COMMENTARY

How can drug addiction help us understand obesity?

Nora D Volkow & Roy A Wise

To the degree that drugs and food activate common reward circuitry in the brain, drugs offer powerful tools for understanding the neural circuitry that mediates food-motivated habits and how this circuitry may be hijacked to cause appetitive behaviors to go awry.

Until recently in our evolutionary history, addictive agents have been ingested in foods. Many are secondary plant metabolites that evolved because they discourage ingestion by animals[1]. The hungers that arise from bodily needs are non-directive; they merely encourage us to put things in our mouth. The more acute the hunger, the greater the range of substances we will ingest[2]. We learn to return to the yellow banana, the purple fig, the pink peach. We also learn to chew the tobacco leaf and drink the nectar of fermented fruits and grains. Because of the need for the nutrients in plants containing addictive substances, many species have learned to accept mildly intoxicating amounts of these compounds. Paradoxically, some of the poisons that evolved in plants to discourage animals from returning are—like the nutrients that the plants offer—habit-forming in their own right.

Addiction and obesity each results from foraging and ingestion habits that persist and strengthen despite the threat of catastrophic consequences. Feeding and drug use involve learned habits and preferences that are stamped in by the reinforcing properties of powerful and repetitive rewards. Palatable food activates brain reward circuitry through fast sensory inputs and through slow post-ingestive consequences (such as raising glucose concentration in blood and brain), whereas drugs activate these same pathways mostly through their direct pharmacological effects on the reward circuitry. The repeated supra-physiological stimulation of reward pathways by drugs not only stamps in response habits and stimulus preferences, but also triggers neurobiological adaptations that may make the behavior increasingly compulsive and lead to further loss of control over intake.

Not all humans who are exposed to habit-forming drugs become addicted, just as not all humans who are exposed to high-fat, high-calorie foods become obese. Although some classes of obesity can be linked to known genetic polymorphisms, the recent epidemics of obesity and of certain addictions are more clearly correlated with the increased availability of 'comfort foods' and of drugs or drug forms such as methamphetamine and 'crack' cocaine than to drift in the genome. Thus obesity, like addiction, is linked strongly with exposure to powerful reinforcers.

Genetic factors in obesity and addiction

Individuals suffering from addiction or from obesity are stigmatized in part by the belief that the decision to overeat or to take drugs is completely under voluntary control. Yet addiction and obesity are multifactorial disorders that have significant genetic components.

As much as 40–60% of the vulnerability to addiction[3,4] and 50–70% of the variability in body mass index[5] might be attributed to genetic differences under the specific circumstances of the studies. However, estimates of heritability under one set of circumstances are not necessarily valid for others. The contributions of genetic and environmental factors are not simply additive; rather, they interact in complex and sometimes counterintuitive ways. For example, the contribution of genotype to variability in the body mass of sheep is greater in September than in June[6] and the genetic contribution to the variability of smoking in women is greater now than in earlier decades when social restrictions on females were stronger and fewer women tried cigarettes[3]. Just as the genetic influences in addiction vary between cultures with differential availability of alcohol, so too is the genetic contribution to obesity likely to differ between societies that differ in the acceptance and availability of high-calorie, high-fat foods.

Genetic studies have revealed point mutations that are of importance for obesity[7] and for addiction[8]. However, addiction and obesity are also thought to be under polygenetic control. Addiction-prone and addiction-resistant rat phenotypes are associated with differing sensitivity to the various stressors in the environment[9,10], and stress has a potential role in obesity[11]as well as addiction[12]. Moreover, broad-based factors such as gender affect both feeding[13] and drug taking[14]. Thus, it is very possible that there are polygenic genotypes that confer risk for both obesity and addiction.

