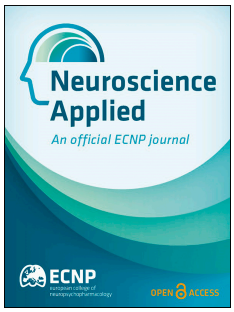

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Is obesity the next step in evolution through brain changes?

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ABSTRACT

Obesity is a disease of complex and multifactorial nature characterized by the interplay of genetic and environmental factors. The prevailing consensus suggests that obesity arises from an imbalance in energy homeostasis, largely driven by excessive consumption of a high-caloric diet and insufficient physical activity. Over time, therapeutic interventions have traditionally focused on addressing this energy imbalance, as well as the medicalization of all types of obesity. However, there is an alarming increase in the prevalence of obesity, reaching pandemic proportions, with significant consequences for the health of a substantial part of the global population, undoubtedly necessitating a change in strategy.

Our purpose is to analyze the obesity pandemic from an evolutionary perspective, and review how its social and cultural causes interact with its pathophysiological determinants. Thus, the culture-brain co-evolution hypothesis is proposed as a compelling framework within niche construction theory that acts as an evolutionary driver for brain expansion and physiological changes in the human species. Some cultural innovations as the invention of tools, and the adoption of processed and cooked foods, have enabled greater energy intake and improved nutrient quality for human diets. These behavioral changes results in the expansion and growth of the human brain, while simultaneously reconditioning the digestive apparatus, leading to a shortening in the time dedicated to foraging and food digestion. These adaptations may have been favored by natural selection, promoting the survival and reproductive success of individuals carrying genetic variants conducive to brain growth and to shape our evolutionary trajectory.

In the 20th and 21st centuries, the obesogenic environments were placed in our lifestyles, characterized by extreme sedentary behaviors and the spread of highly processed and high-energy diets. These evolutionary mechanisms may inevitably contribute to the emergence of a new niche that, in addition to explaining the obesity pandemic, could ultimately lead to the "normalization" of phenotypes and genomes associated with obesity. This phenomenon represents a predictable outcome that derives from our biological predispositions developed over countless generations. Addressing this global challenge necessitates the creation of non-obesogenic environments that promote healthy lifestyles to reduce the prevalence of obesity. The failure to take action could perpetuate the current evolutionary trajectory toward a human species characterized by obesity-related genotypes and phenotypes.

Introduction. The current state of obesity pandemic

Obesity is an escalating global issue, responsible for 2.8 million annual deaths according to the World Health Organization (WHO) [1]. This is primarily attributed to the significantly increased risk of developing type 2 diabetes mellitus, which can be three to twelve times higher in obese individuals. Obesity is also associated with the development of various chronic diseases, such as several forms of cancer, cardiovascular disease, dementia, and others [2–6]. In a noteworthy shift, a substantial portion of the world's population now resides in countries where overweight and obesity contribute to more deaths than malnutrition [1].

Despite these alarming statistics, the WHO has not officially classified obesity as a disease. However, it recognizes it as a severe medical condition due to its enduring adverse health effects and acknowledges it as a global epidemic and a substantial public health concern demanding a comprehensive approach to prevention and treatment. In contrast, the American Medical Association formally recognized obesity as a disease in 2013 [7]. This declaration did not come without controversy. Many experts in epidemiology and public health expressed their disagreement, a sentiment vividly articulated by D.L. Katz in Nature, where he unequivocally stated that "the misguided impulse to pathologize this condition reflects society's failure to accept the need for prevention" [8]. The roots of obesity extend beyond biological factors and are shaped by cultural and socioeconomic elements, including poverty and limited access to education. According to WHO, from 1975 to 2016, the worldwide prevalence had tripled. In 2016, 39% of adults over 18 were overweight and 13% were obese, as defined by BMI. In numerical terms, all these data represent more than 1.9 billion adults overweight and over 650 million adults obese worldwide. It is very concerning that 41 x 106 children under 5 were overweight. In children over 5 to 18 years old, 18% (340 x 106) were overweight and 6% (120 x 106) were obese. It is alarming that among young people aged 20 to 44, the percentage of obesity has increased from 33% to 41% in 10 years [1,9–12]. It should be noted that these figures are approximate, as the prevalence of obesity may vary by region, country, and age group.

