Full Title : ENVIRONMENT AND OBESITY

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ABSTRACT

The aim of this review was to identify and, particularly, to classify all the numerous environmental factors that play a significant role in the environment-dependent body weight dysregulation. The main environmental obesogenic factors are related to built environment such as city plan, transport and school, inactivity, TV and screen-related immobility, smart-phone, video games; they are followed by agroalimentary factors such as imbalanced ingredients, pollutants, speed eating, portion size, sweet drinks, nibbling and junk foods supported by publicity, sociocultural and ethnic factors beside the global environmental changes and seasonal light/dark photoperiod. Beside the analytical examination of the obesogenic factors it is mentioned the cumulative effect that tends to coexist in the same population and thus magnify their pathogenic consequences. In addition, more than one obesogenic factors are present in the same population because they are the expression of another underlying common cause - poverty; such a recognition leads towards socio-economic considerations and consequently towards 'political' solutions that are beyond our scientific approach.

The mechanism of action of the environmental influence includes the serotonergic system and insulin resistance. More recently, it was shown an environment dependent powerful microbiotic implication. Since obesity is influenced by genetically transmitted changes modulated by environment and lifestyle risk factors it is important to understand the genomic mechanism that allows these interactions. It was shown that obesity-predisposing gene variants that interact with environmental exposures use the DNA methylation epigenetic mechanism.

1. INTRODUCTION

An increasing prevalence of obesity is a major health concern in many countries, particularly in the USA where obesity ($BMI \geq 30$) is present in 34% of adults. Obesity is increasing in almost every country in Europe and the rest of the industrialized world. This review deals particularly with the situations that prevail in societies of the 'western' world. It will not deal with several unique environmental factors, ethnic and/or religious settings and the genomic makeup of special populations.

The adaptive evolution of *Homo sapiens* has equipped our regulatory mechanisms for the struggle against caloric deficit rather than caloric surfeit because the environment in primitive multimillennial conditions was close to permanent paucity if not chronic shortage of nutrients. Even if we consider that the 'neolithic evolution', i.e. the wide-scale transition from a lifestyle of hunting and gathering to one of agriculture and social organization of primitive societies resulted in better (not ideal) nutritional conditions, they were invented and extended only during the Neolithic age which represents only a tiny interval of 6,000 to 10,000 years in our species' tri-millennial (300,000 years) lifespan. Such a 'short' period was not sufficient for adaptive mutations to take place and to be selected and consolidated (in terms of Darwinian evolution). Although the human regulatory system possesses a degree of defense these forces are not as powerful as those that act to result development of under-weight. Consequently, the principal means of struggle left to humans against the abundance of the new nutritional environment is their power of resistance reinforced by enlightened, scientific knowledge and its effective implementation by a large part of the industrialized population.

Body weight and its variants such as obesity depends on the balance or the imbalance between energy intake and expenditure. Fundamentally, obesity results when energy consumption chronically exceeds energy expenditure. Each of these two components depends both on an individuals' genome and on his/her environment during both development and adult life.

This review is concerned with the role of the environment. All the environmental factors that influence the energy intake/expenditure rate are particularly influential in childhood, both at home and in school and in spaces set aside for recreation. It has been demonstrated that environmental factors exert an active effect throughout the development process, including pre-natal life[1].

In addition to the environmental influences that occur during the entire development process it has been shown that environmental factors can induce obesogenic changes that are transferable from one generation to the next. This notion of heritability of phenotypic alterations was traditionally supported by the classic case of Dutch families in German-occupied Holland. Following the Dutch famine of 1944, there were body weight repercussions over two generations that affected the victims' grandchildren[2].

The domain of the environment-obesity interaction has become more promising since starting to extend beyond the descriptive approach and develop ~~the~~ into one based on the mechanism of action and its genetic background. Indeed, discoveries in these domains are applicable to ~~in~~ the emerging field of personalized medicine. Implementation of personalized medicine may be exported to give rise to improved therapies. In addition to the therapeutic possibilities, these approaches will lead to better understanding of the eternal question of the relative roles of nature versus nurture as they affect the distribution of BMI with a given population.