Environmental factors

Of the environmental factors that influence obesity and addiction, the availability of seductive foods and drugs is the most obvious. For the greater part of human evolution, sweet taste was associated with fruits that afforded quick energy. However, genes that were favored under conditions of food scarcity have become a liability in societies where high-energy, highly refined foods are prevalent and readily affordable. Indeed, the recent escalation in the prevalence of obesity has developed over a period when the genome has changed little but the availability of low-cost, high-fat, high-carbohydrate foods has changed dramatically (for instance, in vending machines, convenience

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Table 1 Comparison of food and drugs as reinforcers

	Food	Drug
Potency as a reinforcer*	++	Oral: ++ Snorted: +++ Smoked, injected: ++++
Delivery	Oral	Oral, snorted, smoked, injected
Mechanism of reward	Somatosensory (palatability), chemical (glucose)	Chemical (drug)
Regulation of intake	Peripheral and central factors	Mostly central factors
Adaptations	Physiologic	Supraphysiologic
Physiological role	Necessary for survival	Unnecessary
Learning	Habits, conditioned responses	Habits, conditioned responses
Role of stress	+++	+++

*Potency as reinforcer is estimated based on the magnitude and duration of increases in dopamine induced by either food or drugs in the nucleus accumbens, and is an approximate comparison, as potency will be a function of the particular foodstuff or of the particular drug and its route of administration.

stores and fast food restaurants). Similarly, recent epidemics of addiction to cocaine and heroin have accompanied increased availability and lower cost of these drugs.

The quality of the reinforcer is another factor of importance for addiction and obesity (**Table 1**). In addiction, the strength of a drug as a reinforcer depends on its route of administration (intravenous and smoking routes are more reinforcing than snorting or oral administration) and dose. This is partly because smoked or injected drugs reach the brain more quickly and partly because they reach the brain in higher concentration[15]. In addition, drugs of abuse are not equally addictive. When animals are given unlimited access to intravenous amphetamine or cocaine[16], they self-administer the drug to the point of death, whereas animals given unlimited access to intravenous nicotine[17] do not.

Just as different drugs establish different levels of compulsive behavior, so do different foods. Individuals in a high-fat, high-carbohydrate environment are at considerably greater risk than those in a vegetarian environment. Notably, low-carbohydrate and low-fat diets have each been recommended as methods for weight loss, and each is effective for the time it is practiced. The common denominator of such diets is that neither allows consumption of the very caloric and seductive foods that combine high fat with high carbohydrates.

Another important environmental factor is stress. Acute as well as chronic stress influences both food intake and the propensity to take drugs. For example, childhood stress has been associated with elevated risk for problems with weight during adolescence or early adulthood[18] and also with a higher risk of substance abuse and addiction[19]. The role of stress is mediated in part by the corticotropin-releasing factor (CRF) and related peptides[20]. CRF not only controls the pituitary-adrenal axis but also serves as a neuropeptide cotransmitter in neurons orchestrating the central effects of stress[21]. CRF is well-known to be involved in the regulation of energy balance and food intake[22]. Similarly, in addiction, CRF is recognized for its involvement in stress-induced reinstatement of drug taking and vulnerability to relapse[20] and in the responses to acute drug withdrawal[12].

Developmental factors

Developmental processes also seem to influence the behaviors associated with food consumption and drug taking. Experimentation with drugs often starts in early adolescence[23]. Behaviors such as risk-taking, novelty-seeking and response to peer pressure increase the propensity to experiment with drugs. The adolescent onset of these behaviors may reflect delayed maturation of the prefrontal cortex, a brain region involved with judgment and inhibitory control[24]. In addition, drug exposure during adolescence can result in different neuroadaptations from those that occur during adulthood. For example, in rodents, exposure to nicotine during the period corresponding to adolescence, but not during adulthood, leads to significant changes in nicotine receptors and an increased reinforcement value for nicotine later in life[25]. Exposure to drugs during fetal development may also increase the vulnerability to drug use later in life. Indeed, smoking during pregnancy increases the risk of nicotine dependence in the offspring[26]. Interestingly, it also increases their risk for obesity[27]. Similarly, early exposure to certain diets during fetal life and the immediate postnatal period can influence the food preferences of an individual later in life[28]. Moreover, the marked increases in childhood and youth obesity in the United States (which has tripled in the past 30 years) highlights the importance of investigating the interactions between developmental variables and the environment in this disorder.