Katz argues that the focus on treating obesity's effects rather than its causes may be hindering progress in obesity treatment. Despite significant scientific advances, clinical advancements in obesity treatment have been limited. Throughout history, obesity has been seen as a result of an imbalance between energy intake and expenditure, with individuals held responsible. This perspective has remained relatively unchanged for

centuries, with figures like Hippocrates describing obesity as a disease caused by this imbalance and recommending low-calorie diets and exercise [13]. Plato was among the first to suggest the state's role in regulating food for societal well-being [14,15].

While basic research has advanced our understanding, clinical controversies persist regarding the impact of food on health, and miracle diets are still promoted. Healthcare systems continue to invest in treating severe obesity. New treatment paradigms are emerging, incorporating "omics" [16] and morpho-functional techniques [17] for personalized therapy. Novel therapeutic targets have been identified, with some drugs achieving weight reduction of 15% to 17.4% in year-long treatments [18–20]. Research into peripheral targets to enhance adipose tissue function and induce thermogenesis is ongoing [21], and there is growing interest in the role of the microbiota in obesity development and treatment [22–24]. There is a shift toward personalized approaches to treating obesity, with healthcare professionals considering individual factors contributing to obesity and tailoring treatment plans accordingly. As knowledge about the causes and treatment of obesity continues to expand, health professionals are striving for more effective and personalized obesity management [25–28].

Scientific and clinical approaches play a crucial role in managing the morbidity and mortality linked to obesity, but they primarily address the issue after its development rather than addressing the underlying problem. Additionally, these therapeutic interventions do not guarantee a cure, and the recurrence of obesity following medical or surgical treatment is common, posing challenges to sustaining long-term weight loss. Research indicates that as many as 95% of individuals attempting weight loss through diet will regain it within two to five years, often exceeding their original weight, a phenomenon known as the yo-yo or rebound effect [29,30]. While bariatric surgery is more effective than relying solely on diet for long-term weight loss, it's worth noting that obesity recurrence remains a possibility. Approximately 20% of bariatric surgery patients may experience weight regain within five years, with recurrence rates varying based on the surgical procedure employed [31–33]. The predisposition to this rebound effect in response to current weight-reduction treatments, whether nutritional or surgical, is linked to a specific hormonal and molecular profile that may contribute to the limited success of obesity therapy [34–38].

The primary hypotheses aimed at elucidating the obesity pandemic

Caloric intake has exhibited historical variations. In ancient Greece, the typical daily caloric intake for an active adult male was approximately 3,000 calories [39]. During medieval Europe, it decreased to around 2,500 calories per day, a pattern that continued until the 18th century [40]. The 19th-century Industrial Revolution in the United States led to increased food availability and a rise in average daily caloric intake per person, climbing from about 2,500 calories in 1900 to over 3,600 calories in 2000. European countries also observed an increase, with daily caloric intake per person going from approximately 2,500 calories in 1900 to about 3,000-3,500 calories per day in the 1970s [41–43]. Nonetheless, in certain developing countries, average caloric intake can be considerably lower, ranging from around 1,500 to 2,500 calories per day [44]. Data suggest a correlation between the increase in caloric consumption and the prevalence of obesity [9,45–48]. Nevertheless, the recent explosive emergence of the obesity epidemic cannot be solely attributed to an increase in caloric intake [9,45–47]. Obesity results from the intricate interplay of genetic, biological, and environmental factors. Various evolutionary-based theories have been proposed to explain the causes and development of this pandemic: The thrifty gene hypothesis suggests that certain genes evolved to facilitate efficient energy storage in times of food scarcity, contributing to obesity in today's food-abundant environment [49]. Another hypothesis posits that the elimination of predation threats through human societal development, fire control, and toolmaking disrupted the balance between fat storage and leanness, favoring genetic drift that led to the obesity pandemic [50]. Other theories revolve around the concept of "sick-fat," where dysfunctional adipose tissue contributes to metabolic diseases such as obesity, insulin resistance, type 2 diabetes, and cardiovascular disease [51–54]. More recently, thermogenic adaptation has been suggested as a factor contributing to the obesity pandemic, enabling organisms to adjust their metabolic rate and heat production in response to ambient temperature changes [55-57].