2. ENVIRONMENTAL FACTORS

Many environmental factors that affect relative weight can be classified under sixteen headings. The first of them, the built environment factors that act upon body weight balance include physical, chemical, biological agents, urban housing and social conditions, transportation and pollution related to the proximity of influential agricultural or industrial environmental centers of activity.

2.1. BUILT ENVIRONMENT

2.1.1. SCHOOL, TRANSPORT, ELEVATORS

There is a statistically significant relationship between some aspects of the built-up environment and risk of obesity. Understanding the influence of both opportunities for physical activity and access to healthy foods is critical to obtaining a comprehensive picture of this connection. For each of the above factors research to date has focused on the three life stages: childhood, adolescence, and adulthood at varying levels of psychosocial and physical development[3]. It was shown that young children, as compared with adolescents or adults, are more influenced by their immediate environment. Youngsters with limited access to recreational facilities had a 68% greater chance of being obese. Research on the constructed environment in adults has not, for the most part, distinguished between the age-dependent stages. However, there is evidence that the built-up environment has a distinct impact on older adults. A British research project has identified two aspects of the perceived neighborhood environment, i.e. availability of services for seniors and “neighborliness”, as having independent effects, net of individual characteristics, on the physical functioning of home-dwelling persons aged 65 years or older. Given the increasing numbers of older adults in developed countries, as well as the many barriers to healthful aging associated with obesity, a better understanding of the built-up environment’s relation to diet and activity among the elderly is needed[4, 5].

2.2. SCREENS: TV, SMART-PHONE, SOCIAL NETWORKS, VIDEO-GAMES.

These factors play their obesogenic role firstly as they contribute in the sedentary life in addition to being responsible for other obesogenic factors such as nibbling and junk-food consumption related to this kind of lifestyle, particularly among the young. The time spent watching TV varies depends on specialized statistics and on age clusters and ranges from 20% to 70% of the working life of a subject. This behavior is more common in early life and among the elderly.

Participants who watched three hours of TV per day almost doubled their ~~being~~ overweight prevalence and were likely to be obese when compared to non-TV watchers. The duration of self-reported TV watching and the lack of readily accessible places for physical activity were both associated with elevated levels of overweight and obesity.

The time span spent in front of a 'box' decreases as the children grow and switch to ~~in favor of~~ other screens such as smart-phones, or video games. The posture in front of these screens is less passive than simply watching TV but this practice is more obesogenic because it is accompanied by nibbling and junk food consumption for prolonged periods. As for the TV, the time spent engaging in this 'activity' varies depending on the statistics and on the age clusters, ranging from five to ten hours per 'day'. Unfortunately, youngsters also often spend large periods at night to the expense of sleeping; as a result, they suffer from somnolence at school and other activities. The obesogenic consequence of this 'screen-watching habit is currently estimated to account for a 5% to 15% body weight increase[6].

2.3. AGROALIMENTARY ENVIRONMENT

2.3.1. POLLUTANTS.

The theory of environmental obesogens proposes another causal facet to obesity, that prolonged exposure to ambient chemicals may change the body's metabolism and thereby affect energy balance.

For example, a well-established obesogen is smoking before and during pregnancy that increases the risk of obesity twofold in children of school age[1]. However, it is also well known that habitual cigarette smoking reduces energy intake and acts to prevent body fat accumulation.

Endocrine disruptors. The dramatic increase in the use in agricultural settings of various chemicals, and for some of them, their massive production and disposal in the environment,

multiplies the chances that some of them will turn out to be chemical competitors or actors in our regulatory systems or as covert carcinogens. The number of neurochemical or hormonal factors that constitute the pantheon of regulators of human body weight has increased enormously in the recent years, thus increasing the probability of interference in human metabolism of this increasing number of new molecules at or near the top of the list of pollutants and those that have being synthesized as hormones consumed and excreted. Many of these agents in storage, particularly antibiotics and steroids are currently administered in order to improve the anabolic efficiency of foods.

