industrial populations and populations from low to middle income countries were underrepresented. This bias masked a large inter-populations variability in the socio-ecological environments they are living in. Although food availability, social structure, and lifestyles influence diet and physical activity patterns and health, they have been overlooked in previous comparative studies<sup>[57]</sup>. Yet they differ between pastoralists, agriculturalists, horticulturalists, hunter-gatherers, etc. For example, the “traditional” societies in South Africa ( $38\pm34$  min/d) and Seychelles ( $38\pm34$  min/d) had much lower levels of MVPA than the Hadza ( $135\pm91$  min/d), but still greater than their counterparts from the USA (Urban Chicago:  $26\pm32$  min/d)<sup>[58]</sup>. Similarly, non-technology dependent agricultural societies have daily activity levels 3-fold higher than levels shown in hunter-gatherers<sup>[59]</sup>. On the other side, we showed that consumption of processed energy-dense food was higher in urban Cameroonians compared to rural ones and that valorization of overweight was associated with obesity status [60]. To fully assess the determinants of body weight regulation and metabolic health in relation to the epidemiological transition and the specific impact of physical activity, future research will need to simultaneously consider the anthro-socio-ecological environment, diet and other lifestyles (e.g. sleep), as well as their interactions.

The need for longitudinal and comparative holistic and systemic studies in traditional populations.

For all the reasons mentioned above, ***we are convinced that only longitudinal studies of populations from pre-industrial countries spanning different phases of the epidemiological transition, including the few remaining traditional populations of agriculturalists, pastoralists and horticulturalists around the world, will improve our understanding of the causes of the obesity epidemic.*** This is challenging because the populations must be selected based on specific anthro-socio-ecological parameters that will allow for defining a near-zero time of changes that closely approximates human lifestyles prior to industrialization, as it is impossible to find nowadays a “true zero time”.

### **Conclusions**

The respective contribution of the different factors associated with the Western lifestyle and known to pose a high risk of obesity remains highly debated. However, diet, physical activity and lifestyle of pre-industrial populations provide the best model to address this challenge. Future research will need to compare these factors in industrial and pre-industrial populations, but also to track the impact of the ongoing transitions on these factors and the associated changes in body weight and metabolic health.

Exciting findings are likely to come from this emerging field of research at the crossroad between metabolism, ecology and anthropology.

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### Declaration of interest

The authors declared having no conflict of interests or competing interests.

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## Figure Legend

**Figure 1. Working model.** Simplified illustration of the impact of epidemiological transition induced by environmental changes on cultural/lifestyles, nutrition and physical activity, and on energy intake, physical activity energy expenditure, and body weight and fat mass.

**Figure 2. Total energy expenditure and its components: definition and methods**

- TEE is calculated with the doubly labelled water method (DLW). The subject ingests a  $^2\text{H}_2^{18}\text{O}$  dose. Total body water is enriched with stable isotope and urine samples are frequently collected to measure the enrichment of  $^2\text{H}$  and  $^{18}\text{O}$ . While  $^2\text{H}$  is excreted from the body as  $^2\text{H}_2\text{O}$ ,  $^{18}\text{O}$  exists the body as both  $\text{H}_2^{18}\text{O}$  and  $\text{C}^{18}\text{O}_2$ . The difference between  $^2\text{H}$  and  $^{18}\text{O}$  elimination rate (in blood, saliva or urine samples) corresponds to the production of  $\text{CO}_2$  production. By using the classical equations of indirect calorimetry, we can estimate the average daily TEE over the period of measurements (usually between 7 and 14 days).
- TEF and RMR are measured by indirect calorimetry (measured of  $\text{CO}_2$  excretion and  $\text{O}_2$  consumption). RMR is measured in fasting state, at thermoneutrality and while the person is awake. TEF is measured for 4-5 hours following a standard meal and corresponds to the increment in energy expenditure above the RMR. TEF can also be estimated as 10% of TEE.
- PAEE is determined by calculation with the formula  $PAEE = TEE - RMR - TEF$  or  $PAEE = 0.9 \times TEE - RMR$  (if TEF is estimated and not directly measured). Moreover, the pattern of physical activity (i.e. time spent in sedentary activities or light, moderate or vigorous activities) can accurately be recorded with 3D-accelerometers measuring both acceleration and postures. PAEE can further be derived by using validated algorithms.

### Insert 1:

- Daily Total energy expenditure (TEE) Is defined as the sum of physical activity-related energy expenditure (PAEE), thermic effect of food (TEF - i.e. energy needed to assimilate and store meal-derived energy) and resting metabolic rate (RMR - i.e. the minimal energy required to ensure vital function maintenance).
- Physical activity-related energy expenditure (PAEE) corresponds to energy required to perform exercise (i.e. structured physical activity) and other daily life physical activities.
- Thermic effect of food (TEF) is the amount of energy required to assimilate and store nutrients after a meal.
- Resting metabolic rate (RMR) is the minimal energy needed to maintain vital functions at rest.