Numerous hypotheses attempt to elucidate the complex global obesity pandemic, with multiple contributing factors. Some even propose that obesity may have beneficial effects in specific contexts, posing an evolutionary paradox. Nevertheless, these hypotheses consistently emphasize the interplay between genetic, environmental, and cultural factors. The crux of the issue lies in human biology, which has dynamically adapted to changing environments throughout evolution. Regrettably, the rapid development of an

obesogenic environment has created a mismatch between these factors, promoting obesity development. While the physiological basis of energy metabolism has evolved over millennia, it has been overwhelmed by modern society's profound cultural shifts in dietary and physical activity patterns. These changes are not in line with human adaptation. In an environment characterized by easy access to highly caloric foods and reduced physical activity, fat storage no longer offers an adaptive advantage and has become a public health concern. The prevalence of obesity and obesity-related diseases has surged due to these cultural changes [47,58–60].

Cultural evolution and obesity pandemics

All this data reflected above suggests that cultural evolution is the main cause of the obesity pandemic, but it may not be given the importance it deserves. Cultural evolution can cause not only epigenetic changes but also genomic changes, which could be the driving force behind the selection of obesity, contrary to natural evolution, through the legacy of the environment, known as ecological inheritance. Ecological inheritance refers to the influence that the environment and ecological conditions can have on the expression of genetic traits and the evolution of populations. Organisms interact with their environment and adapt to its conditions over time, and ecological inheritance is a way in which the environment and ecological conditions can influence the evolution and expression of the genetic traits of organisms [61–63]. In fact, genes and their phenotypic traits carry non-cognitive information that interacts with both biotic and abiotic environments. This transformed environment also carries non-cognitive information that acts upon the genotype and phenotype through natural selection. Specifically, in a given environment, the condition of a resource selects certain alleles, which in turn cause a change in the selection of alleles of other genes, ultimately altering the phenotype. This new phenotype interacts with the environment differently than the original phenotype, and selective forces will cause different responses depending on the selected alleles. The resulting genetic changes can either positively maintain an existing niche or be the cause of constructing a new niche [64,65]. Several examples illustrate how niche construction can initiate co-evolution between the environment and organisms, significantly impacting entire ecosystems. These instances range from the emergence of cyanobacteria, which released oxygen through photosynthesis, profoundly affecting the atmosphere [66], to a milder illustration involving the construction of beaver dams, inducing environmental and habitat modifications that shape the evolution of life in this environment [67]

Cultural animals shaped their ecological niche through cognitive information

Cultural animals, specially hominins (the genus *Homo*), shape their ecological niche through cognitive information. This refers to how humans, through their cultural practices, modify and transform the environment to adapt it to their needs and preferences. These behaviors include developing tools and technologies, domesticating fire, altering ecosystems through agriculture and animal husbandry, and establishing exchange and trade systems. This unique ability of humans to transform their environment and create distinctive ecological and, also, cultural niches is one of the most distinctive characteristics of our species. It has been crucial to our survival and evolutionary success [66,67–79]. The cultural channel also affects the genetic channel, which is mediated by ecological inheritance, by altering the environment and conditioning evolution[75]. Cultural selection can either promote, counteract, or even oppose (through counter-selection) some of the effects of natural selection in the evolution of a species [77,79]. Although there is no absolute consensus, various authors acknowledge that the production of tools and the domestication of fire were significant milestones in the cultural evolution of human primates. These advancements led to notable biological transformations through genetic and epigenetic changes. The subsequent augmentation in energy and protein intake has facilitated profound cerebral expansion in the human species, alongside notable alterations in dentition and the externalization of digestion. These evolutionary modifications have given rise to a more compact and efficient digestive system, substantially diminishing the time required for foraging and food assimilation. These pivotal transformations have paved the way for the establishment of a novel ecological niche, ultimately resulting in the emergence of the quintessential phenotype observed in modern *Homo sapiens*. Furthermore, heightened encephalization appears to exert cascading effects on other facets of physiological composition, notably encompassing gastrointestinal mass, muscularity, and adiposity. In comparison to their primate counterparts, humans exhibit a diminished gastrointestinal tract and a comparatively reduced colon. This particular gut morphology demonstrates a compelling adaptation to a diet characterized by heightened caloric and nutrient content, facilitating ease of digestion. Additionally, humans exhibit a relative deficiency in musculature (i.e., skeletal muscle mass) and an elevated adipose tissue deposition in comparison to other primates of equivalent size[78–84].