2.3.2. SPEEDY EATING, FAST FOOD.

Modern life has brought whit it a "fast food" culture. There is a close correlation between this culture and increase of obesity[7]. It appears that consuming a meal rapidly results in an excess of feeding, as if by the time the meal has been completed, the satiety process has not reached the point of limiting the amount of energy consumed.

2.3.3. PORTION SIZE.

It was shown that people would terminate their meal whether the portion that was provided in restaurants or at home was smaller or larger by as much as 30%. The compensation in the next meal was only partial or absent if the next meal was provided again as an equally reduced or equally large portion[8].

2.3.4. SUGARY DRINKS

As mentioned above, sugary drinks are available everywhere, much more so than pure water. Of course, this is the case in urban more than in rural areas.

A major concern is the modern phenomenon of drinking calorie-rich drinks. It ~~was~~ has been repeatedly shown that the intake of extra-calories taken as a snack ~~does~~ decrease the size of the subsequent meal. In contrast, ~~to~~ the extra-calories taken as a beverage do not affect the size.

It was originally assumed that sugar replacement by artificial sweeteners would prevent the sugary drink problem. As a matter of fact, cheating the regulatory system of our organism is a bad idea. It was shown a long time ago[9] that artificial sweet taste, is, in the few initial consumptions, sensed by the sweet taste buds as if the sweeteners induced taste was induced by sugar proper. As a result, the endocrine responses are inappropriate, creating an early glycemic imbalance because the ‘expected’ post-absorptive inflow of glucose is missing. These inappropriate responses alternate with meals that bring the right post-absorptive inflow of nutrients. The alternation of these mismatch or not cases becomes more lipogenic than occurs under ~~in~~ normal conditions. That is one of the ‘punishments’ that our regulatory system inflicts to our attempted ‘ruses’[10].

2.3.5 NIBBLING, CONSUMING JUNK FOODS.

Today, in ordinary societies, regular foods and junk foods are ubiquitously available both at home and elsewhere. Not only are they easily accessible but also, they are made of the most obesogenic ingredients, i. e. high caloric density and rich in carbohydrates and fat. Under ad libitum conditions adult individuals and particularly children consume 20% more calories when they are encouraged to nibble, particularly when junk foods are consumed[11].

2.4 PUBLICITY-MARKETING, PACKAGING, MEDIA.

Today, food advertising, particularly that promoting junk foods, pervades all media, from TV to the printed press and posters, including packaging. It is difficult to escape particularly in the case of children who are more impressionable.

As a matter of fact, reliable information transmitted via all media should be the ideal tools needed to cognitively teach the appropriate rules and attitudes in urban and rural societies. This might involve, for example, providing better information about appropriate portion size, the energy value of food, and physical activity energy equivalent of food. It might also involve cognitive skill building. Today, it is difficult to overcome the freedom of the media to promote overeating; nevertheless, when the obesity epidemic reaches intolerable levels, a change in mentality and legislation will become mandatory and will remain in the fight against it [12].

2.5. SOCIOCULTURAL ENVIRONMENT

2.5.1. LOW-INCOME

A number of investigations have shown that a low-income contributes in increasing the prevalence of obesity. There is a negative correlation between ~~the~~ level of income and ~~the~~ prevalence of obesity. In addition, low income is associated with other obesogenic factors, such as low education, few sports-practicing facilities etc, that may be additive thereby ~~so~~ amplifying the obesity prevalence in such populations. Among other factors low-income inhabitants often have to rely on cheap calories with little nutritional value[13].

Thus, low-income is a common condition that introduces, in a sort of cascade-like effect, most of the factors favoring obesity described in this review.