Neurobiological mechanisms

The biological mechanisms of feeding and addiction have overlapped throughout our evolutionary history. The opiate antagonist naloxone inhibits feeding in mammals[29], in slugs and snails[30] and even in amoebae[31]. The most clearly established commonality of the mechanisms of food and drug intake is their ability to activate the dopamine-

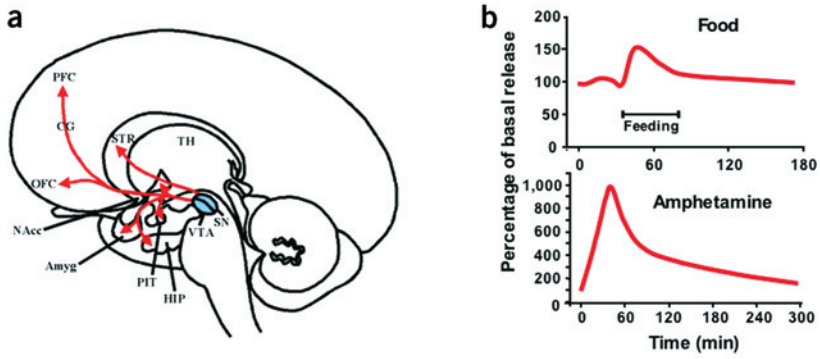

Figure 1 Dopaminergic pathways. (**a**) Dopaminergic pathways. PFC, prefrontal cortex; CG, cingulate gyrus; OFC, orbitofrontal cortex; NAcc, nucleus accumbens; Amyg, amygdala; STR, striatum; TH, thalamus; PIT, pituitary; HIP, hippocampus; VTA, ventral tegmental area; SN, substantia nigra. (**b**) Increases in dopamine in nucleus accumbens induced by food and by amphetamine as assessed by microdialysis in rodents. Graphs modified from ref. 60.

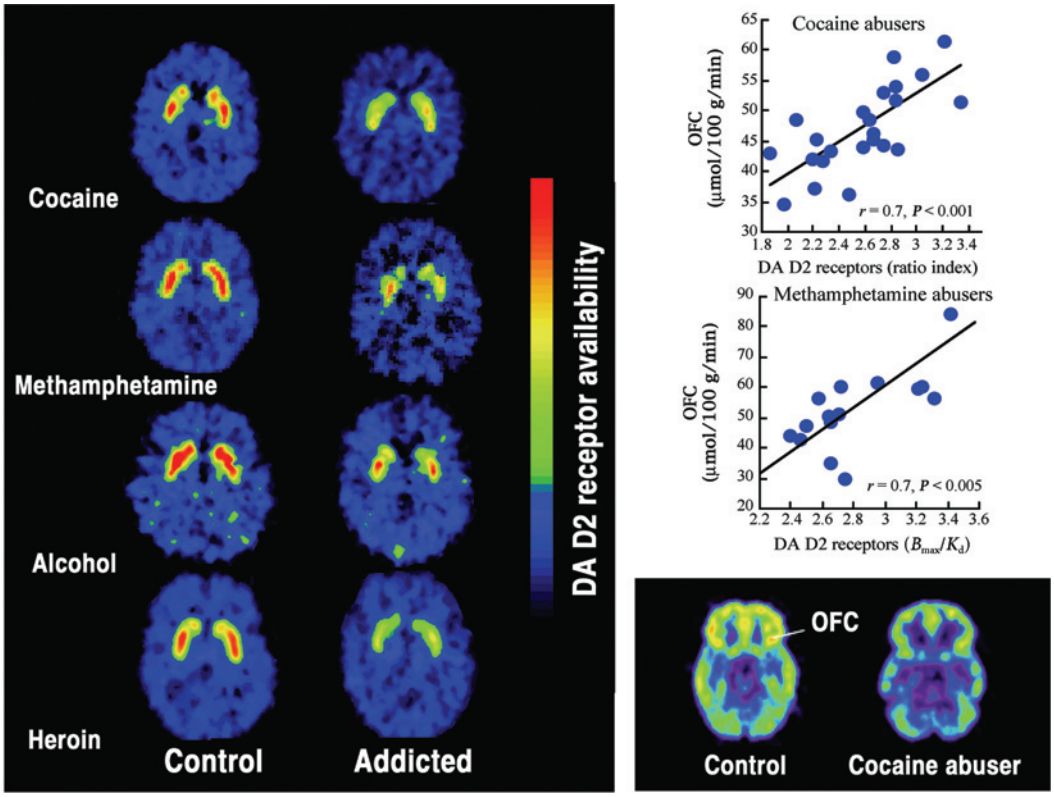

Figure 2 Relationship between dopamine (DA) D2 receptors in the brains of cocaine abusers and methamphetamine abusers, and metabolic activity in orbitofrontal cortex.

containing link in brain reward circuitry[32] (**Fig. 1**). Pharmacological blockade of, or experimental damage to, forebrain dopamine systems attenuates free feeding and lever-pressing for food reward, as well as the rewarding effects of cocaine, amphetamine, nicotine and alcohol[33]. Although the mesolimbic dopamine projection from the ventral tegmental area to the nucleus accumbens is most frequently implicated in reward function, other forebrain dopamine projections are almost certainly involved[34].

Endogenous opioid systems interact at each end of the forebrain dopamine systems. In the midbrain, μ opioid receptors are localized on GABAergic neurons that normally inhibit the dopamine systems; μ opioids inhibit this input, thus disinhibiting the dopamine system and causing dopamine release in nucleus accumbens and related target regions. In nucleus accumbens, μ opioid receptors are localized on GABAergic neurons that receive input from the mesolimbic dopamine system. Injections of μ opioids into each of these regions is rewarding in its own right[35], and injections into each of these regions potentiate feeding[36]. The role of opiates in these areas seems to be to augment the intake of high-fat, high-sugar foods rather than to mimic the effects of nutritive deficit on bland food[37]. Indeed, the endogenous opioid system seems to underlie the rewarding properties of palatable foods[38].

Thus the mesolimbic dopamine system and its afferents and efferents contribute to the rewarding effects of various addictive drugs and of foods. These systems also seem to be modulated by substrates of energy regulation that are the topic of other papers in this issue. Not only does food deprivation potentiate the rewarding effects of food[39], chronic food restriction also potentiates the rewarding effects of lateral hypothalamic brain stimulation[40] and of most addictive drugs[41]. The adipocyte hormone leptin, which is lacking in obese *ob/ob* mice, not only suppresses food intake, but also reverses the effects of food restriction on brain stimulation reward thresholds[40] and on the reinstatement of drug-seeking[42] in an animal model of addiction relapse.

Thus, in broad sketch, there is considerable overlap between brain circuitry that evolved in the service of body-weight regulation and brain circuitry that is usurped by exogenous drugs of abuse. As the finer details of the brain mechanisms of addiction and feeding are worked out—such as the role of GABAergic and cholinergic modulation of the ventral tegmental area and medium spiny neurons in feeding and reward—considerable cross-fertilization between the two literatures can be expected to occur.

Neurobiological adaptations

The regulation of food consumption is much more complex than that of drug consumption because food intake is modulated by multiple peripheral and central signals, whereas drugs are modulated mostly by the drug's central effects. However, addictive drugs, like addictive foods, activate brain circuitry involved in reward, motivation and decision-making[43]. In addiction, it seems almost as if the brain responds to the drug as it would respond to food under conditions of severe deprivation. What leads to the increasing desire for the drug as addiction progresses? Researchers have postulated that neurobiological adaptations initiated by chronic and intermittent supraphysiological perturbations in the dopamine system by a drug trigger changes in some of the regions and neurotransmitter systems modulated by dopamine[44]. Advances in neuroscience have begun to provide insight into the nature of these adaptations.

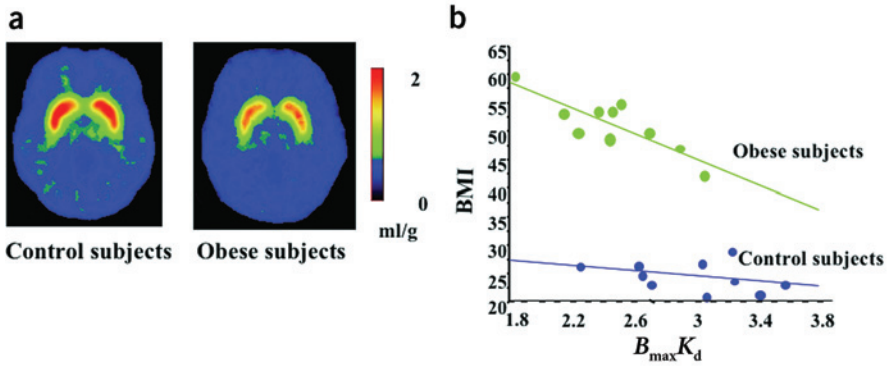

Figure 3 Role of dopamine D2 receptors in obesity. (**a**) Dopamine D2 receptors in controls and in obese individuals. (**b**) Relationship between D2 receptors and body mass index (BMI).

Neurotransmitter adaptations are documented not only for dopamine but also for glutamate, GABA, opiates and CRF, among others[45]. Some of these changes disrupt brain function. For example, in cocaine-addicted subjects, imaging studies show that changes in dopamine brain activity (reductions in dopamine D2 receptors and in dopamine release in striatum) are associated with disruption in the activity of the prefrontal cortex[46] (**Fig. 2**). Disrupted function of the orbitofrontal cortex (OFC) and the anterior cingulate gyrus, regions of the prefrontal cortex involved with salience attribution and with inhibitory control, are particularly informative for the understanding of addiction, as their disruption is linked to compulsive behaviors and poor impulse control[46]. In preclinical studies, drug-related adaptations in the prefrontal cortex specifically enhance activity of the corticostriatal glutamatergic pathway that regulates dopamine release in the nucleus accumbens[47]. Adaptations in this pathway have been linked to drug- and cue-induced relapse into drug-seeking in animal models. The extent to which the prefrontal abnormalities in addicted subjects (reported by imaging studies) result in disruption of corticostriatal glutamatergic pathways (reported in preclinical studies) requires further investigation.

In addition to the adaptations in the targets of the dopamine mesocortical pathway, there is also evidence of adaptations in the targets of the dopamine mesolimbic circuit (including neurons of the nucleus accumbens, amygdala and hippocampus), which may underlie the enhanced motivation for the drug and conditioned responses. Adaptations may also occur in the targets of the dopamine nigrostriatal circuit (including the dorsal striatum)[48], which might underlie habits that are linked with the rituals of drug consumption. The search for neuroadaptations associated with addiction is largely a search within the brain circuitry through which drugs exert their reinforcing effects. To the degree that the same circuitry is important for the reinforcing effects of food, neuroadaptations in this circuitry should affect food intake as well as drug intake.

The relevance of dopamine to obesity has also been documented by both preclinical and clinical studies. In animal models of obesity (including leptin-deficient *ob*/*ob* mice, obese Zucker rats, obesity-prone Sprague-Dawley rats and seasonally obese animals), dopamine activity is reduced in the tuberoinfundibular pathway that projects to the hypothalamus[49]. In these animals, treatment with dopamine agonists reverses the obesity, presumably by activating dopamine D2 and D1 receptors[49]. In humans, brain imaging studies show reductions in dopamine D2 receptors in the striatum of obese individuals that are similar in magnitude to the reductions reported in drug-addicted subjects[50] (**Fig. 3a**). In obese subjects, but not in controls, dopamine D2 receptor abundance is inversely related to body mass index, suggesting that the dopamine system is involved in compulsive food intake (**Fig. 3b**). Further support for this idea is provided by clinical studies showing that chronic treatment with drugs that block dopamine D2 receptors (antipsychotics) is associated with a higher risk of obesity[51]. Though decreases in dopamine D2 receptors have been documented across a wide variety of drug addictions and in obesity, by themselves they are insufficient to account for these disorders, and their role is likely to be one of modulating vulnerability.

Similarly, imaging studies in obese subjects document abnormalities in prefrontal cortex[52]. When food-related stimuli are given to obese subjects (as when drug-related stimuli are given to addicts[46]), the OFC is activated and cravings are reported[53]. Several areas of the prefrontal cortex (including the OFC and cingulate gyrus) are implicated in motivation to feed[54]. These prefrontal regions could reflect a neurobiological substrate common to the drive to eat or the drive to take drugs. Abnormalities of these regions could enhance either drug-oriented or food-oriented behaviors, depending on the established habits of the subject.

Neuroadaptations are also documented in the opioid system in cocaine abusers[55] and in alcoholics[56]. Though there are no published studies in humans, preclinical studies show adaptations in the opioid system after administration of palatable foods (reviewed in ref. 57). The neuroadaptations resulting from chronic food intake are likely to be more complex than those observed with drugs and are known to include changes in neuronal circuitry that modify the motivation to eat, as well as neuroadaptations that modify energy efficiency and metabolic thresholds[57].

Prevention

One of the most successful prevention interventions in public health in the last century was in promoting smoking cessation. Over a period of 30 years, the prevalence of smoking in adults in the United States dropped from 42.4% in 1965 to 24.7% in 1995 (ref. 58). The success of this intervention can be linked to an effective educational campaign based on solid scientific information about the deleterious health effects of smoking. Policy changes that made cigarettes more expensive, selling of cigarettes to minors illegal and smoking much more restricted in public spaces also contributed to its success. The campaign also alerted the medical community to the importance of evaluating and treating smokers. All of these factors were effective in producing dramatic changes in the attitude of the public toward smoking.

The success of this intervention for an addiction (to nicotine) can be used to suggest and design an effective campaign to reduce obesity. As for the antismoking campaign, this should include education regarding healthy eating and exercising (as sedentary lifestyles have also contributed to the increase in obesity). Interventions should be initiated in early childhood, because this is when children develop life-long eating habits and start to become overweight. It should also involve the medical community, which should be prepared to evaluate and treat obesity, along with the food industry, which should be encouraged to make healthy foods more attractive, palatable and less expensive, and policy makers, who should consider incentives to facilitate these changes. Finally, a campaign to reduce obesity should involve institutions such as schools, with

efforts to remove junk foods from dispensing machines and cafeterias where they help to seduce young people into obesity, just as readily available cigarettes helped, until recently, seduce them into addiction.

One unique challenge for the prevention of obesity arises because food, unlike drugs, is indispensable to survival. Thus, it will be much harder for a society to implement regulations to constrain the easy access to food that can facilitate compulsive eating. What can be hoped for, however, is more restricted access to high-fat, high-calorie foods that are seductive and unnecessary for good health, particularly in public places such as schools.

Treatment

As in the treatment of drug addiction, scientific knowledge about the involvement of multiple brain circuits (reward, motivation, learning, cortical inhibitory control) would suggest a multimodal approach to the treatment of obesity. For obesity as well as for addiction, promising pharmacological interventions may be those that interfere with various processes, including the reinforcing value of the substance (food or drug); with conditioned responses to these processes; and with stress-induced relapse after temporary successes are achieved. Indeed, in some instances the same medications that are effective in interfering with (or reducing) food consumption in animal models of obesity are also effective in interfering with (or reducing) drug consumption by self-administration in animal models of drug abuse (for example, cannabinoid CB_1 antagonists).

In a similar fashion, some of the behavioral interventions that are beneficial in the treatment of addiction are also helpful in the treatment of obesity. These include incentive motivation, cognitive-behavioral therapy and 12-step programs. However, the interventions for obesity are complicated by the impossibility of completely refraining from eating, as is frequently recommended for drug addiction. For example, we know that for relapse to drug-seeking, the priming effects of the drug are very potent[59]; thus 12-step programs stress absolute abstinence, a strategy that avoids the danger of priming. Alcoholics note that it is easier to draw a line between zero drinks and one drink than between the first and second or the sixth and seventh. In the case of food, a similar effect is more difficult to achieve because food consumption is essential and long periods of total abstinence are not feasible. However, strategies that avoid food rich in carbohydrates or fats, or their combination, should help at-risk individuals to sidestep priming effects that trigger compulsive eating.

Like addiction, obesity is a chronic condition with periods of protracted abstinence (restriction of seductive foods) and periods of relapse (compulsive eating). Thus, treatment will in most cases require continuous care.

Large-scale prevention and treatment programs for obesity (like those for addiction) will require the participation of the medical community. The engagement of pediatricians and family physicians might facilitate early detection and treatment of obesity in childhood and adolescence. Unfortunately, as with addiction, physicians, nurses and psychologists receive little training in the management of obesity.

Conclusion

Obesity and addiction are special cases of the consequences of ingestive behavior gone awry. Each develops in some but not all individuals, and each is subject to genetic predispositions and the availability of a powerful reinforcer. In each case, there appear to be periods of developmental vulnerability. Although each condition has its own interface with brain mechanisms of motivation, the motivational mechanisms themselves largely overlap. In each case, neuroadaptations resulting from excessive intake may make the ingestive behavior more compulsive. The guidelines for prevention and treatment of the two disorders are remarkably similar, and some of the same pharmacological interventions that are promising for the control of drug intake are also promising for controlling the intake of food. Few fields seem to offer as much potential for cross-fertilization as the fields of addiction and obesity research.

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COMPETEING INTEREST STATEMENT

The authors declare that they have no competing financial interests.

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