In summary, the interplay between genes, culture, and niche construction intertwines to create a complex and dynamic scenario in human evolution. The question at hand is whether a culturally obesogenic society can, through these evolutionary mechanisms, induce progressive changes that make obesity not only a prevalent phenotype but also a norm in the human genome. This would result in the emergence of a distinct human species from the current one. At present, there is evidence from the epigenome that supports this speculation as a realistic possibility [85-88]. In fact, an specific epigenome was associated with obesity [89,90] and this epigenome can be reversed with therapies to lose weight [91–93]. It is an indisputable fact that the obesogenic culture, characterized by dietary patterns rich in calories and low physical activity levels in certain communities, is passed down from generation to generation, contributing to the development of the obesity pandemic [45,46,48].

Sexual selection can play a role in discouraging obesity. However, as society becomes more accepting of obesity, it could actually contribute to the problem. Society often favors thin individuals, which can lead to discrimination against those who have overweight or obesity. But at the same time, these “beauty” stereotypes can also influence partner selection and contribute to the spread of obesity. Partner selection is influenced by many factors such as personal preferences, values, beliefs, and cultural factors. Research shows that there is a phenomenon called "weight homophily," where individuals with obesity tend to choose other partners with obesity over thin ones. Studies on humans have found that individuals with obesity tend to partner up with other individuals with obesity more frequently than with thin ones [86,94]. It's important to remember that parental obesity is a risk factor for obesity in children [95–99]. With the normalization of the obese stereotype, the prevalence of obesity is likely to increase, exacerbating the impact of the pandemic [97,98].

It is important to remember that sexual selection can lead to the development of traits that, while enhancing reproductive capacity, may reduce an individual's chances of survival. Many examples of this phenomenon can be found in nature, such as the peacock's tail, bird songs, elk antlers, and so on. In each of these cases, a costly trait in terms of survival has been sexually selected, often making the individual more vulnerable [99,100]

What a cultural evolution also shaped brain evolution

The evolutionary process of the brain is a multifaceted and captivating phenomenon that has transpired over millions of years, which is strongly intertwined with the evolution of feeding and an organism's capacity to locate and consume food [72, 74, 83, 84, 101,102]. The estimated metabolic cost per neuron in primates about 5.44 x 10^{-9} micromoles of glucose per neuron per minute, with a corresponding metabolic rate of 6 kcal per billion neurons per day [103]. Given that the human brain comprises approximately 100 billion neurons, the maintenance of its normal function necessitates the utilization of 129 g of glucose daily, equivalent to 516 kcal. Presently, the human brain constitutes only 2% of total body mass yet requires a staggering 25% of the body's total energy expenditure for optimal functioning [103]. Furthermore, a mere 1% decline in cerebral blood glucose flow can induce fainting and loss of consciousness.

In natural habitats devoid of modern conveniences like supermarkets and refrigerators, an animal's caloric intake is not only limited by the availability and quality of food but also by the duration of foraging [104]. An organism's ability to obtain sufficient calories to meet the physiological demands of its body and brain is crucial for its energy viability. Larger animals require a greater number of calories per hour and consequently require more hours of foraging. For instance, smaller primates can obtain their necessary food intake within two hours, while non-human great apes such as orangutans and gorillas require between seven and eight hours of foraging to survive [105, 106, 107]. Alpha male gorillas, with a weight of up to 250 kg, must obtain food from subordinates since dedicating the necessary hours to foraging and feeding would be impractical [106,107].