2.5.2. NEIGHBORHOOD AND FOOD ENVIRONMENT

Social environmental influences may include community norms and values related to eating and activity as well as contextual influences such as social networks and social support for behaviors such as leisure walking, whether or not these persons feel “out of place” among the other activities at a given time of day.

Compositional demographic characteristics, such as the age and structure of a neighborhood, may become social-contextual influences on community life, itself more or less favorable towards sports and other calorie-consuming activities. We encounter in the presence of factors including the types of retail food outlets and the availability, quality and price of different kinds of foods, portions in chain and independent restaurants. In addition, this parameter intermingles with low-income factors that amplify obesogenic conditions[14].

2.6. EDUCATION

There is a negative correlation between the level of education and the prevalence of obesity. In fact, this parameter is also correlative with that of low/high income[15].

Education as a cause of obesity and the way healthy foods should be preferred is insufficiently provided. Given the dramatic level the obesity epidemic is reaching today, *ad hoc* courses on nutrition equivalent to history or geography teaching should be systematically provided

at school, both at the level of primary and secondary levels. Such an education should be combined with a systematic organization of energy-spending activities, in addition to classic gymnastics[16].

In addition, a special extracurricular education should be developed, given the efficacy of proper teaching as a means to fight obesogenic habits. Today, there are attempts in this direction provided by individuals or by associations; they need to be better organized at the state level.

2.7. FASHION, ARTICLES.

In the sophisticated 'Western mind' elegance is commonly identified with leanness. Instead this attitude of playing a positive role against obesity contribute to the stigmatizing women (and increasingly men), not only the 'overweight' ones but even some who BMI are not far from the median of the Gaussian distribution.

This problem raises questions concerning the cause of our taste which was first expressed in the western civilization and is expanding throughout the entire planet, often being at odds with the local 'taste' and concept of feminine beauty. There are numerous examples, but I can cite one taken from a close to Europe country, Turkey. In Turkey, if you want to say such a girl is beautiful, you use the term "giobeklide", which literally means "having a nice fat belly".

Esthetic taste and the prevailing body mass index appear to be proportional to the availability of food and the probability of falling into a prolonged period of famine and/or the kind of gastrointestinal infection that prevent the patient from eating.

Also, in the paleolithic age Homo sapiens societies were living in hunter-gatherer societies in environments that yielded limited amounts of food resulting in a chronic undernutrition. Under those conditions, initially overweight individuals had better chances of surviving than lean ones.

2.8. FAMILY ENVIRONMENT

Twins separated at birth and adopted by two different families, one family being predominantly lean and the other family being predominantly fat, showed statistically significant different body weight. Those adopted by a family where both mother and father were overweight or obese were themselves overweight[17].

There are many families who are fat or lean independently of their genetic make-up.

2.9. ETHNIC GROUPS outside of their natural environment.

Investigations of ethnic groups who live outside than maternal environment are particularly necessary in countries such as the USA where a number of ethnic populations live either within neighborhoods environments or are more widely dispersed[18].

In USA, according to the *Centers for Disease Control and Prevention (CDC)*, blacks and Hispanics have obesity rates that are 51% and 21% higher than whites, respectively. ~~But,~~ Communities made up by these members are often impoverished. As a result, inhabitants ~~often~~ have to rely on cheap calories with little nutritional value. Also, the built-up environment is less favorable and more obesogenic in these populations. Again, we are facing the eternal question of a cascade-type phenomenon the origin of which poverty is.

Considering the comparison across populations and societies, most of the research on the relationship between built-up environments and obesity has been conducted within non-Hispanic white populations in the United States. An understanding of the nature of the built-up environment-obesity relationship in different racial/ethnic groups may aid in the development of culturally tailored community-level obesity prevention programs in communities with high rates of obesity. Second generation Japanese in USA suffer a 15% increase in prevalence of obesity[19].

Each ethnic population is characterized by a given gaussian distribution of body weight the

median, average and extreme values are specific and supported by a given genome. Such genomic compositions are reinforced by territorial conditions.

2.10. LIGHT/DARK PHOTOPERIOD

As *Wurtman J* and *Wurtman R* have shown, obesity can also be a complication of seasonal affective disorders. It is related to an atypical form of depression, that usually appears in November-December, the months with the shortest number of daylight hours. It is characterized by increased food intake during these months, generally leading to weight gain. The increased consumption of carbohydrate-rich foods may be driven by an attempt to use such foods to counteract their dysphoric states: patients described an attenuation of their depression after ingestion of carbohydrates, but not after eating protein[20].

2.11. GLOBAL ENVIRONMENTAL CHANGES

Global environmental changes will affect future health and obesity prevalence, particularly in tropical countries. For example, higher ambient temperature can disrupt glucose metabolism via a reduction in brown adipose tissue activity. Rising global temperatures contribute to the current worldwide prevalence of glucose intolerance and various metabolic disturbances that favor the incidence of obesity.

Besides this specific dysregulation global environmental changes will affect many health outcomes, of which obesity is only one consequence[21].

Pessimistic predictions about metabolic disregulations and increasing ambient temperature worsen if we consider the fact that the victim populations had multimillennial years to acquire their Darwinian adaptation to the present climate.

3. POSSIBLE MECHANISMS OF ACTION

Several mechanisms of action of environmental assaults against our vulnerable biological properties are increasingly well understood.

3.1 MICROBIOTA AS A STEP FOR THE MACRO-ENVIRONMENT-RELATED OBESOGENICITY

Both genetic ancestry and environmental factors have a role in determining microbiome composition. On the other hand, there are significant similarities in the composition of the microbiomes of genetically unrelated individuals who share a household. Over 20% of interpersonal microbiome variability is associated with factors related to diet, drugs and anthropometric measurements[22].

Animal studies have shown that the gut microbiota populations can produce afferent signals that directly or indirectly impinge on energy homeostatic systems affecting both feeding and energy balance, i.e. weight gain or loss and energy stores, whether normal or excessive[23].

Host exposures of microbiota potentially modify genetic predisposition to obesity and affect weight management[24].

In particular the gut microbiota increase fat mass in the host because they influence the energy regulating specific parts of the CNS. It was shown that the gut microbiota decrease the expression of anti-obesity brain-derived neurotrophic factor (BDNF) and GLP-1. Thus, decreased BDNF and GLP-1 could mediate the obesogenic effect of gut microbiota[25].

Serguey Fetissov postulated that the dynamics of bacterial growth in the gut underlie the daily rhythm of host appetite[26]. In fact, the study by his team has shown that the action of bacteria-derived molecules on host satiety pathways depends on the bacteria's own growth phase[27] and that specific gut bacteria produce a mimetic protein of the host's anorexigenic neuropeptide alpha-MSH[28].

3.2 SEROTONINERGIC RELEASE.

Environmental factors and particularly the light/dark cycle are among other causes that play a role in depression. The mechanism leading from depression to obesity may involve the consumption of foods that are rich in dietary carbohydrates (and fats) to enhance brain serotonin synthesis[20].

A similar path leading to overeating and obesity may be a side effect of psychotropic drugs that affect appetite.

3.3 INSULIN RESISTANCE

Insulin resistance (IR) plays a role in the augmentation of the occurrence of obesity.

According to NL Rasgon and BS McEwen[29] the worsening of IR following an environmental stress is in direct association with depressive disorders in accelerating onset of dementia and the overall augmentation of rates of obesity in populations suffering increasingly poor diet and exercise habits. In particular, chronic diseases begin in childhood and even before as a result of prenatal *in utero* influences related to poverty. Such health-damaging behaviors result in

different degrees of dysregulation of the mediators of the neuroendocrine, autonomic, immune and metabolic systems in general and IR in particular.