According to calculations, humans require at least 9-10 hours of daily foraging to satisfy the energy requirements of their body and brain, which exceeds the 8-hour limit for viability [107, 108]. As a result, the species had to adapt. Bipedalism improved foraging efficiency [109,110], but it was not enough to meet the increased brain needs of more advanced species.

Not always size matters

The genetic basis of these evolutionary changes is highly complex and not yet fully understood. Currently, it is unknown whether the genetic adaptations governing the increase in brain size are shared among primates or have species-specific origins. Based on current evidence, there are few solid reasons to justify the assumption that all changes

in the human evolutionary line represent exclusive adaptations of humans. Recent findings suggest that genes with potential functions in cell proliferation, neuronal migration, and neurological disorders play conserved roles in the evolution of brain size in anthropoids. To gain a comprehensive understanding of human evolution, it is essential to embrace the phenotypic diversity present in our close relatives and utilize this diversity to design more informative genomic analyses [111].

The list of genes involved and potentially involved is extensive and intricate [112-113]. Let's consider, for example, a specific genetic mutation that emerged approximately 60 million years ago [105]. This mutation affected the GFAP-1 gene, which is present in astrocytes, key multifunctional cells in the brain [107-109]. This mutation allowed for the generation of new neurons through hyperplasia, primarily in the neocortex, without a significant increase in brain mass [106]. This mechanism is unique in primate evolution and has played a fundamental role in the development of brain function [78]. This mutation that impacts all primates has achieved its most pronounced effects in humans, primarily due to their ability to circumvent metabolic limitations resulting from heightened caloric requirements. As elucidated earlier, the establishment of a cultural niche, promoting highly efficient nutrition, may have played a substantial role in this process.

About the importance of cooking

While debate exists, the prevailing hypothesis posits a direct relationship between brain development and the consumption of cooked food, as well as the invention of tools [72, 76, 77, 78, 105, 114-118]. The preparation and cooking of food enabled partial externalization of digestion, significantly increasing the number of calories consumed and the quality of nutrients, leading to the growth and expansion of the human brain, as well as reducing foraging and digestion time [120]. This is how the viability of the large brains of our ancestors was achieved [121–123].

It has been postulated that natural selection may have favored genetic variants that enhanced glucose availability in the brain, facilitating greater energy consumption and promoting brain development [108]. Mutations such as the genetic variant in the MCPH1 gene have been associated with greater brain volume in modern humans [124]. Additionally, regulatory mutations in SLC2A1 and SLC2A4 appear to have contributed to the evolution of a larger human brain by shifting energy allocation from skeletal muscle

to the brain. Evidence includes cross-species gene expression comparisons, genetic studies in humans and mice, and sequence comparisons of regulatory regions. These findings raise important questions about species-specific expression levels during development, the specific impact on brain cells, the responsible mutations, and potential expression differences in skeletal muscles related to energy trade-offs and locomotion costs [125]. It is unlikely that SLC2A1 and SLC2A4 are the sole genes involved in this energy trade-off, as other genes related to metabolism also show signs of positive selection during human evolution. Additionally, the reduction in gut size may have played a role in human brain evolution. Exploring the evolutionary history and functional consequences of mutations in these genes will enhance our understanding of the evolution of this unique human trait.

Cooking food, an activity unique to humans, has resulted in a distinct evolutionary trajectory. Adler posited that cooking is a prerequisite for culture [126]. This evolution is consistent with the notion that cultural selection could have been favoring a genome that would, in turn, enhance cultural evolution. The process of cooking food leads to molecular changes that improve nutrient availability [127]. The denaturation of proteins and the breakdown of complex carbohydrates into simple sugars make them more easily absorbed and metabolized in the small intestine [81, 128,129].