The above trans-generational epigenetic effects are likely to last for generations, as can be deduced from the build-up of this gradual epidemic since the middle of the century.

IR acts upon metabolic and behavioral dysregulations by means of brain mechanisms. Antisense inactivation of the insulin receptor in the hippocampus leads to cognitive impairment without systemic consequences, whereas antisense inactivation of the hypothalamic insulin receptor creates systemic insulin resistance and dyslipidemia[30].

4. GENETIC MECHANISMS

The other crucial property that either amplifies or diminishes the effect of the environmental factors upon obesity is genomic, either at the individual level or as an ethnic variant. Once again, the eternal question of nature versus nurture is raised.

Since obesity's prevalence is influenced by an interaction of genetically transmitted changes that involve nutrition, environment and lifestyle risk factors, the importance of understanding the mechanism of this trans-generational transmission takes a special significance[31].

Today, this environment-obesity trans-generational problem is better understood thanks to new knowledge about epigenetics (from the Greek prefix epi- επί- meaning "over"). Epigenetics implies features that are "on top of" or "in addition to" the traditional genetic basis for inheritance without changing the background genetic code. In effect, ~~today~~ we now know that a heritable phenotypic change may take place without a modification of the genome's nucleotide sequence, but

rather in changes of DNA methylation and histone modification. These two changes alter how genes are expressed or controlled through the action of repressor proteins that attach to silencer regions of the DNA without altering its sequence. In effect, epigenetic studies have demonstrated that obesity related genetic variants may be affected by environmental exposures which act on DNA methylation[32] and also histone modifications (*Costa e Silva et al; ibid*).

Parallel to developments in genomic technology, new epidemiological designs and newly developed statistical approaches are increasingly introduced. They provide an important tool in this domain. An extended review of the subject is published in this issue by *Reddon* (mentioned above).

This new knowledge opens a large domain of future possibilities for preventive and therapeutic strategies. For example, because individual and ethnic variations in the genome represent a subject's predisposition to obesity, the proper use of this genome could help to improve the management of obesity and maintenance of a healthy weight.

5. DISCUSSION

The aim of this review has been to identify and classify the environmental factors that play a significant role in environment-dependent body weight dysregulation. But, this subject covers a vast domain of research and each year additional reports bring to our attention new environmental factors that contribute to the development of obesity.

Each environmental factor is mentioned as if it were acting alone because that reflects the condition under which the original study was conducted. But, it is obvious that none of the environmental factors may, by itself, account for the epigenetic influence on body weight

dysregulation; the problem is that we do not know what the nature of the arithmetical (i.e. positive or negative) additivity of these factors is.

Despite that difficulty, it is possible to attempt to examine the cumulative effect of some of the environmental factors described in the corpus of this paper.

For example, there is one demonstrative case; more than one of the above-mentioned obesogenic factors is present in the same population because such factors are the expression of another underlying common cause - poverty. Obviously, the preventive therapist should consider this common underlying cause. The problem is that such an approach would likely call for socio-economic and consequently 'political' solutions.

In the absence of such preventive power, one can pinpoint each of the obesogenic factors that tend to coexist with poverty and thus magnify the attention of the 'caretaker' and the 'preventive medicine agency resources that do not always exist in our advanced societies.

The potential effectiveness of this type of approach varies from one country to another depending on the financial potency of the institution(s) in charge of the problem; but, whatever the case, urban planning may be conceived and implemented in a way that avoids the obesogenic and favors the anti-obesogenic conditions mentioned above.

In addition, better identifying and understanding the 'mechanisms' through which environmental factors favor obesity will aid in improving the currently scant community-socioeconomic intervention strategies.

The problems and the strategies to oppose environmental obesogenic factors hold true today but it will become much more urgent in the near future because the epidemic is growing rapidly and it is expected to further worsen owing to the inexorable increase in climatic warming.

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Conflicts of interest

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