Cooking also enhances the bioavailability of micronutrients, such as iron and calcium, which can be poorly absorbed in raw foods [120, 121]. Moreover, cooking facilitates the release of essential nutrients like omega-3 fatty acids, including docosahexaenoic acid (DHA), which is vital for brain development and function [81]. Thermal processing of food significantly affect the availability of dietary antioxidants for absorption. Studies suggest that heat and homogenization can make compounds more accessible, contradicting the belief that heat-processed foods are nutritionally inferior [130]. For instance, modifying the glycosidic structure of flavonoids can also impact their bioavailability. Cooking also enhances the bioavailability of fat-soluble pigments, such as lycopene, lutein, and zeaxanthin, which have potent antioxidant properties [127,131-133].

Additionally, cooking can reduce the content of antinutrients and toxins, which improves food safety [127]. However, cooking can also degrade heat-sensitive vitamins, and thus, it is important to balance the benefits of cooking with its potential drawbacks [127].

Another cultural factor that may have played a pivotal role in this process is a diet once again enriched in fermented foods [134]. This dietary shift could have contributed to

greater diversification of the intestinal microbiome, enabling an enhanced capacity to extract nutrients from food and provide the additional energy required to sustain an increasingly larger and more complex brain, while also boosting neurotransmitter production. As elaborated upon later, this phenomenon is establishing a new paradigm: the gut-brain axis, which holds significant importance in understanding metabolism and cerebral physiology [35-137] (see " The immediate surrounding environment, the brain and obesity").

Overall, the evolution of the human brain has been a complex interplay of genetic, environmental, and cultural factors. The human brain's constant growth, increased size, and complexity have allowed for the development of advanced cognitive abilities that have been instrumental in the success of the human species.

Brain adaptations to the environment leading to obesity pandemic

The brain plays a crucial role in regulating appetite and energy metabolism through complex mechanisms involving both hormonal and neural signals. The hypothalamus, the brain region involved in the control of energy balance, receives input from a variety of peripheral signals, including hormones such as leptin, ghrelin, PYY, and insulin, and integrates this information to adjust food intake accordingly [138,139]. Leptin, an adipocyte-derived hormone, acts on the hypothalamus to suppress appetite and increase satiety. The arcuate nucleus of the hypothalamus is a key site for leptin signaling, where it modulates the activity of neurons that control feeding behavior. Ghrelin, on the other hand, is mainly produced in the stomach and stimulates appetite and food intake by acting on receptors in the hypothalamus and other brain region. Another hormone that influences appetite and satiety is PYY, which is produced by endocrine cells in the small intestine. PYY signals in the hypothalamus and other brain regions to decrease appetite and increase feelings of fullness. Insulin, a hormone produced by the pancreas to regulate blood glucose levels, also has an appetite-suppressing effect mediated by its signaling in the brain.

In addition to these hormonal signals, neuronal circuits in the brain are also involved in the regulation of appetite and satiety. The hypothalamus, brainstem, and prefrontal cortex are key brain areas involved in the control of feeding behavior [140]. These circuits integrate peripheral signals and modulate neural activity to regulate food intake and energy balance.

The dysregulation of these mechanisms may contribute to the development of obesity, a global epidemic with significant health consequences. Understanding the complex interactions between the brain and metabolic signals is crucial for the development of effective strategies to prevent and treat obesity. Multiple factors can disrupt the normal functioning of the brain in regulating appetite and metabolism, leading to the development of obesity. A term coined as "obese brain" or "adipose brain" has been used to describe how prolonged exposure to a high-fat, high-sugar, and processed food diet can induce alterations in brain function, changing the response to satiety signals, and increasing appetite and basal metabolism, ultimately contributing to obesity [141-145]. These studies have shown that consumption of processed and ultra-processed foods can modify the release of satiety-regulating hormones, thereby increasing the risk of developing obesity and type 2 diabetes. Furthermore, the chemicals and compounds present in these foods can negatively impact glucose metabolism regulation, increasing the likelihood of developing metabolic syndrome [141,146].

A high-fat diet has also been identified to alter the function of the blood-brain barrier, allowing the entry of inflammatory molecules into the brain, leading to brain inflammation [138,139]. In addition, a diet high in fats and sugars has been linked to cognitive impairment through hippocampal dysfunction, affecting memory and learning [147,148]. Furthermore, it has been demonstrated that a diet rich in processed and hypercaloric foods has addictive effects, leading to changes in food preferences, making it more appealing [149,150], further complicating the problem [151].

In addition, exposure to an obesogenic environment during the prenatal and postnatal period can produce epigenetically-regulated alterations in gene expression related to energy metabolism in the brain and liver of the fetus, thereby affecting the regulation of appetite and energy metabolism [152-153].

Thus, the obesogenic environment has led to the development of brains with a heightened attraction towards consuming highly caloric foods that are readily available in supermarkets and processed food industries. Many of these foods are considered calorie bombs, further contributing to the obesity epidemic.

The immediate surrounding environment, the brain and obesity

In recent years, significant attention has been given to the relationship between the brain and the intestinal microbiome, which comprises a complex community of

microorganisms inhabiting our gut. Evidence from several studies indicates that the microbiome can significantly influence brain function, behavior, and mental health through multiple bidirectional communication pathways, including nervous and hormonal signals, as well as the production of metabolites and neurotransmitters that can impact the central nervous system +(CNS) [154,155].

Various communication pathways and molecular mechanisms mediate the interaction between the brain and the microbiome. The microbiota-gut-brain axis represents a critical bidirectional communication axis between the intestinal microbiota, the enteric nervous system (ENS), and the CNS, involving nervous, hormonal, and immune signals. Furthermore, intestinal microorganisms produce metabolites that can affect the brain and the CNS, such as gamma-aminobutyric acid (GABA) and serotonin. These metabolites can have a relaxing and anxiolytic effect on the brain and regulate mood and appetite, respectively. In addition, modulation of the immune response by the microbiome can also impact the brain and behavior, as certain bacteria can modulate the activity of immune cells in the gut and produce anti-inflammatory substances that can have positive effects on cognitive status. The microbiome can also influence the activity of the Hypothalamus-Pituitary-Adrenal (HPA) axis, which regulates stress, and in turn, HPA activity can influence the composition and function of the microbiome [156].

Apart from these impacts on behavior and cognitive status, the microbiome also plays a significant role in regulating appetite and energy metabolism [22,157]. Recent studies suggest that microbiota composition can influence metabolic homeostasis, nutrient absorption, and the synthesis of hormones and neurotransmitters regulating appetite and satiety [158-161]. Transplantation of intestinal microbiota from obese mice to germ-free mice resulted in increased body fat accumulation and decreased energy expenditure, indicating that the microbiome contributes to the development of obesity. Moreover, studies in humans have found an association between microbiota composition and obesity, metabolic syndrome, and insulin resistance [162-164].

The specific mechanisms by which gut-microbiome interact with host brain is still pending to be elucidated. Among the proposed hypothesis, the role of epigenetics in the microbiome-host dialogue is the most plausible. It was proposed that microbiome can regulate the gene expression by epigenetic mechanisms by the action of gut-microbial products and also by the action of the microbiota itself that mediate the interactions between genome and environment and therefore, it can be considered and epigenetic entity [165].

The relationship between the brain and the microbiome is multifaceted and complex, with bidirectional communication pathways and molecular mechanisms mediating this interaction. It has far-reaching implications for behavior, mental health, and metabolic regulation, and research in this field is ongoing to shed light on the underlying mechanisms and potential clinical implications. Diet plays a pivotal role in regulating the composition and function of the microbiota. The consumption of a diet rich in fiber, such as the Mediterranean diet, has been shown to increase the diversity of the microbiota and reduce the prevalence of metabolic and cardiovascular diseases [166-169]. Conversely, the excessive consumption of refined fats and sugars has been associated with an increased prevalence of metabolic diseases and alterations in microbiota composition that promote obesity [162-164, 170]. This emphasizes the importance of a diet that not only influences obesity, but also cognition. Dietary interventions aimed at modulating the microbiota may be an effective therapeutic strategy for the prevention and treatment of metabolic diseases, as well as the improvement of mental health [162-164, 170-176]. In this regard, research have highlighted epigenetics as a key mediator of the diet effects on gut microbiota diversity and function, with a consequent translation in human health [177,178].

In sum, nutrition has played and continues to play a critical role in the evolution of the human brain, influencing appetite regulation and energy metabolism through multiple hormonal and nervous signals. Changes in diet can impact the gut microbiome, the availability of nutrients required for optimal brain function, regulating the epigenetic machinery as mediator of microbiota-gut–brain interaction and potentially, resulting in positive or negative effects on short- and long-term cognitive development.

Is it too late to prevent the emergence of a species that is characterized by obesity, the "homo obesus"?

Although it is essential to treat obesity in both men and women, it is not enough to combat the obesity pandemic. Prevention should be the primary focus, and efforts must be made to address the factors contributing to an increasingly obesogenic society. Policies should be developed to improve education and nutrition, and physical activity programs should be implemented in schools, workplaces, and communities. Poverty must be alleviated, and the food industry should be regulated to prevent the normalization of obesity [179-182]. Reversing the obesity pandemic requires a comprehensive approach involving individuals, communities, healthcare providers, and policymakers working together to

create a healthier environment. This approach includes promoting healthy lifestyle habits, creating supportive environments, implementing policies and legislation to prevent poverty, zoning laws that encourage physical activity, and nutritional counseling, and laws that make it difficult to develop and sell high-calorie foods. Increasing access to healthcare that includes early identification and treatment of obesity and prevention of obesity-related health conditions is also crucial [1,45,58,183-185].

Successful past experiences, such as in Finland, support the implementation of health policies to combat the obesity pandemic. Finland reduced obesity rates by promoting a healthy diet, creating environments that encourage physical activity, imposing taxes on foods high in saturated fats, and implementing a national program for obesity prevention and treatment [186-187]. Similarly, policies implemented in Japan, France, New York, and Australia that promote a healthy and balanced diet, restrict the advertising of unhealthy food, encourage physical activity, and increase taxes on sugary foods have demonstrated potential effectiveness in reducing obesity rates [188–192].

In terms of measures to advance obesity prevention, research funding should also be a priority for political and health authorities. We need to know which mechanism is deregulated by the action of the obesogenic environment to which current society is subjected. This knowledge would allow us to predict those people who are more predisposed and also to prescribe effective therapeutic strategies in those patients in whom obesity is already established. The research findings to date on the pathophysiology of obesity have been focused specifically on the dysfunction of appetite regulation and energy homeostasis at the level of the central nervous system. However, it is known that appetite may also be regulated at the peripheral level, from adipose tissue function, activation of thermogenesis, enhancement of muscle function and even the effect of the microbiota. All of these mechanisms could be potential targets for effective therapeutic strategies in the fight against obesity. On the other hand, we also need to investigate which environmental factors specifically constitute the obesogenic environment that has the greatest effect: high-fat diets, ultra-processed foods, sedentary lifestyles, the homes ambient temperature or environmental pollutants, among others. Knowing exactly which factor could be the major trigger for the increase in obesity could help to establish more effective prevention policies.

In summary, tackling the obesity pandemic requires a multifaceted approach that involves prevention, treatment, and policy intervention. Prevention efforts should focus on educating individuals and creating supportive environments that encourage healthy

lifestyle habits. Policy interventions should include regulating the food industry, implementing taxes on unhealthy foods, and promoting healthy food options in schools and workplaces. Successful experiences serve as examples for other countries to follow in their efforts to combat the obesity epidemic. Ultimately, a collaborative effort is needed to create a healthier environment and reduce the prevalence of obesity and related health conditions. Will these actions suffice to prevent the pervasive obesogenic culture? Can we put a halt to the potential evolution towards a 'homo obesus'? It has become evident that the time has come to reconceptualize the very notion of obesity.

It is fitting to end with a quote from Katz himself, which remains highly relevant today as the obesity pandemic continues to grow unabated: "*Obesity warrants medical as well as cultural legitimacy and respect. (….) But the blame for hyperendemic obesity, and its best remediation, resides not within bodies that work as they ever did, but all around, with the collective actions of the body politic*" [8].

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: