Obesity Treatment and Prevention: New Directions
Obesity Treatment and Prevention: New Directions

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Preface

Obesity continues to be a major problem for global public health. Despite best efforts by health care providers, public health agencies, and the private sector, few prevention efforts have been effective. As a result, bodyweights have continued their upward surge, contributing to ill-health among both children and adults. Although many treatment programs are available, few can boast of long-term success, with minimal risk of relapse and weight regain.

One glimmer of hope has been the recent leveling off in obesity rates in the US and in European countries. Whether temporary or permanent, it provides a much-needed breathing space. This is the opportunity to regroup, reexamine past approaches, assess relative success rates, and point to new directions for the future. Those new directions can be global in their reach. Obesity and diabetes are no longer limited to wealthy societies. Their rates in developing countries, while still relatively low, are on the rise.

Clearly, obesity treatment and prevention can benefit from a major paradigm shift. The standard advice to eat less and exercise more is both simplistic and often ineffective. The science presented at this workshop suggested a sequence of steps that could result in new ways to address obesity at the personal as well as at the population level. First, we need to achieve a clear understanding of who becomes obese, where, and for what reason. Second, we need to parse out the likely contributions to overeating by the brain, biology, economics, and the environment. Then, based on our understanding of disease etiology and its distribution by geography and by social strata, we need to develop targeted yet comprehensive strategies for obesity prevention and treatment for both individuals and groups.

The conventional disease model of obesity, built around the individual patient, needs to be reconciled with some of the contemporary thinking about obesity in its social and environmental context. That may require a shift of emphasis from the individual to the group and a full consideration of the biological as well as the social and economic determinants of health.

One issue that deserves serious study is the observed social gradient in obesity. Obesity rates, especially for women, are strongly influenced by the social
and economic environments. In developing countries, it is the more affluent urban women who are gaining weight. In developed countries, higher rates of obesity are observed in relatively more deprived areas. In both cases, women’s bodyweights are affected by the changing social conditions more than bodyweights of men. The global obesity epidemic can thus be viewed through the prism of social disadvantage and women’s health.

Clear thinking about the biological and social determinants of weight and health is essential to the success of any intervention, whether at the individual or population level. Few studies have examined the success of prevention or treatment strategies across different socioeconomic strata. Little is known about social and economic barriers to the adoption of lower energy density diets and more active lifestyles. If the reasons why some women gain weight and others do not are either misunderstood or ignored altogether, then the proposed prevention plans will fail. If the reasons why some people stay with a diet regime whereas others fail are unclear, then the treatment plans will be ineffective in the long-term. Barriers to treatment success may be inherent in the brain, the biology, or the environment.

Current advances in research – discussed here – have the power to change our thinking. The traditional disease model holds that people become obese through a combination of genetic predisposition, faulty metabolism, and acquired bad habits. The new emphasis must move beyond a focus on personal responsibility, calorie counting, and the macronutrient composition of the diet. We need a greater understanding of behaviors determining food intake and physical activity and how environmental and biological influences combine to determine food choices, amounts consumed, and activity levels. Appeals to individual motivation need to be tempered by the recognition that food-seeking behaviors are bound by biological, economic, social and environmental constraints.

Our thinking about the role of the adipose tissue has also undergone a paradigm shift. Formerly viewed as a passive fat repository, the adipose tissue is now regarded as an active neuroendocrine organ functioning in concert with body physiology. Similarly, the obese person is often thought of as the victim of passive overeating. Our thinking about obesity could benefit from a broader integrative approach that places more emphasis on how obese people behave and function within the surrounding food environment. On one hand, food choices and dietary behaviors are driven by biology and the brain. On the other hand, access to healthy foods and opportunities for physical activity can be limited by material resources, transportation, and the built environment. New studies on spatial epidemiology and behavioral economics provide a contextual framework for cutting-edge research on biology, human development and behavior.

The chief aim of this workshop was to summarize some of the key issues in obesity treatment and prevention in order to promote novel and interdisciplinary approaches and to explore cutting-edge ideas that spanned child development, nutrition, behavioral sciences, economics, geography and public health.
We discussed a variety of approaches and disciplines, ranging from molecular biology to ethnographic research and public health policy and practice. With each topic, it was important to consider both personal and public health. On one hand, individual decisions, choices, and behaviors that lead to overeating and weight gain remain important and cannot be overlooked. On the other hand, food systems, food cultures and food environments are of critical importance. It is those systems, not human physiology, that have undergone dramatic changes over the past few decades. Should we try to influence the person or improve the food environment? New strategies should demand that we do both.

Adam Drewnowski
Barbara J. Rolls
A fifth of all global deaths today can be attributed to overweight or obesity. At least 2.8 million adults die each year as a result of being overweight or obese; according to the WHO report (May 2012), 44% of the diabetes burden, 23% of the ischemic heart disease burden and between 7 and 41% of certain cancer burdens are attributable to overweight and obesity; moreover, as reported by the WHO, the obesity epidemic is spreading widely – by 2002 the number of people in the world who were overweight or obese had exceeded the number of people who were undernourished.

And this is not only a problem in adults. It affects adolescents and young children too, taking its burden into the future. In 2010, around 43 million children under 5 years were overweight (www.who.int/dietphysicalactivity/childhood/en/). Having been previously considered a problem restricted to high-income countries, overweight and obesity rates are now also rising in low- and middle-income countries. Close to 35 million overweight children under 5 years are living in developing countries and 8 million in developed countries. Indeed, developing countries now suffer from a dual burden of disease – obesity and undernutrition. Unacceptably high rates of obesity, diabetes and metabolic syndrome in developing countries may well become a global health problem in the near future.

Overweight and obesity, as well as their related noncommunicable diseases, have become a burden for the society due to a decrease in the physical nature of work and the increase in morbidity and mortality rates in obese people; but this is largely preventable. While obesity management and prevention certainly require an effort by individuals, the problem should also be a key area of focus for public health systems and services and governments.

Thus, this 73rd Nestlé Nutrition Institute Workshop has been dedicated to epidemiology and strategies to prevent obesity, treatment strategies, clinical outcome, and future trends in scientific research. In addition, genetic and epigenetic aspects were considered. The discussions held focused on the day-to-day challenges and opportunities in obesity treatment, and when and how to start preventive measures.
We highly appreciate the renowned chairpersons Prof. Barbara Rolls and Prof. Adam Drewnowski who prepared such a high level of scientific program and brought together distinguished world experts in the area of obesity.

Finally, we would like to acknowledge the great work and organization of Laura Taylor and her team from Jenny Craig, thanks to which we could enjoy the scientific discussions in SanDiego, Calif.

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Brain Reorganization following Weight Loss

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Abstract
The long-term stability of bodyweight despite wide variation in energy intake and expenditure suggests that at usual weight energy intake and output are ‘coupled’ to maintain body energy stores. Our model for some of the molecular mechanics of this regulation of energy stores is based on the concept of a neurally encoded ‘threshold’ for minimum body fat, below which compensatory physiology is invoked to restore body fat. The existence of such a centrally encoded threshold is supported by the similarities in response to maintenance of a reduced weight between lean and obese individuals, and the tendency for weight-reduced individuals to regain weight to levels of fat stores similar to those present prior to initial weight loss. Brain responses to food and the observed changes in energy expenditure that occur during maintenance of a reduced weight are largely reversed by the administration of the adipocyte-derived hormone, leptin.

Introduction: Evidence That Bodyweight Is Regulated

Obesity has become the most prevalent and costly nutritional problem in the United States, and currently accounts for over 15% of total US health care spending [1]. Modest (10%) weight loss will prevent or ameliorate many of the major medical/metabolic consequences of obesity [2]. While most patients can achieve such weight loss by conventional means, the majority cannot maintain the reduced weight [3] for extended periods of time.

The long-term constancy of bodyweight (the average American adult gains only about 0.5–1.5 kg per year despite ingesting over 900,000–1,000,000 kcal), the 80–85% recidivism rate to previous levels of adiposity following otherwise successful weight loss, the observation that individuals successful at maintaining
weight loss engage in dietary restriction and increased physical activity compared to weight-matched controls, and the demonstration that there is similar metabolic opposition to sustained weight loss in both lean and obese individuals all support the view that energy stores are physiologically regulated around an individualized centrally perceived ideal (based on genetics, development, and environment) [4–7]. The long-term persistence of hypometabolism [8] and hyperphagia [9] in weight-reduced individuals compared to themselves prior to weight loss or to individuals ‘naturally’ at the same weight, provides ample evidence for the ‘biological’ basis of the difficulties in sustaining weight loss.

The steadily increasing prevalence of obesity suggests that metabolic ‘defenses’ against gain of fat are inherently weaker than those resisting its loss. One model for the molecular mechanics of this regulation is based on the concept of a centrally encoded ‘threshold’ for minimum body energy stores (fat). The critical role of fat stores in reproduction and survival during periods of undernutrition supports the idea of evolutionary ‘emphasis’ on preserving somatic fat stores [6]. These inferences are consistent with genetic arguments related to the so-called ‘thrifty genotype’ [10] and suggest that the conventional ‘thermostatic’ model of ‘set-point’ regulation of body fat [11] is not correct. More likely, the control system is designed to keep body fat above a critical lower limit or ‘threshold’ against threats of physical or reproductive extinction during times of undernutrition. As a corollary, relative metabolic and behavioral ‘leniency’ regarding increases in body fat would be anticipated for their survival advantage.

The genes and developmental processes that affect bodyweight do so by affecting the molecular and structural components of a CNS system that sense and react to ambient concentrations of leptin, insulin, metabolic substrates, and other molecules that reflect the mass and functional status of somatic fat (energy) stores. This construct operates as a threshold sensor for relevant signals such as leptin. The threshold for any ligand (e.g. leptin) is determined by the functional sensitivity (by virtue of differences in rates of expression or structural/functional integrity) of its central and peripheral molecular components, e.g. leptin, insulin, ghrelin, melanocortin, and melanocyte-concentrating hormone receptors, and various orexigenic and anorexigenic neuropeptides, and other molecules such as AMP-kinase, acetyl CoA-carboxylase, carnitine palmitoyl transfersase-1, malonyl CoA, FoxO1, PI3 kinase, etc. [6, 12].

In this model a major, but not the only, afferent signal is the adipocyte-derived hormone leptin. Subthreshold circulating and CSF concentrations of leptin invoke changes in energy expenditure and intake that result in regain of bodyweight (fat) [6, 13]. The threshold determines the signal intensity required to affect gene expression, neural connections, other cellular elements (glia) [6]. Both the level at which this threshold is set and the intensity of responses to deviations below this threshold are the result of genetic, developmental, and environmental (e.g. nutritional) factors.
Obese individuals are still frequently perceived as willful agents of their excess adiposity by community [14], health professionals [15], and even by themselves [14]. The inability of most individuals to sustain weight loss is attributed to a psychological lack of ‘will power’ (somehow lean individuals who are unable to sustain even a small degree of weight loss are spared this bias) [15]. In the context of this threshold model, the metabolism and behaviors that make it so difficult for even highly motivated individuals to sustain weight loss are predominantly the predictable biological consequences of CNS-mediated processes that occur as a result of decreased energy stores rather than indications of a pathological lack of willpower that is somehow unique to formerly overweight or obese individuals. The obese and never-obese differ primarily in the level at which this threshold for body fatness is set rather than in response to deviations below that threshold. Obesity is thus a chronic disease that continues to manifest itself through persistent metabolic and behavioral opposition to sustaining a reduced bodyweight even after the physical and comorbid manifestations of the illness may have been ‘cured’ by weight reduction [5–9].

Energy Intake and Expenditure during Reduced-Weight Maintenance

In both never-obese and obese subjects, maintenance of a 10% or greater reduction in bodyweight is associated with reductions in energy expenditure adjusted for metabolic mass, circulating concentrations of bioactive thyroid hormones, sympathetic nervous system (SNS) tone, and satiety, and increases in parasympathetic nervous system (PNS) tone and skeletal muscle work efficiency that act together to favor restoration of body energy stores [5–7]. Thus, attempts to sustain weight loss are ‘opposed’ by alterations in metabolism, neuroendocrine function, autonomic function, and behavior that ‘conspire’ to favor the regain of lost weight. Most of these changes, which are discussed below, are reversed by repletion of the adipocyte-derived hormone leptin following weight loss [5–7, 13, 16, 17]. Both the effects of weight loss and leptin repletion are largely predictable from what is known about leptin action in the CNS.

In humans, maintenance of a 10% or greater decline in bodyweight (approximately 70% of this loss is fat mass) lowers energy expenditure per unit of remaining metabolic mass by ~22%, which represents a reduction of about 15% (300–400) kcal below that predicted based on changes in body composition [5]. Twenty-four hour energy expenditure (TEE) is the sum of resting energy expenditure (REE: cardiorespiratory muscle work and the biochemical work of maintaining transmembrane ion gradients at rest; ~60% of TEE), the thermic effect of feeding (the work of digestion; ~5–10% of TEE), and non-resting energy expenditure (NREE: energy expended in physical activity above resting; ~30–40% of TEE) [18]. The major effect of a 10% or greater weight loss is to decrease NREE by approximately 30–40% [5]. The decline in NREE after weight
loss is due primarily to an approximate 20% increase in chemomechanical work efficiency of skeletal muscle rather than to a decrease in time spent in physical activity [5, 13, 19]. The disproportionate decline in energy expenditure and increase in skeletal muscle work efficiency following weight loss are most likely the consequences of centrally mediated declines in circulating concentrations of bioactive thyroid hormones (approximately –10 to 25%) and SNS tone (approximately –45%) and increase in PNS tone (approximately 90%) [5]. More specifically, these autonomic and neuroendocrine changes directly affect skeletal muscle gene expression and contractile efficiency predominantly by increasing the expression of the more efficient isoforms of the myosin heavy chain (MHC) and sarcoplasmic endoplasmic reticular Ca²⁺-dependent ATPase (SERCA) [13, 16, 19, 20]. These changes occur following weight loss in both lean and obese individuals and [5, 21] and do not abate over time [8]. Functional brain imaging studies show that maintenance of a reduced weight is associated with leptin-responsive decreased neuronal activity in the hypothalamus in response to visual food stimuli which would make sense in the context of the known effects of hypothalamic lesions or disruption of hypothalamic leptin signaling on both

**Table 1.** Effects of maintenance of reduced bodyweight on energy expenditure, autonomic function, neuroendocrine function, and skeletal muscle [5, 6, 16, 19, 21, 23, 24]

<table>
<thead>
<tr>
<th>System</th>
<th>Effects of sustained weight loss (~10% or greater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy expenditure</td>
<td>↓ TEE (~15% below predicted based on body composition/weight change)</td>
</tr>
<tr>
<td></td>
<td>↓ REE (~5% below predicted based on body composition/weight change)</td>
</tr>
<tr>
<td></td>
<td>↓ NREE (~35% below predicted based on body composition/weight change)</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td>↓ SNS tone (~–45%)</td>
</tr>
<tr>
<td></td>
<td>↑ PNS tone (~90%)</td>
</tr>
<tr>
<td>Neuroendocrine function</td>
<td>↓ Leptin (proportional to loss of fat mass)</td>
</tr>
<tr>
<td></td>
<td>↓ T₃ (~–10%)</td>
</tr>
<tr>
<td></td>
<td>↓ T₄ (~–5%)</td>
</tr>
<tr>
<td></td>
<td>↓ TSH (~–15%)</td>
</tr>
<tr>
<td></td>
<td>↑ rT₃ (~–5%)</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>↑ Chemomechanical efficiency (~20%)</td>
</tr>
<tr>
<td></td>
<td>↑ MHCI expression (~−20%)</td>
</tr>
<tr>
<td></td>
<td>↑ SERCA2 expression (~30%)</td>
</tr>
</tbody>
</table>

TEE = Twenty-four-hour energy expenditure; REE = resting energy expenditure; NREE = non-resting energy expenditure; T₃ = triiodothyronine; T₄ = thyroxine; TSH = thyroid-stimulating hormone; rT₃ = reverse T₃; MHCI = myosin heavy chain I; SERCA2 = sarcoplasmic endoplasmic reticulum Ca²⁺-dependent ATPase 2.
energy expenditure (decreased) and intake (increased) [22]. Data regarding adaptive thermogenesis in response to reduced weight maintenance are presented in table 1.

The decline in energy expenditure following weight reduction would have little clinical consequence if energy intake were proportionately reduced. However, maintenance of a reduced bodyweight, as well as other ‘low-leptin’ states (see below), is also associated with decreased satiation and increased hunger, thus creating the optimal biological circumstance to promote weight gain in leptin-deficient and weight-reduced humans and rodents [6, 7, 25]. Individuals maintaining a reduced bodyweight after non-surgical weight loss are inclined towards greater rather than diminished energy intake [9, 17]. More specifically, subjects maintaining a reduced weight show delayed satiation, decreased perception of how much food has been eaten, decreased desire to switch to a different food, increased hunger and craving for food, and an increased preference for calorically dense foods [6, 7, 9, 17, 26, 27].

Regional Changes in Brain Activity in Response to Weight Loss

Functional magnetic resonance imaging (fMRI) studies of individuals before weight loss and during maintenance of a 10% or greater reduced weight on a constant composition liquid formula diet demonstrate leptin-responsive increases in food reward and decreases in food restraint following weight loss. Maintenance of a reduced bodyweight is associated with fMRI changes consistent with increased emotional and cognitive response (reward) and decreased emotional and cognitive control (restraint) regarding food intake (table 2).

Behaviorally, these changes in neuronal signaling would be predicted to result in delayed satiation, as is seen in states of leptin deficiency [28]. This is, in fact, true; individuals maintaining a reduced bodyweight demonstrate delayed satiation, decreased perception of how much food has been consumed, and increased hunger, despite the fact that they are in a eumetabolic state rather than actively losing weight [9, 17]. As discussed below, most of these changes are reversed by leptin ‘repletion’ following weight loss [13, 16, 17, 22].

Individuals in the National Weight Control Registry (individuals successful at sustaining long-term weight loss) demonstrate increased activity in brain areas related to cognitive control around food compared to non-weight-reduced individuals [29], which may reflect behavioral traits that were present prior to weight loss or traits that are learned in order to sustain weight loss. Patients who have undergone Roux-en-Y banded gastroplasty demonstrate decreased activity in brain areas related to food reward [30] with little effect on areas related to restraint. Taken together, these observations suggest that it should be possible to identify individuals more likely to succeed in sustaining weight loss based on prescreening, i.e. identifying those individuals with greater activity in brain areas...
related to food restraint or decreased activity in brain areas related to food reward as better candidates for lifestyle intervention. Furthermore, it should be possible either to train individuals or to provide pharmacotherapy to alter their behavior and reduce risk for weight regain, and to monitor progress by examining brain function in response to food. For example, transcranial direct current stimulation of the prefrontal cortex has been shown to reduce food cravings [31].

The autonomic (decreased SNS tone and increased PNS tone), neuroendocrine (decreased circulating concentrations of bioactive thyroid hormones, leptin, and, if weight loss is sufficiently large, gonadotropins), and metabolic (decreased energy expenditure largely due to increased skeletal muscle work efficiency) effects of sustained weight loss are mediated centrally and, to a lesser degree, peripherally.

The central and peripheral mechanisms accounting for changes in autonomic, neuroendocrine, and metabolic systems relevant to energy homeostasis are summarized in table 3.

**Autonomic Nervous System**

The decline in SNS tone following weight loss reflects decreased epinephrine production by the adrenal medulla – probably mediated by adrenal medullary leptin sensing cells as well as centrally mediated suppression of SNS

### Table 2. Effects of weight loss and leptin repletion following weight loss on energy and neuronal signaling (blood oxygen level-dependent fMRI signals in response to food vs. non-food visual cues)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Putative functions related to food intake</th>
<th>Weight loss effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain areas integrating peripheral signals with neural tracts regulating energy intake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>Signal processing (food recognition)</td>
<td>Increased</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Integration of humoral/brain stem signaling</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Brain areas related to restraint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal cortex (multiple gyri)</td>
<td>Sensitivity to caloric density and regulation of food intake in response to sensory stimuli</td>
<td>Decreased</td>
</tr>
<tr>
<td>Cingulate</td>
<td>Self-control/error recognition (cognitive control)</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Brain areas related to reward</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>Food reward</td>
<td>Increased</td>
</tr>
<tr>
<td>Lingual + superior temporal gyri</td>
<td>Emotional and cognitive response to food</td>
<td>Increased</td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>Reward and motivation</td>
<td>Increased</td>
</tr>
<tr>
<td>Weight loss effect</td>
<td>Proposed mechanism</td>
<td>Supporting evidence</td>
</tr>
<tr>
<td>--------------------</td>
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<td>---------------------</td>
</tr>
<tr>
<td><strong>Centrally mediated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓T₃, T₄, TSH</td>
<td>↓leptin→↓POMC (ARC) →↓pro-TRH (PVN)</td>
<td>No effect of weight loss on TRH response but leptin reversed decline in T₃ and T₄ [13]</td>
</tr>
<tr>
<td>↓SNS tone (norepinephrine)</td>
<td>↓leptin →↑MCH (lateral hypothalamic area) and ↓CART→↓SNS tone</td>
<td>Leptin reverses decline in SNS tone [13]</td>
</tr>
<tr>
<td>↑PNS tone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed satiation and increased hunger</td>
<td>↓leptin →↓POMC and ↑NPY/AgRP expression and ↑ sensitivity to satiety signals (e.g. CCK) →↑energy intake</td>
<td>Leptin reverses behavioral and neuronal changes in intake behavior [17, 22]</td>
</tr>
<tr>
<td><strong>Peripherally mediated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓Leptin</td>
<td>Reduced weight maintenance →↓ fat mass →↓leptin; negative energy balance →↓leptin expression/fat mass</td>
<td>Following weight loss, there is little effect on circulating leptin per unit fat mass; during weight loss circulating leptin per unit fat mass is decreased relative to during weight stability [32]</td>
</tr>
<tr>
<td>↑Reverse T₃</td>
<td>↓ Activity of 5’ deiodinase 1 and ↓ transport of T₄ into the liver and kidney where it would be converted to T₃ lead to ↓ clearance and ↑ production of rT₃</td>
<td>Undernutrition leads to ↓clearance of rT₃ [33]</td>
</tr>
<tr>
<td>↓SNS tone (epinephrine)</td>
<td>↓Leptin-stimulated epinephrine release from the adrenal medulla (probably less clinically significant than centrally mediated effects on SNS tone)</td>
<td>Leptin stimulates adrenal catecholamine release [34] and reverses decline in SNS tone [13]</td>
</tr>
<tr>
<td><strong>Consequences for energy expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Skeletal muscle chemomechanical efficiency</td>
<td>↑T₃ and SNS tone →↑ expression of more efficient isoforms of MHC and SERCA →↑efficiency and utilization of FFA as fuel by muscle</td>
<td>↑MHC and SERCA2 expression, ↑utilization of FFA as fuel, are largely reversed by leptin [13, 16, 19, 20] repletion</td>
</tr>
<tr>
<td>REE</td>
<td>↓T₃ and SNS tone lead to reduction (~–15%) in REE [21]</td>
<td></td>
</tr>
<tr>
<td>NREE</td>
<td>↑Skeletal muscle chemomechanical efficiency leads to large (~–40%) reduction in NREE [19, 21]</td>
<td></td>
</tr>
</tbody>
</table>

ARC = Arcuate nucleus of the hypothalamus; PVN = paraventricular nucleus of the hypothalamus.
(norepinephrine-mediated) activity. Low leptin states increase expression of melanin-concentrating hormone (MCH) in the lateral hypothalamus. Increased MCH results in increased inhibition of activity in preganglionic sympathetic neurons in the brainstem and spinal cord. Centrally mediated declines in SNS tone are likely to have a much more significant effect on overall energy homeostasis than the peripheral effects of weight loss, and therefore decreased leptin, on epinephrine release from the adrenal medulla. Low leptin and fasting states are also associated with decreased expression of cocaine- and amphetamine-regulated transcript (CART) which is expressed in the arcuate nucleus of the hypothalamus, lateral hypothalamus, and in neurons throughout the brain [35]. CART neurons suppress MCH release in the lateral hypothalamic area and innervate sympathetic preganglionic neurons in the spinal cord and brainstem. Following weight loss, CART expression is decreased and would contribute to the decreased SNS tone. The increase in efferent PNS tone must reflect increased central activation of the vagus nerve via the dorsal motor nucleus and/or the nucleus ambiguus [5, 13]. The mechanism by which weight loss promotes increased PNS tone is not clear. Vagal afferents and efferent neurons both express functional long forms of the leptin receptor [36] and leptin potentiates the effects of CCK on activation of vagal afferents in the brain stem, thereby potentiating inhibition of feeding [36]. While central leptin injection inhibits gastric emptying, possibly due to decreased vagal motor activity in the stomach [37, 38], no such effect is observed following intraperitoneal leptin administration [37, 38] perhaps indicating that supraphysiological CNS leptin levels are required to provoke a clinically significant change in PNS tone.

Neuroendocrine Function

The decline in circulating concentrations of triiodothyronine (T₃) and thyroxine (T₄), without a compensatory increase in thyroid-stimulating hormone (TSH) production, following weight loss indicates central effects of weight loss on the hypothalamic-pituitary-thyroid (HPT) axis. TSH release in response to thyroid-releasing hormone (TRH) is not diminished following weight loss; therefore, the predominant effect of weight loss on the HPT axis must be via decreased production of TRH. As discussed below, this most likely occurs as the result of decreased hypothalamic (arcuate nucleus) pro-opiomelanocortin (POMC) in low leptin states coupled with leptin-sensitive decreased activity of prohormone convertases in the arcuate and paraventricular nuclei of the hypothalamus [39]. The net effect of decreased expression of POMC and the prohormone convertases would be decreased production of the cleavage product of POMC, α-melanocyte-stimulating hormone, which stimulates production of hypothalamic pro-TRH in the paraventricular nucleus of the hypothalamus. The increase in circulating concentrations of reverse T₃, the bioinactive enantiomer of T₃, is due to decreased clearance of T₃ as a result of decreased expression of deiodinase 1 and decreased transport of T₄ into the liver and kidney where it would normally be converted
to T₃ (resulting in a net increased availability of T₄ for conversion to reverse T₃). Leptin is made almost exclusively by adipose tissue, and the decline in leptin following weight loss is mostly a reflection of decreased adipocyte volume. The even more pronounced decline in leptin during active weight loss reflects direct metabolic effects on rates of leptin production per adipocyte [40].

**Skeletal Muscle**
The increase in skeletal muscle work efficiency is of sufficient magnitude to account for most of the reduction in energy expenditure following weight loss [5, 8, 13, 16, 19, 20]. The centrally and peripherally mediated autonomic and neuroendocrine changes described above directly impact skeletal muscle. As noted above, the molecular phenotype of skeletal muscle in individuals following dietary weight loss is one of increased expression of the more chemomechanically efficient myosin heavy chain I (MHCI) and SERCA2 isoforms [5, 16]; these molecular phenotypes are characteristic of slow twitch muscle fibers whose chemomechanical efficiency is greater than that of fast twitch fibers. The promoter region of the MHCI isoform contains inhibitory T₃ response elements that result in increased MHCI expression in hypothyroid states [41]. The decline in SNS tone following weight loss promotes decreased expression of the more powerful, less efficient, MHCII isoform, decreases thermogenesis in brown adipose tissue, and contributes to the decreased circulating concentrations of T₃ [5, 24]. The slow-twitch muscle isoform (SERCA2) is encoded by a gene whose transcription is inhibited by T₃ (unlike SERCA1 whose expression is stimulated by T₃) [16], and β-adrenergic stimulation decreases the expression of SERCA2a in cardiac muscle and increases the ratio of SERCA1/2 in skeletal muscle [42]. Skeletal muscle expresses both the long- and short-forms of the leptin receptor. Perfusion of isolated mouse hearts with leptin results in increased fatty acid oxidation and decreased chemomechanical work efficiency, which is consistent with findings of increased muscle work efficiency in low leptin states [13, 19].

**Caloric Intake**
Caloric intake, assuming that there is ad libitum availability of nutrients, represents the central nervous system’s response to the sum total of multiple internal and external sensory inputs. These inputs include short-term (e.g. glucose) and longer-term (e.g. leptin) internal ‘biological’ signals regarding levels of energy stored, food anticipation (based in part on environmental stimuli such as the time of day), hunger, satiation, wanting of food, and liking of the food that is available [43]. These signals determine how hard an individual will work for food, what type of food will be preferred, how much will be eaten, how fast, and when feeding will cease [44]. During dynamic weight loss, i.e. during negative energy balance, one could argue that changes in energy intake behaviors are due to alterations in short-term signals relevant to systemic energy status, and not
to any reorganization of the responses to food. For example, a decline in blood glucose will provoke food seeking behavior regardless of whether one is losing weight or not. Changes in energy intake behavior and physiology that are evident during maintenance of a reduced bodyweight, i.e. in a eumetabolic state at a lower weight, must reflect changes in the brain’s responses to food-related cues that occur as the result of changes in long-term signals – such as leptin – regarding the status of body energy stores.

The Role of Leptin

As discussed above, maintenance of a 10% or greater reduction in bodyweight in obese or never-obese individuals is associated with reduced energy expenditure adjusted for metabolic mass, reduced circulating concentrations of bioactive thyroid hormones and SNS tone, delayed satiation, and increased PNS tone, skeletal muscle work efficiency, and hunger that act synergistically to favor restoration of body energy stores [13, 21, 24, 45]. The similarity of phenotypes between maintenance of a reduced bodyweight (in which circulating leptin concentrations are decreased), fasting or semi-starvation (in which leptin concentrations are even further reduced) [46, 47], and congenital leptin deficiency (in which circulating functional leptin is absent) [25] support the hypothesis that these weight-reduced phenotypes are secondary to the effects of decreased concentrations of leptin following weight loss on central systems regulating energy homeostasis. It should be emphasized that decreased circulating leptin concentration is clearly not the only signal mediating weight regain. Both leptin-deficient and leptin-resistant rodents show increased hypothalamic NPY and decreased POMC expression and rebound hyperphagia and weight regain after fasting [48]. The decline in TSH, increase in PNS tone, and increase in expression of SERCA2A in weight-reduced individuals persists even after leptin repletion [13, 16]. Similarly, not all of the effects of weight loss on neural signaling in response to food are ‘reversed’ following leptin repletion [22] (see table 4).

The metabolic and behavioral effects of exogenous leptin administration depend on the nutritional context within which the leptin is given, and are consistent with the threshold model discussed above. Administration of physiological (low-dose) leptin to weight-reduced and leptin-deficient humans or mice reverses many of the behavioral, metabolic, autonomic, and neuroendocrine phenotypes that act coordinately to oppose the maintenance of reduced weight [13, 49] thus affecting both energy intake and output. In subjects undergoing dynamic weight loss, exogenous leptin administration ‘reverses’ some of the decline in satiation, but has little effect on energy expenditure [50, 51]. Finally, much higher doses of leptin are required to provoke even small behavioral or metabolic effect in mice or humans at usual weight [52].
Conclusions and Perspective

The primary physiological role of leptin is to defend body fat by increasing food intake and decreasing energy expenditure when fat stores are insufficient [5–7, 53]. Leptin concentrations above a centrally encoded ‘threshold’ have little if any additional effect, hence the apparent ‘resistance’ to increased ambient leptin concentrations whether due to obesity or exogenous leptin administration [52] and the evident ‘resistance’ of obese individuals to their endogenously elevated circulating leptin concentrations [6]. Leptin concentrations below the functional threshold evoke vigorous compensatory responses designed to increase leptin availability [48, 49] – hence the identity of the leptin-reversible metabolic, autonomic, and neuroendocrine opposition to the maintenance of a reduced bodyweight in lean and obese individuals [13].

The mechanisms by which the molecular and structural predicates of this CNS-mediated defense of a minimum level of somatic fat are established remain a critical area of research. Almost certainly, gene-mediated differences in the performance
of hypothalamic, brain stem and ‘higher’ centers coordinating energy homeostasis are involved. The likelihood that the relevant cell bodies and circuits are to some extent malleable contravenes more conventional notions of the fixity of the anatomy of a mature central nervous system. Developmental (structural, gene imprinting) effects conveyed in utero or in early development, and later effects of circulating metabolites (e.g. cytokines, and paracrine effects of glial cells) are all tenable candidates for mediating a functional plasticity that could enable apparent elevations of the threshold (defense of higher body fat) in individuals chronically exposed to suitable environments [6, 12, 54, 55]. Such a capacity further rationalizes efforts to prevent obesity, and raises the question of whether there are age/develoment-related ‘critical periods’ when the threshold is set and during or before which weight reduction would not be resisted as it is afterwards [56, 57]. The apparent inflexibility of the threshold in the downward direction indirectly validates these ideas by suggesting that evolutionary selection has enabled change in the upward direction while prohibiting organisms from ‘accepting’ levels of body fat that could endanger survival and reproduction [5–7].

These findings should be viewed as providing potential mechanisms for the successful long-term treatment of obesity. It may ultimately be possible to identify what type of non-surgical or, if necessary, surgical intervention would most likely be successful in sustaining weight loss based on pre-weight loss phenotyping and genotyping. It should be possible to devise behavioral and pharmacological therapies, affecting the leptin signaling and other pathways, that are specifically geared towards maintenance of reduced weight. This pharmacology is likely to be substantially different from that used to induce weight loss, since its goal is to rectify a dysmetabolic state rather than to induce one. The understanding of the functional biological and physiological bases underlying the difficulty in sustaining weight loss should alleviate some of the biased public perception that overweight or obese individuals are unlikely to sustain weight loss because they are necessarily lacking in will power compared to lean individuals. From the standpoint of the weight-reduced individual, the frustration at the supposed psychological failings attributed to them by society, health professionals and themselves should be replaced by the knowledge that they are still confronting the biology of weight regulation and that this problem can be addressed.

Acknowledgements

This work was supported by NIH grants RO1DK64773, RR00645 and UL1 TR000040.

Disclosure Statement

The authors declare that no financial or other conflict exists in relation to the content of the chapter.
References


Dr. Drewnowski: Far being from me to ask a provocative question, but one issue that has been occupying the public and was recently published in the Lancet is the equivalency between 3,500 calories and one pound of weight gain or loss [1], and this has been the absolute bible for decades. Every dietitian, every health professional equates 3,500 calories to a pound of weight gain or loss. It does not seem to be exactly true. What is your position on this?

Dr. Rosenbaum: You are asking, what is the caloric density of weight change? No generalization is absolutely true, and the caloric density of weight gained or lost depends upon its composition as fat mass, fat-free mass, and, of course, water. The average person who loses weight by diet alone loses about two thirds to three quarters of it as fat and a quarter to a third of it as lean body mass. But people lose weight by different means in terms of diet composition and exercise. Clearly, if you are losing energy stores due to the same degree of negative energy balance, the proportion of energy stores lost as fat mass and fat-free mass will be affected by the type and intensity of the exercise. The caloric density of fat is roughly 7 times that of muscle, so whether you are losing energy as fat or muscle is going to make a difference in terms of how much absolute weight you lose.

Dr. Drewnowski: I am trying to get at the issue of public health policy. There was a paper published in American Journal of Public Health [2] suggesting that if people in California went to a fast food restaurant, looked at the menu labeling, and as a result ate 100 calories less, then 100 calories per day per year would equate into millions of pounds lost and the obesity epidemic in California would go away. This was one spin on the relation between calories and pounds lost. The other spin was a study published in the
American Journal of Clinical Nutrition [3] suggesting that the reduction of 100 calories per day for a year would lead to a weight loss of only 800 g. Clearly, the truth is some place in between. How would you respond to this issue?

Dr. Rosenbaum: Any change in energy storage must follow the first law of thermodynamics and reflect a difference between energy intake and output. The conclusion of the American Journal of Public Health paper as you have cited it implies that when you decrease your caloric intake by 100 kcal/day there is no compensatory decline in energy expenditure. The correct statement would be that if you consistently cut your intake by 100 calories a day relative to your energy expenditure, you would lose 36,500 kcal worth of stored energy per year, which would be substantial. The problem is that as you are losing weight due to caloric restriction, your energy expenditure is declining both by virtue of the natural loss of metabolically active tissue that’s occurring, and also is a result of the additional hypometabolism that’s occurring as a result of decreased circulating concentrations of bioactive thyroid hormones and leptin, decreased sympathetic nervous system tone, increased parasympathetic nervous system tone, and increased skeletal muscle work efficiency [4]. This is the idea that they are getting at in the American Journal of Clinical Nutrition paper. The view that our bodies fight against weight loss and weight gain by disproportionately increasing or decreasing energy expenditure, respectively, goes back to the work of Neumann in 1902 [5]. He noted the remarkable stability of his bodyweight over a year with no attempts to control either his energy intake or his expenditure. He used the term ‘Luxuskonsumption’ to describe what he believed to be the body’s facultative ability to raise rates of energy expenditure to oppose relative excesses of energy intake. Keys, Brozek, and many others have made similar observations during dynamic weight loss [6]. The consequence of these changes is that you won't lose or gain as much weight as you think you would like to, or calculate that you should, by diet alone. Furthermore, our own work [7] and that of the National Weight Control Registry group [8] have shown that you will need to restrict your intake and/or increase your expenditure beyond what you would like or predict that you would need to if you wish to keep the weight off. In this sense, obesity is a disease that continues to manifest itself in the form of decreased energy expenditure and increased appetite even after it has been supposedly ‘cured’ by weight loss.

Dr. Finegood: I will just speak up on that because I think more important in Kevin Hall's paper [9] was the point about the nonlinearity of the relationship between energy imbalance and weight changes. Have you ever actually looked at the dynamic phase of your studies as opposed to just the steady states, and do you see any genetic component that contributes to the dynamic phase?

Dr. Rosenbaum: The answer is yes and no. We have looked somewhat at the dynamic phases of our studies and we have not looked at the genetics behind subject phenotypes during the dynamic phase. The basic pattern of dynamic weight loss is extremely similar between most subjects. There is an initial rapid weight loss phase reflecting mostly water loss due to the decreased carbohydrate in the diet and subsequent excretion of sodium. Following this, there is a period of slower weight loss that presumably would eventually asymptote. As you suggested, there is a large interindividual variation in the rate of weight loss. For example, other studies have demonstrated ethnic differences in the distribution of weight lost (greater visceral adipose tissue loss in white versus black women) [10] and the changes in energy expended in physical activity following weight loss (higher in white versus black women) [11].
A corollary to your question is whether the changes in energy homeostatic systems that occur during weight loss are distinct from those that occur during reduced weight maintenance. We looked at the differences between dynamic weight loss and static reduced weight maintenance by studying subjects at the very end of weight loss and comparing them to themselves when maintaining a similar weight. This allows separation of the effects of dynamic weight change and weight maintenance at similar weights. There are marked differences between subjects during dynamic weight loss (negative energy balance) and maintenance at the same weight (eumetabolism). For example, there is a tremendous decline in resting energy expenditure during dynamic weight loss and a much more profound decline in thyroid hormones and in leptin during dynamic weight loss than during static weight maintenance. It should also be noted that leptin is not the only signal operant in states of weight loss. For example, we have found that the increase in parasympathetic nervous system tone and decrease in TSH persist in weight-reduced individuals even after leptin repletion [12]. So, there are clearly signals affecting energy expenditure that are related to energy balance as opposed to absolute bodyweight, i.e. those are present during weight loss as distinct from reduced weight maintenance, and some of these are not leptin dependent, i.e. those that are evident even in leptin-deficient mice. Your question as to whether genotype would be predictive of phenotypes, such as the composition of weight loss or the decline in energy expenditure or thyroid hormones during dynamic weight loss is a good one that we have not examined.

Dr. Bray: Because Dr. Drewnowski brought up epigenetics, it is important to note that there is more and more evidence that at least methylation is much more labile than we think it is. Is it possible that when you are giving a liquid diet for such long periods of time, the methylation patterns can actually change in a way that turns on and off genes that results in what you have seen which is depressed metabolism?

Dr. Rosenbaum: This is an interesting question, but we have not looked at the effects of weight loss or a liquid formula diet on the methylation of relevant genes.

Dr. Bray: Related to that is if you gave 800 calories of lettuce or something that was not your liquid diet, do you think you would see exactly the same response?

Dr. Rosenbaum: The composition of weight lost is clearly going to be somewhat sensitive to diet composition. On a high carbohydrate or high salt diet one might anticipate a smaller initial loss of water weight. Sacks et al. [13] looked at the effect of diet macronutrient composition (low fat versus high fat, average protein versus high protein, and highest and lowest carbohydrate content) on the change in bodyweight over 2 years. At 6 months, participants had lost about 7% of their initial bodyweight with no group differences. Some weight regain had occurred in all groups at 12 months. No between-group differences were evident at 2 years. The authors concluded that there was no evidence of any major macronutrient influence on weight loss.

There is also a substantial body of data suggesting that diet composition does not have a big effect on energy expenditure during maintenance of a reduced weight. Rudy Leibel showed that wide variations in macronutrient composition of a liquid formula diet did not affect energy requirements to maintain weight in inpatients [14]. It should be noted that subsequent to this meeting, Ludwig’s group [JAMA 2012;307:2627–2634] reported that subjects who had lost weight had greater energy expenditure on a very low-carbohydrate diet than on an isocaloric low glycemic index or low-fat diet; while this would suggest that some of the decline in TEE and REE following weight loss may be attenuated on a very low-carbohydrate diet, the anticipated clinical consequences of
such differences in energy expenditure (increased loss of calories on a very low-carbohydrate diet) were not reported. In the National Weight Control Registry, individuals who are successful at maintaining weight loss report that they must eat less and still exercise about 60 min more per day than individuals naturally at the same weight [8, 15]. So even on an outpatient solid food diet they remain hypometabolic. Work by the late Dr. Roland Weinsier, in collaboration with Dr. Goran who is here today, is also relevant in this regard [16]. They studied a group of overweight outpatient women before and after a 10% dietary weight. They found that there was no decline in weight maintenance calories following weight loss beyond what was attributable to body composition changes. At first, this would seem to contradict our finding that there is a disproportionate decline in 24-hour energy expenditure following inpatient weight loss on a liquid formula diet. But, if you read the fine print in the article, the women in Roland’s study reported being 30% more physically active after they had lost weight. These data are entirely consistent with ours. Roland finds that outpatient subjects are able to spend 30% more time moving, and they have to pay for it, whereas in the hospital where they can’t spend any more time moving, they just pay 30% less for it. It’s the same difference. It is, of course, probable that diet composition has substantial effects on the long-term dietary compliance in some individuals. It just does not appear to have a big effect on thermogenesis.

Dr. Rolls: You suggested that we might be able to phenotype people and match treatment to their particular characteristics in weight loss settings. Do you have some ideas of how to do this phenotyping?

Dr. Rosenbaum: I think that the model for this is something like the National Cancer Institute where everybody who receives treatment is entered into a database which can then be mined to determine whether certain characteristics of individuals are indicative of a better response to one type of therapy versus another [17]. In our case, the data would come from obesity clinics from all over the country. Each individual would be phenotyped, perhaps one day even genotyped, in a standardized manner and entered into a national database. One could then look at that database and see if there were characteristics that predicted success, or lack thereof, in response to exercise, diet, pharmacotherapy, or bariatric surgery.

Dr. Rolls: What are the phenotypes you are looking at?

Dr. Rosenbaum: Of course ideally each individual would have their phenotype catalogued in the detailed way that we do, but I don’t think you could practically do that. Historically, you might look at age at onset of obesity, gender, which parent is obese, previous types of unsuccessful attempts to lose weight, basic lifestyle, and even at the number of known obesity risk genes that are present. Clinically, you might look at fat distribution, presence of comorbidities, certain biochemical markers, etc. Behavioral phenotyping could be done by having individuals complete a questionnaire about their food and exercise habits. You could really do some nice translational work. Angelo Del Parigi [18] and others [19] showed that individuals successful at keeping weight off in the National Weight Control Registry had greater neural activity in brain areas related to control in response to food. It is not clear whether this increased control was present in these individuals prior to weight loss or whether it is a learned trait. If it was present all along, then maybe individuals with that trait would be more likely to sustain weight loss.

Dr. Rolls: I agree that we need tools. Those of us working in this field have found that eating behavior in particular has been difficult to characterize.
Dr. St. Jeor: I am interested in phenotyping too. Would you include the T₃ levels and compare them against some other norms? I think we are returning to the time when everybody thought that people were obese because their thyroid was not functioning, and thyroid medication seemed to be the answer. Do you have any thoughts on how you might approach that and include that in your assessment and your treatment?

Dr. Rosenbaum: We are looking at this now in the same way we did in our leptin studies [20, 21]. We are doing thyroid studies of subjects at their usual weight and following weight loss while they are receiving a placebo or T₃ repletion in a crossover design. Physiological doses of thyroid hormone would not promote weight loss but may assist in reduced weight maintenance. The basic idea is that the treatment to maintain a negative energy balance and lose weight is not going to be the same as remaining in a eumetabolic state to maintain weight loss.

Dr. Drewnowski: Another idea is that the brain is incapable of perceiving calories presented in liquid form. What’s your take on that?

Dr. Rosenbaum: I think the brain knows when and what you have been eating. The similarities between our studies and the outpatient studies of Weinsier and of the National Weight Control Registry would all suggest that the brain perceives ingested calories regardless of the physical form in which they are presented to the gut. In the same vein, many feeding studies are done with subjects ingesting milkshakes or other liquids, and it seems that the intake of these liquids is predictably affected by CCK and other interventions. It is likely that the central nervous system perception of calories given intravenously, thereby bypassing most if not all gut peptide signaling, would be different from that of ingested calories.

Dr. Finegood: Maybe there is a difference between sugar-sweetened beverages and a mixed meal.

Dr. Rosenbaum: If you are asking whether there are differences in how our brains react to sugar-sweetened beverages versus a mixed meal, then I would say that there probably are significant distinctions. Diet composition will acutely affect multiple signals regarding energy homeostasis including CCK, ghrelin, and other gut peptides, and all of these will impact on appetite. The immediate biochemical responses to what has been eaten might be viewed as signals predominantly reflecting short-term energy intake, while others that reflect energy stores, such as leptin, might be viewed as signals better reflecting longer-term energy balance.

References


Physical Activity and Weight Loss

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Abstract

Weight loss interventions involving diet and physical activity typically result in 8–10% weight loss within 6–12 months after initiating treatment. Physical activity is a key component of these interventions for a variety of reasons. Weight loss achieved with physical activity averages approximately 1–3 kg, and the effects of physical activity on weight loss appear to be additive to what is observed with dietary restriction alone. Moreover, physical activity is an important behavior for prevention of weight regain and maintenance of significant weight loss resulting from dietary restriction, and physical activity contributes to weight loss in patients who have undergone bariatric surgery. However, there is significant interindividual variability in the weight loss resulting from physical activity, with both biological and behavioral factors contributing to this variability. Thus, additional research is needed to understand the role of physical activity in energy balance and body weight regulation, along with an understanding of the optimal intervention strategies to promote physical activity participation in overweight and obese individuals.

Introduction

The prevalence of overweight and obesity has risen significantly worldwide within the past few decades. Within the United States, the prevalence of overweight is estimated to exceed 65% of the adult population with obesity exceeding 30% [1], with similar trends shown in other countries throughout the world. This is of significant public health concern because of the association between excess bodyweight and many chronic diseases including cardiovascular disease, diabetes, certain forms of cancer, and musculoskeletal disorders [2].

A variety of interventions have been developed and implemented to reduce bodyweight in overweight and obese individuals. However, the cornerstone of interventions includes lifestyle modification for both eating and physical
activity behaviors. Lifestyle interventions are estimated to reduce bodyweight by 8–10% within the initial 3–6 months of treatment [3]. However, it is estimated that on average weight regain of 33–50% occurs within 1–3 years following initial weight loss [4]. Thus, there is a need to develop and implement effective interventions to reduce bodyweight in overweight and obese adults, and for these interventions to result in long-term weight loss maintenance. For example, the multicenter Diabetes Prevention Program, which implemented a very intensive lifestyle intervention, is considered by many to be one of the most successful lifestyle interventions for weight loss. This intervention resulted in weight loss of approximately 7 kg at 12 months with weight loss receding to 5.6 kg at a mean follow-up of 2.8 years, a weight regain of 20% of initial weight loss [5]. The multicenter Look AHEAD Trial, which again used an intensive lifestyle intervention, reported weight loss of 8.6% at one year with weight loss regressing to 4.7% at 4 years, equivalent to weight regain of approximately 45%. Similar patterns of weight regain have been shown in other intervention studies [6, 7].

**Effect of Physical Activity on Weight Loss**

Physical activity is an important component within weight loss interventions because of its ability to enhance initial weight loss, enhance maintenance of long-term weight loss, and have an independent effect on health-related conditions that are typically associated with excess bodyweight. Jakicic et al. [8] reported that an intervention focused on home-based physical activity that did not include a prescribed reduction in energy intake resulted in an average weight loss of approximately 2% at 6 months and 1% at 18 months. This magnitude is similar to the 3- and 6-month weight loss resulting from physical activity that has been reported by Hagan et al. [9] and Wing et al. [10], respectively. A systematic review of the literature conducted for the 2008 Physical Activity Guidelines Advisory Committee Report also suggested that a physical activity intervention consisting of 180–270 min per week would result in weight loss ranging from 0.5 to 3.0 kg [11]. The more recent Position Stand published by the American College of Sports Medicine (ACSM) [12] concluded that there is a dose-response between physical activity and the magnitude of weight change. This review concluded that interventions that included <150 min per week of physical activity resulted in no significant change in bodyweight, whereas physical activity of >150 and 225–420 min per week resulted in weight loss of 2–3 kg and 5–7.5 kg, respectively.

The National Heart, Lung and Blood Institute has recommended that lifestyle interventions for weight loss include reduced calorie intake combined with physical activity [2]. When combined with modest reductions in energy intake, equivalent to a reduction of 500–1,000 kcal/day, the addition of physical
activity appears to improve weight loss by 2–3 kg above the magnitude achieved with the dietary intervention alone. For example, Goodpaster et al. [13] studied adults classified with class II or III obesity and compared a diet only intervention prescribed at 1,200–2,100 kcal/day with the diet intervention combined with physical activity over a period of 6 months. Weight loss resulting from the diet alone intervention was 8.2 kg compared to 10.9 kg in the combined diet and physical activity intervention, a difference of 2.7 kg. Wing et al. [10] reported that the combination of diet plus physical activity improved weight loss by 1.2 kg compared to the magnitude of weight loss observed with a diet intervention alone (9.1 vs. 10.3 kg). These findings are consistent with the conclusions based on a review conducted by Curioni and Lourenco [14].

While the magnitude of weight loss achieved with physical activity over a period of 6 months may be considered to be modest, physical activity may play an important role in the maintenance of weight loss. As indicated above, it is common for initial weight loss to be followed by weight regain of the magnitude of 33–50% over a period of 1–3 years [4]. However, there is evidence that physical activity may enhance long-term weight loss, or minimize or prevent weight regain. For example, Jakicic et al. [15] reported that individuals who achieved a weight loss of 14.2 kg (16.8% of initial bodyweight) at 24 months had increased their physical activity to approximately 1,500 kcal/week above baseline levels, whereas individuals achieving less weight loss were engaging in physical activity that was on average <700 kcal/week above baseline levels. In another study that involved the combination of diet plus physical activity, Jakicic et al. [16] reported that overweight and obese women who engaged in physical activity of 291 min/week from 0 to 6 months, 282 min/week from 7 to 12 months, and 281 min/week from 13 to 18 months reduced weight by 13.1 kg by the end of the 18-month intervention. This weight loss at 18 months was significantly greater than the 8.2 and 3.5 kg observed in individuals averaging approximately 210 or 121 min/week of physical activity across the 18-month intervention, respectively. Unick et al. [17] have also reported that physical activity is an important predictor of the ability to lose ≥10% of initial bodyweight within 6 months and to sustain this weight loss at 24 months. These findings support the importance of physical activity for improving long-term weight loss. However, as indicated within the 2009 ACSM Position Stand [12], support for physical activity to improve long-term weight loss comes mainly from secondary post-hoc analyses or observation studies. This may suggest the need for additional randomized studies with sufficient sample sizes to better understand the role of physical activity for improving long-term weight loss and prevention of weight regain.

Physical activity has also been shown to be important for patients who have undergone bariatric surgery to induce weight loss. It has been shown that physical activity contributes to improvements in weight loss at 6–24 months following bariatric surgery [18–20]. Evans et al. [20] reported greater weight loss
in bariatric surgery patients who participated in ≥150 min per week of physical activity compared to those patients participating in <150 min per week. Thus, it is important for patients who undergo bariatric surgery to participate in sufficient amounts of physical activity to maximize the weight loss achieved with bariatric surgery. However, as summarized by O’Brien [21], research gaps remain in our understanding of the role of physical activity for patients who have undergone bariatric surgery, and this warrants additional research.

**Physical Activity: Responders versus Nonresponders**

As described above, on average, physical activity may have modest effects on weight loss yet be an important contributor to long-term weight loss outcomes. However, the large variability in weight loss reported in many studies does suggest that some individuals may lose significantly more weight than the average that is reported. For example, Jakicic et al. [8] reported that the average weight loss at 18 months in response to an intervention with physical activity prescribed at 150 or 300 min/week was −0.9 ± 4.7 and −1.2 ± 5.6%, respectively. However, as shown in figures 1 and 2, some individuals were extremely successful with weight loss while others were not. This is not atypical and is commonly observed in our laboratory. Moreover, this is similar to the pattern of individual weight loss observed in response to 16 months of supervised exercise reported by Donnelly and Smith [22]. Thus, it is important to consider potential mechanisms or pathways that may explain the individual variability in weight loss that is observed with physical activity.
It has been shown that there is a genetic influence on the effect of physical activity to regulate bodyweight [23, 24]. Research conducted by Bouchard et al. [24] in which diet and physical activity were highly controlled over a period of 4 months showed that weight loss ranged from 5 to 12% of initial bodyweight, which was equivalent to absolute weight loss of 3–12 kg. These findings provide evidence of variability in weight loss resulting from a standardized dose of structured physical activity between individuals with energy intake held constant.

Bouchard et al. [23] also conducted a study of 7 pairs of identical male twins examined over a period of 93 days. Subjects were supervised 24 h per day with energy intake held constant and structured activity performed on a cycle ergometer twice daily. Mean weight loss resulting from this protocol was 5.0 ± 0.6 kg. However, there was greater variance between pairs of twins than within pairs of twins, and the intraclass coefficient for within pair changes in bodyweight was $r = 0.74$. Similar findings were observed for measures of body composition and body fat distribution. These findings support that there are biological factors that contribute to the variability of individuals to lose weight in response to an increase in physical activity.

Factors Influencing Adherence to Physical Activity
A potential factor that can influence the effectiveness of physical activity to reduce bodyweight is adherence to prescribed doses of physical activity. Jakicic et al. [8] reported that individuals who lost ≥3% of initial bodyweight over a period of 18 months reported an increase of 228 min/week above baseline at 6

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Fig. 2. Individual variability in 18-month weight change in response to a prescribed dose of 300 min/week of physical activity. Unpublished data based on the study conducted by Jakicic et al. [8].
months and 161 min/week above baseline at 18 months. This level of physical activity was significantly higher than the physical activity of individuals who remained weight stable or gained weight over this same period of 18 months. Thus, it is important to better understand factors that contribute to adoption and adherence to sufficient levels of physical activity that may induce weight loss and assisting in bodyweight regulation.

There may be biological factors that contribute to one’s decision to participate in physical activity. Rankinen [25] has concluded that genetic factors do contribute to the propensity of being physically active or sedentary. In a study of children, Cai et al. [26] reported that the heritability estimate was 55% for total physical activity, with similar heritability estimates reported for sedentary, light, and moderate levels of physical activity. Stubbe et al. [27] have reported that the median heritability for physical activity participation in twin studies is 62%. Despite these findings, it is clear that not all the variability in physical activity is explained by these factors, which suggests that additional factors need to be considered.

Behavioral and psychosocial factors have also been shown to contribute to the adoption and maintenance of physical activity. Data from studies conducted in our research center have consistently shown that there are selected factors that appear to be associated with physical activity in overweight and obese adults participating in a behavioral weight loss program. One such factor is self-efficacy. We have reported that physical activity self-efficacy increases in response to a behavioral weight loss intervention, with higher levels of self-efficacy associated with higher levels of physical activity after a 6-month intervention [28]. However, recent analysis of unpublished data has shown that on average the increase in physical activity may not be sustained at 24 months, with self-efficacy returning to baseline levels despite ongoing intervention through 24 months. We also found that physical activity self-efficacy at 24 months continued to be significantly associated with 24-month level of physical activity (correlation coefficient = 0.33). This may suggest that interventions need to target self-efficacy to facilitate the adoption of physical activity in overweight and obese adults. However, the focus on self-efficacy needs to continue long-term to facilitate ongoing participation in physical activity that can impact body-weight regulation.

Identifying barriers to physical activity and developing interventions to reduce these barriers is important for improving physical activity in overweight and obese adults [29]. In response to a traditional 6-month behavior weight loss intervention, barriers to physical activity decreased, and physical activity at 6 months was associated with fewer barriers to physical activity [28]. Analysis of unpublished data across the 24-month intervention period showed that fewer barriers continued to be significantly associated with higher levels of physical activity (correlation coefficient = –0.30). Thus, an important intervention target appears to be identification of barriers to physical activity in overweight
and obese adults, and the development and implementation of interventions to overcome these reported barriers.

Influence of Physical Activity on Other Components of Energy Balance
The ability to reduce bodyweight is ultimately dependent on the balance between energy intake and energy expenditure. When energy intake, determined by the number of calories consumed, is equivalent to energy expenditure, determined by the number of calories burned, an individual is considered to be in energy balance and theoretically should be weight stable. For weight loss to occur, energy expenditure needs to exceed energy intake (negative energy balance), and an increase in physical activity has the potential to increase total energy expenditure to create a state of negative energy balance. Physical activity is the most variable component of total energy expenditure, which suggests that this should be a target for interventions focused on weight loss [30].

There is some evidence, however, that an increase in physical activity may influence other components of energy balance, which may either enhance or inhibit weight loss. For example, Unick et al. [31] compared ad libitum intake at 1–2 h following a seated rest period versus a period of moderate-intensity physical activity in overweight and obese women. Results showed that 58% of participants consumed more calories following the activity period compared to the seated rest period. These findings are similar to those reported by Finlayson et al. [32] in which approximately 50% of participants had a positive increase in energy balance following a 50-min bout of physical activity. These findings may suggest that there is variation in eating behavior in response to periods of acute physical activity, with activity potentially contributing to an increase in energy intake in some individuals while potentially having a satiating effect in others. This warrants further investigators to better understand the potential pathways by which this phenomena may occur, which may provide valuable information to better understand how physical activity may affect energy balance and ultimately bodyweight regulation.

Weight loss is commonly associated with an observed reduction in resting metabolic rate (RMR) [33], and RMR commonly comprises the largest portion of total daily energy expenditure. When comparing trained versus sedentary individuals, RMR is typically higher in those individuals who are trained [34], and it has been shown that there is an acute effect of physical activity on RMR. This may suggest that the addition of physical activity to a weight loss intervention may prevent or blunt the decrease in RMR. However, significant decreases in RMR are observed with weight loss even when physical activity is included within the intervention paradigm [33]. Thus, the potential pathway by which physical activity creates a state of negative energy balance to facilitate weight loss and weight loss maintenance may not be through its effects on RMR, but though alternative pathways and mechanisms that may require further investigation.
Health Benefits of Physical Activity beyond Weight Loss in Overweight and Obese Adults

In addition to the potential benefits of physical activity on weight loss, there are additional health benefits that may be realized in overweight and obese individuals through participation in physical activity. One of the key benefits of physical activity is an improvement in cardiorespiratory fitness. Recent reviews of the literature concluded that higher levels of physical activity or cardiorespiratory fitness are associated with improvements in health-related outcomes [35–37]. The association between higher levels of physical activity or cardiorespiratory fitness and reduced health risk is present in overweight and obese adults even in the absence of weight loss. Thus, overweight and obese adults can realize significant health benefits from participation in physical activity, and the added weight loss may further enhance these benefits, as illustrated in figure 3.

Conclusions

Physical activity can contribute to both short-term and long-term weight loss in overweight and obese adults. These benefits of physical activity are also present in individuals who have undergone bariatric surgery. In addition, physical activity and the concurrent improvement in fitness are associated with improvements in a variety of health-related outcomes. However, there is significant interindividual variability in the weight loss that is achieved with physical activity, with
both behavioral and biological factors contributing to these findings, which warrants further investigation. Regardless, physical activity should be included as a component of a comprehensive intervention for weight loss for overweight and obese adults.

Disclosure Statement

Dr. Jakicic reported serving on the scientific advisory board for Alere Wellbeing, has received an honorarium for a scientific presentation from Jenny Craig and from the Nestle Nutrition Institute, and has served as the Principal Investigator on research grants awarded to the University of Pittsburgh from the Beverage Institute for Health and Wellness and BodyMedia, Inc.

References


**Discussion**

*Dr. Bray:* You made a statement that dietary modification and exercise are effective for weight loss, and the combination of these behaviors is more effective than either one alone. If people persist in these behaviors, they will maintain their current weight or their weight loss. I am interested in your comments about whether our focus in interventions should be on adherence to these behaviors and understanding why adherence diminishes over time despite initial success at weight loss. This may require a better understanding of both metabolic and/or psychological factors that may be influencing adherence.

*Dr. Jakicic:* It is clear that the combination of an energy-restricted diet and physical activity is the most effective non-surgical and non-pharmacological intervention for inducing and maintaining weight loss. Thus, the focus of interventions should be on promoting adoption and maintenance of these key behaviors. Results of 18- to 24-month studies conducted in our laboratory have supported that both components of energy balance result in improved weight loss [1, 2]. Behavior change is complex, with many interactions that need to be considered to understand the most effective strategies for improving adoption and adherence to these key behaviors related to energy balance and weight control. For example, when considering behavioral constructs, data from our studies have consistently shown that self-efficacy is predictive of adoption and maintenance of exercise behavior in overweight and obese adults. What is interesting is that self-efficacy for physical activity and structured exercise prior to initiating an intervention are not predictive of behavior change. Rather, it is the change in self-efficacy once the intervention is undertaken that is predictive of future physical activity behavior. This suggests that we need to focus our interventions on exposing participants to physical activity experiences that allow them to realize that they can do a physical activity and that this activity can be beneficial to them. Too many times clinicians may simply prescribe activity to patients without addressing the issues that may influence self-efficacy, which ultimately does not result in meaningful or sustained behavior change. In addition, we need to consider the barriers that exist related to modifying eating and activity behaviors. For example, simply instructing a patient to exercise without also addressing barriers will be less effective than an intervention that is specifically designed to identify and address the barriers to exercise. Moreover, eating and exercise are not independent behaviors. For some individuals, exercise has been shown to stimulate a decrease in energy intake, and for others exercise has been shown to stimulate an increase in energy intake. Whether this is a result of cognitive control or other metabolic or physiological control mechanisms is not well understood. Regardless of the mechanism, the interaction of these behaviors may be important in understanding factors that influence adoption, maintenance, and effectiveness of these behaviors for weight control, and this needs further investigation.

*Dr. Bray:* Another observation from our studies is that adherence is associated with higher intensity exercise rather than with the moderate-intensity exercise in many of the public health recommendations. We may need to consider this as well when examining factors that influence adherence.

*Dr. Jakicic:* This may be related to how exercise intensity is defined. For example, typical public health recommendations for physical activity intensity are based on data
that have defined intensity as an absolute value based on energy expenditure. For example, moderate intensity activity is defined as 3 to under 6 metabolic equivalents, also termed METS, with vigorous intensity defined as ≥6 METS. However, it may be important to consider the relative intensity of the exercise, which is based on a percentage of the maximal fitness level of the individual, rather than on the absolute intensity, which is based on the energy expenditure of the activity.

It is also important to examine the literature in this area to better understand how intensity may influence weight loss outcomes and adherence. For example, when energy expenditure has been held constant, it appears that moderate and vigorous intensity exercise results in similar magnitudes of weight loss. Conversely, when considering adherence, King et al. [3] reported that vigorous rather than moderate exercise improved long-term exercise adherence. It is also important to understand if there is a minimum dose of exercise that results in optimal adoption and maintenance that also stimulates the desired physiologic and metabolic responses that will optimize bodyweight regulation. In some instances, it may be important to promote a higher intensity of exercise; however, more research is needed to confirm the optimal intensity and volume of physical activity that results in desired benefits in physiological, metabolic, psychological, and overall health for overweight and obese adults.

**Dr. Oppert:** I would like to discuss bariatric surgery because this might be very different when compared to non-surgical interventions for weight loss. When we conducted and published a recent review of physical activity in bariatric surgery patients, we observed that there were limited intervention studies of physical activity in this population. This makes it difficult to understand the influence of physical activity because there are changes that occur simply in response to surgically induced weight loss. In addition, few studies of surgically induced weight loss report on changes in body composition, especially as it relates to how physical activity may influence these changes.

**Dr. Jakicic:** Data on body composition in these types of studies are lacking. Moreover, and possibly more important, is the lack of understanding of how skeletal muscle metabolism and physiology, along with similar adaptations in fat depots, respond to surgically induced weight loss and whether physical activity influences these adaptations. Studies are underway in these areas of research. What we may find is that the influence of physical activity on total bodyweight may be modest in response to surgically induced weight loss, but there may be important influences on body composition, the physiologic and metabolic properties of the tissues that influence bodyweight, and the health-related outcomes.

In response to your point about cause and effect, that too is interesting, and I agree that we need systematic research in these areas. We have observed in our own data that in response to surgically induced weight loss, individuals with the largest weight loss show the greatest improvements in self-report and objectively measured physical function, which reflects one's ability to get out of chair, balance, walk, etc. However, when we look at our data from objectively measured free-living physical activity, individuals with the highest level of physical functioning do not necessarily engage in the greatest amount of physical activity. What I take from this is that we need to better understand how physical activity is influenced by surgically induced weight loss and how to best intervene in this population to increase participation in adequate doses of physical activity to result in maintenance of weight loss along with metabolic and
physiological adaptations that influence weight and health outcomes. To date, most of what we know about this has been from observational or cross-sectional studies, with few studies using well-designed paradigms to better understand these important research questions.

Dr. Ard: Observations from our studies have suggested that self-efficacy may decline over a period of an 18-month intervention despite exposure to well-designed and implemented behavioral interventions. This may be a result of initial perceptions related to ease of behavior change or the health benefits of change in these behaviors not matching what actually occurs once exposed to the intervention. Thus, the perception is reset based on these initial experiences which influence self-efficacy. For example, many individuals undertake exercise to reduce bodyweight, and after 2 months see very little change in bodyweight, which results in a change in their perspective of the importance of exercise which ultimately influences adherence to this behavior. Moreover, regarding weight maintenance, it appears that there is a need for individuals to continue to have to increase their dose of exercise over time to continue to maintain their weight loss, which may influence long-term adherence, and this may be a result of continued muscle efficiency resulting from exercise participation. It may be important to consider factors around the optimal timing and dosing of exercise in the course of weight reduction and in the course of weight maintenance, so that this continued increase in exercise dose may not be necessary to maintain weight loss.

Dr. Jakicic: Your observation that self-efficacy for physical activity is difficult to sustain long-term is consistent with data from our own studies. We have shown that in response to a behavioral weight loss intervention, self-efficacy for physical activity increases over the initial 6 months of the intervention, with a gradual decline thereafter. However, when we examine the data in greater detail, participants who maintain higher levels of physical activity at 12 months continue to also sustain higher levels of self-efficacy for physical activity. This suggests that maintaining self-efficacy needs to remain a focal point of behavioral interventions. However, it is important to better understand factors that contribute to the ability of some participants to maintain higher levels of self-efficacy versus others being unable to maintain self-efficacy for physical activity, which appears to be associated with the inability to sustain physical activity behavior. Whether this is a result of a physiological drive due to improved muscle efficiency needs further examination and understanding. This decline in self-efficacy over time may also be a result of the modest weight loss of 0.5–3.0 kg that occurs with regular exercise, which may be less weight loss than most individuals expect based on the effort required to engage in sufficient levels of physical activity. Thus, further work is needed to understand how to improve the effectiveness of our interventions for sustaining physical activity.

Dr. Haschke: With regard to the measurement of body composition, all of the devices rely on certain assumptions. One of those assumptions is that the percentage of water in fat-free mass is constant. However, during a dynamic process like weight loss, water content in fat-free mass is changing, and therefore our assumptions may not be correct, and this may influence the accuracy of the measurement. My question is whether other traditional measures such as subcutaneous fat measurement using skinfold measurement or just abdominal circumference would be sufficient from a clinical perspective because this may provide valuable information relative to health risk. It may not be body composition per se, but rather changes in fat deposition at specific anatomical sites that is important to measure and to understand.
Dr. Jakicic: I agree that many of the body composition methodologies, including DXA and hydrostatic weighing, rely on assumptions that may be influenced during the dynamic process of weight loss, or even weight gain. I also agree that site specific fat has been shown by many to be critical to understanding the health risks associated with excess body fatness. Thus, the use of techniques such as girth measures or skinfold measures may be sufficient and feasible in clinical settings. However, my experience in training many individuals over the years indicates that there is significant variability between individuals when performing these measures, and these can be very difficult to perform on the severely obese. Thus, for us to use these techniques broadly, we need to have standardized protocols and provide adequate training to allow for valid and reliable measures. Moreover, the concerns over body fatness go beyond just traditional measures of body composition, because in many cases you can simply look at an individual who is obese and realize that they have excess body fatness. Given this, one of the interesting perspectives is whether the concerns are related to the volume or quality of the tissue. For example, with regard to fat-free mass, should we be concerned about the quantity of muscle, the quality of the muscle tissue, or both of these factors? An obese individual who has a high amount of fat-free mass but of poor quality could actually lose muscle mass but also increase the quality of the mass that remains, and this would be beneficial from a health perspective. This was observed in some of the early studies of very low-calorie diets in which total lean mass decreased in the presence of exercise, but the cross-sectional area of the muscle based on muscle biopsy actually increased in response to exercise. So, quality of tissue may be more important than quantity of tissue in some circumstances. However, to understand these factors, we need to continue to use measurement techniques that are more sophisticated that a simple girth measurement or skinfold measurement.

Dr. Lovejoy: You highlighted that there may be sex differences in the response to exercise as it relates to changes in bodyweight. The evidence suggests that exercise may have a greater influence on weight in men compared to women. I am concerned about the implications of this, especially as it is related to commercial weight loss programs in which women are the primary consumers, and women from certain ethnic and racial groups may have the greatest need for weight-related interventions. I am curious about why women may be less successful than men to effectively use exercise as a strategy to control bodyweight, and whether this may be linked to dietary composition? Maybe there is a lower threshold of exercise that influences eating behavior or other factors? From a practical standpoint, this raises the question of whether exercise recommendations may need to vary for men and women to promote optimal weight loss and weight loss maintenance.

Dr. Jakicic: The points and perspectives that you raise are interesting. My experience in working with many individuals over the past 20 years is that men tend to gravitate to exercise and focus less on dietary change to control their bodyweight, whereas women try to find a balance between energy intake and physical activity. Not only are the responses to interventions potentially different, but preferred interventions may differ between men and women. My impression is that it will be difficult to secure research funding to conduct a study in which we focus on varying the interventions for weight loss based on gender. What is interesting is that as part of the Midwest Exercise Study, the weight loss change in response to 45 min per day of exercise performed 4–5 days per week resulted in different patterns of weight change for men and women [4]. This
amount of supervised exercise led to weight loss for men but prevention of weight gain for women. However, an interesting finding in this study was that for a fixed duration and intensity of exercise, the men expended approximately 600 calories per session and the women expended about 400 calories per session, and this probably contributed to the observed difference in weight change in response to the exercise. In studies in which the energy expenditure of the exercise was held constant for both men and women, similar reductions in bodyweight were observed. To achieve this similar energy expenditure, women would have to exercise longer or at a higher intensity compared to men, which may also have implications from an adherence perspective. Finding the balance between energy expenditure and energy intake that results in optimal adherence may be necessary from a clinical perspective to make these programs feasible and effective for both men and women.

Dr. Rosenbaum: The evidence presented illustrates the challenges for behavioral programs to elicit and sustain substantial weight loss. This may suggest that the emphasis should be on interventions to behaviors to improve health rather than behaviors to lose weight. If true that a high volume of exercise is required to lose and maintain significant weight loss, this may pose significant barriers for many individuals due to the time commitment that is required. So, perhaps we should de-emphasize the influence of behavior change on weight loss because for many this may be modest, and instead place a greater emphasis on good health that may include resting heart rate, blood pressure, lipids and lipid particle size, and other health outcomes. Maybe this will influence behavior change to a greater magnitude than placing the emphasis on bodyweight.

Dr. Jakicic: I agree that ultimately the focus should be on health-related outcomes. However, I do not believe that there is evidence from clinical trials showing that a focus on these health outcomes improves adherence compared to a focus on weight loss. Substantial work remains to be done to better understand how to best influence behavior change and whether the focus of interventions should be on weight or some other health outcome. We also have to consider the dose of key behaviors patients can adopt and maintain to influence desired health-related outcomes.

Dr. Goran: You alluded to the health effects of exercise that appear to be independent of the health effects of weight loss. Is there dose at which the health effects of exercise are observed?

Dr. Jakicic: There is an important influence of exercise on many health outcomes, and the health improvements appear to be present, independent of changes in bodyweight. In general, the typically recommended minimal dose of 150 min of moderate-intensity physical activity per week appears to be sufficient. However, public health recommendations for physical activity also state that additional health benefits may be achieved with more physical activity. Whether significant health benefits can be achieved with a lower dose or intensity of physical activity is less clear from the available evidence.

Dr. Bray: The majority of research supporting physical activity and the dose of physical activity appears to be based on research that examined cardiovascular forms of activity. Are similar data available for resistance training?

Dr. Jakicic: Within the past few years, the American College of Sports Medicine and American Heart Association have more clearly defined the resistance training that may be necessary to elicit a variety of health benefits. A major benefit of resistance training is
the improvement in muscle strength and function, which for an obese individual can be very important to facilitate movement and activities of daily living. Where data are lacking from clinical trials is in the long-term health benefits of resistance training, probably because of the difficulty in conducting these types of studies and the need to provide access to equipment and facilities.

*Dr. Bray:* Most of the recommendations for resistance exercise recommend doing it 2–3 days per week. I wonder if this is a sufficient dose of resistance exercise to influence bodyweight.

*Dr. Jakicic:* There is probably not sufficient evidence to make a recommendation for the optimal dose of resistance exercise for weight control. In particular, the evidence on the long-term influence of resistance exercise on bodyweight is sparse and needs to be an area of focus for future research.

**References**

Dietary Strategies for Weight Management

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Abstract
In an ‘obesogenic’ environment, getting people to eat appropriate amounts is challenging. Several food-based strategies have the potential to control hunger and promote satiety in order to moderate energy intake. Components of foods such as macronutrients and functional ingredients can affect satiety; however, for weight management a more comprehensive approach is needed that emphasizes behavioral strategies to improve the overall diet. Research shows that large portions of energy-dense foods facilitate overconsumption and that reductions in portion size and energy density are associated with reduced energy intake. While this suggests that people should eat smaller portions, recent data show that if people lower the energy density of their diet, they can continue to eat their usual amount of food while limiting calories. Furthermore, serving larger portions of low-energy-dense foods can be used strategically to encourage their consumption and reduce dietary energy density, and this has been shown to be associated with decreased energy intake while maintaining satiety. This new understanding of how portion size can be used positively to manage energy intake has the potential to help people achieve sustainable improvements in their energy intake and bodyweight. Science-based strategies that increase the availability of affordable nutrient-rich, lower energy-dense foods are urgently needed.

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In an ‘obesogenic’ environment characterized by large portions of palatable, inexpensive, energy-dense foods, finding ways to encourage people to eat appropriate amounts is challenging. This paper will consider food-based strategies that have the potential to control hunger and promote satiety in order to moderate energy intake. The available research encompasses: a biological approach aimed at developing foods that affect satiety mechanisms, a behavioral approach
focused on understanding eating behaviors that affect satiety, and an environmental approach that could help to make low-energy-dense foods a more likely choice. In this review, opportunities and challenges related to utilizing these approaches for the management of obesity will be considered.

**Biological Approach**

*Macronutrients and Satiety*

Short-term studies have demonstrated that a number of properties of foods can affect satiety and energy intake, including the proportions of macronutrients, various ingredients, and even the physical form. The standard experimental paradigm for assessing satiety is to ask study participants to consume a fixed amount of a food at the start of a meal. Following this preload, changes in ratings of hunger and satiety (fullness), and of biological variables such as glucose, insulin, and gut hormones can be tracked and related to later intake [1]. Such studies have led to the hypothesis that there is a hierarchy for satiety such that protein is the most satiating macronutrient, followed by carbohydrate, with fat the least satiating [2].

While this hierarchy has dominated satiety research, the results of numerous studies comparing the impact of macronutrients on satiety have been inconsistent. One reason for this variability is that each macronutrient category has different types with different physiologic effects. For example, carbohydrates include sugars, starch, and fiber, and it is not clear where they should be considered in the hypothesized hierarchy. Furthermore, macronutrient proportions affect other properties of food that could influence satiety, such as the palatability and energy density (calories per gram). While the hierarchy hypothesis has provided a useful framework for studies of satiety, its utility for weight management has not been established.

The emphasis on macronutrients has dominated the dietary management of obesity; however, the results of randomized controlled trials aimed at determining the effects of diets with different proportions of macronutrients have been mixed [3]. Even when a particular macronutrient was associated with the amount of weight lost during the active treatment phase, significant differences were not sustained during the maintenance phase. The authors of one large, 2-year trial that compared diets with four different macronutrient compositions concluded that: ‘Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize’ [4]. Furthermore, diet composition did not affect satiety, hunger, and satisfaction with the intervention. With similar results coming from several recent large trials, health policy recommendations for weight management have shifted away from macronutrient-based advice to a food-based approach emphasizing control of portion size and total calorie intake [5].
Another major thrust of satiety research is the characterization of functional ingredients that affect hunger and satiety mechanisms. While much of the focus in this area has been on various types of fiber [6] or protein [7], the scope for new products is broad and will continue to grow as the biological bases of hunger and satiety become better understood. However, the utility of such products for weight management remains to be established [8]. Demonstrating that an ingredient or a functional food affects hunger, satiety, or energy intake in the short-term does not indicate that these effects are robust or persistent enough to resist physiological regulatory systems for the maintenance of energy balance. Nor does it show that in the context of an obesogenic environment bodyweight will be affected [9].

A critical question that is raised by studies of food components that enhance satiety is whether any one of these can have an impact on its own. Is it realistic to expect the addition of a few grams of fiber or protein to not only control hunger but also to decrease daily energy intake and reduce bodyweight? Perhaps effects will only be seen if such food components are consumed in combination or as part of a more comprehensive approach to both dietary and behavioral strategies that facilitate weight management.

Behavioral Approach: Understanding Properties of Foods That Affect Eating Behavior

While the emphasis in studies of eating behavior has often been on the mechanisms controlling satiety and energy intake, recent data indicate that people readily ignore biological satiety signals when surrounded by large portions of palatable, energy-dense foods. Such overconsumption begins early in life [10] and often becomes a habitual pattern that continues to be reinforced over the lifespan. Dietary interventions that rely on people making changes in established eating patterns to achieve negative energy balance are often unsustainable in an obesogenic environment.

Changing eating behavior represents one of the greatest challenges in obesity prevention and treatment. Ultimately, parental and childhood interventions along with government and food industry initiatives are needed. These initiatives will benefit from sound research that identifies robust behavioral responses to food that could help to moderate intake. Such responses include the effects of portion size and energy density on energy intake.

Portion Size

The goal of much of the research on portion size has been to establish a relationship between large portions of energy-dense foods and overconsumption. It is clear that portion size has a powerful, sustained effect on the amount of food
consumed. This effect has been demonstrated for different types of foods and beverages in both laboratory and natural environments, and in overweight and normal-weight men and women [11]. Of particular importance is that bouts of overeating associated with large portions are not followed by a compensatory reduction in intake. For example, when the portion size of all foods served over 11 days was increased, there was a persistent and significant effect of portion size on energy intake [12]. Thus, characteristics of the eating environment such as the ready availability of large portions of energy-dense foods can override the regulation of energy balance over prolonged periods.

Since the effects of portion size are robust and sustained, it is possible that they could be used to increase intake of nutritious, low-energy-dense foods such as vegetables. Recent dietary advice relies on this premise. The 2010 Dietary Guidelines for Americans [5] urge people not only to eat less overall and to avoid oversized portions, but also to increase the proportion of vegetables and fruits served at a meal. There is some evidence that this could influence intake. In one study, increasing the proportion of a low-energy-dense vegetable served on a plate by substituting it for the meat and grain significantly increased vegetable intake and reduced energy intake at the meal (see fig. 1) [13]. Other studies show that in both children and adults increasing the portion of vegetables served at the start of a meal increases vegetable intake [14] and can decrease energy intake at a meal. Such findings support the suggestion that variations in portion size can be used beneficially to influence the types and amounts of

Fig. 1. Portion size can be used positively to increase vegetable intake and decrease energy intake at a meal. As the amount of vegetables served at a meal was increased and the amount of other meal components (meat and grain) was decreased, vegetable intake of 48 adults increased by half a serving (29%) and energy intake decreased by 40 calories (7%). Reprinted from Rolls et al. [13].
foods consumed at a meal, but there are no data on the effects of such strategic manipulations of portion size on sustained changes in intake or bodyweight.

Another portion control strategy that individuals can utilize is to structure their food environment so that exposure to large portions of energy-dense foods is limited during several eating occasions in a day. This can be achieved with pre-portioned foods (PPFs) such as entrées, snack foods, or liquid meals that are packaged individually in portions appropriate for a meal or snack. Existing evidence suggests that the consumption of liquid PPFs helps to limit energy intake and promotes weight loss [15]. There is also limited evidence on the efficacy of solid PPFs for weight management. Providing participants with most or all of their foods as pre-portioned items facilitated weight loss [16]. It is also likely that solid PPFs contributed to weight loss and weight loss maintenance over 2 years in a recent trial that compared a structured weight loss program including free prepared meals to usual care [17]. Although PPFs show promise as a useful tool for weight management, little is known about how characteristics such as their energy content and energy density affect efficacy [18]. Nor is it known if their use leads to better understanding of appropriate portions and whether their consumption will be continued so that they facilitate weight loss maintenance.

More research is needed to determine the impact of specific portion control strategies on body weight regulation. In particular, there is an urgent need for evidence-based strategies to help consumers limit the overconsumption associated with large portions of energy-dense foods. In the current environment, it is difficult for many individuals to eat appropriate amounts of food. Getting intake back in synchrony with energy needs will be challenging since consumers equate large portions with good value and they have a distorted idea of how much food is appropriate. If people were to heed the frequently offered advice simply to ‘eat less’, and were to reduce the portion size of all the foods consumed, they would probably feel deprived and would not sustain this eating pattern. A promising approach that would allow people to eat satisfying portions would be to reduce the energy density of the diet or at least of selected foods.

Energy Density
Dietary energy density has emerged in recent years as one of the most consistent influences on satiety and energy intake. While the energy density of food is often related to its fat content, the water content can have an even greater effect. The combination of water with the macronutrients in foods determines the energy density, and variations in water can be used to separate the effects of energy density from those of the macronutrients. A number of systematic studies show that when the macronutrient content of foods was varied, but the energy density was kept constant, the effects of fat, carbohydrate, and protein on satiety were similar [19]. On the other hand, the energy density of foods is a robust and significant determinant of satiety and energy intake regardless of macronutrient composition [19].
Most of the studies on the effects of energy density have been relatively short-term, examining individual meals or effects over several days. These studies show that consuming a large low-energy-dense preload of a water-rich food such as soup, salad, or fruit, was associated with reduced energy intake at a meal [2, 19]. In other studies, the energy density of meals was reduced by increasing the proportion of vegetables, and it was found that adults who were offered ad libitum access ate a consistent weight of food. This meant that energy intake varied directly with changes in energy density. Subjects reported similar ratings of hunger and fullness even when reductions in energy density led to a decrease in energy intake of approximately 25% over 2 days [19, 20]. The response to energy density emerges early in life as indicated by studies in preschool children showing they too consumed significantly less energy when the energy density of the available foods was lowered [21]. This suggests the possibility of using reductions in energy density strategically to prevent excess energy intake in young children as well as in adults [10].

While much of the evidence related to energy density comes from short-term studies, reductions in energy density show promise as an effective approach for weight management. In a year-long trial, daily incorporation of a low-energy-dense food into a reduced-energy diet increased the magnitude of the weight loss compared to the incorporation of snack foods higher in energy density [22]. In another year-long trial, obese women who were counseled to reduce dietary energy density by increasing intake of fruits and vegetables along with reducing intake of fat had greater weight loss than those who were advised just to reduce fat intake [23]. Over the course of the year, participants randomly assigned to the lower energy-dense diet (higher in fruits and vegetables) reported consuming an average of 25% more food and reported less hunger than those in the fat reduction group. In the multi-center PREMIER trial that included three different lifestyle interventions, dietary changes that reduced energy density were related to greater weight loss after 6 months [24]. Furthermore, participants with both large and modest decreases in energy density increased the amount of food they consumed. Eating a greater amount of food while decreasing energy intake could contribute to the long-term acceptability of a low-energy-dense eating pattern since it could help to control hunger.

The association between energy density and bodyweight is supported by both longitudinal and epidemiological studies that have tracked dietary patterns. In a 6-year longitudinal study, it was observed that young women who reported a diet higher in energy density gained two and a half times as much weight as those reporting a diet lower in energy density [25]. Longitudinal studies in children have also found an association between dietary energy density and changes in body fatness [10]. Population-based studies in adults provide additional support for associations between energy density and energy intake, the amount of food consumed, diet quality, and weight status. Surveys of self-reported intakes by free-living adults have shown that normal-weight individuals consume diets
with a lower energy density than obese individuals [26]. Furthermore, increases in dietary energy density were associated with greater weight gain in a prospective study of 50,000 middle-aged women over 8 years [27].

While data suggest that reducing dietary energy density can facilitate weight management, more long-term studies are needed to understand how to implement this approach and facilitate the maintenance of low-energy-dense eating habits. If people were to adopt lower energy-dense eating patterns, they would be able to eat satisfying amounts of foods appropriate to meet both energy and nutrient needs. However, long-term compliance with any diet that requires deliberate and sustained changes in established eating habits is difficult. A key question is whether the food environment can be modified to help people lower the energy density of their diets and to eat appropriate amounts in order to prevent the development of obesity and facilitate weight management.

**Environmental Approach**

The types of foods that are readily available, affordable, and fit with consumers’ preferences and lifestyle can influence energy intake. This suggests the possibility that the eating environment could be strategically designed to encourage consumers to choose more foods that are appropriate in portion size and lower in energy density. A range of strategies has been proposed including education and nutritional information such as menu labeling, increased promotion and availability of low-energy-dense foods such as vegetables and fruits, more opportunities to choose smaller portions of energy-dense foods, and pricing or tax incentives to encourage selection of appropriate portions of nutrient-dense, low-energy-dense foods [28, 29].

At present, there are few data to support the effectiveness of such environmental approaches for weight management, and they have economic ramifications for the food and restaurant industries that could present barriers to implementation. Some of these barriers are evident in surveys asking food providers such as chefs about the items they serve. In one survey, chefs reported the portions served were primarily influenced by the presentation of foods, food cost, and customer expectations [30]. Although most chefs thought that the amount of food they serve influences how much patrons consume, their opinions were mixed about whether it is their responsibility or the customer’s to eat an appropriate amount when served a large portion. In another survey, nearly all chefs thought that calories in menu items could be reduced by 10–25% without customers noticing, but they noted low consumer demand as the primary barrier to making such changes [31]. Clearly, innovative marketing strategies that increase the appeal of healthier options are needed – for both consumers and food providers.

The opinions of chefs agree with lab-based studies showing that both the energy content and portion size of foods can be decreased significantly without
people noticing and that these changes will help to moderate energy intake [20]. Energy density can be reduced in a variety of ways such as the addition of vegetables or fruits to recipes or by lowering the fat or sugar content. Herbs and spices can be used to enhance flavors and mask changes in foods. A particularly effective strategy to reduce energy density covertly is to add puréed vegetables. When the energy density of the main dishes served over a day was reduced by the addition of puréed vegetables, both adults and preschool children consumed significantly fewer calories. Large amounts of vegetables were added without affecting the palatability of the foods, even in people who showed a low preference for vegetables (see fig. 2) [32, 33]. Such innovative strategies to lower dietary energy density need to be applied to the development of a range of foods that are palatable, affordable, and readily available.

Changing the food environment in order to have sustained effects on energy intake will be challenging. However, the effects of portion size and energy density on energy intake are robust and should be utilized to develop dietary strategies for weight management and to promote a healthier eating environment.

Acknowledgements

This work was supported by NIH grants DK082580 and DK059853.

Fig. 2. Reducing the energy density of entrées served at main meals decreased daily energy intake. When puréed vegetables were incorporated to reduce the energy density of the standard entrées (100%) to 85 and 75%, daily energy intake of 41 adults decreased by 202 (6%) and 357 kcal (11%), respectively. Daily vegetable intake increased by 129 g (50%) in the 85% condition and by 217 g (80%) in the 75% condition. Reprinted from Blatt et al. [32].
Disclosure Statement

Dr. Rolls has a licensing agreement with Jenny Craig, Inc. for the use of the Volumetrics trademark.

References

Dr. Ard: Dr. Rolls, you know I am on your side on this. Do you think we shot ourselves in the foot with the diet crazes of the 1980s by going so low fat and being so restrictive that it's going to be really hard to reverse that messaging to get people to understand that they actually need to eat more in order to be successful with managing their weight?

Dr. Rolls: Unless we can figure out ways to make the low energy density, reasonable portion approach more accessible and affordable to become almost the default, I think we are going to have a very hard time changing the way people are eating now. For a while, we have had few popular fad diets, but now a couple of best-selling diet books are back to suggesting that changing the proportions of macronutrients or cutting out whole food groups will make weight loss easy. We need to figure out how to make healthy weight management easier and appealing.

Dr. Finegood: Why is it that food companies such as those that sell cereal advertise the heavily sugar-sweetened, less nutritious cereals but don't advertise healthier ones? There are data to suggest that in a blinded test kids don't necessarily prefer cereal higher in sugar. Is it that the profit margins are much higher or is it because they don't think the lower sugar product will sell well?

Dr. Rolls: I cannot speak for the industry, but one possibility is that they think that they are more likely to get kids to eat cereal in the first place and that kids who eat any...
kind of cereal, even if it's sugar sweetened, have a better diet quality than those eating no breakfast or some other less nutritious option.

**Dr. Finegood:** But we can't disentangle that from the advertising efforts.

**Dr. Rolls:** We know that we have to be marketing the healthy foods more effectively. That is why the recent TV ads suggesting that parents have to be secretive about vegetables in foods are so interesting – kids see the message that vegetables are so bad they shouldn't be told about them. Product developers know how to put more vegetables in foods without affecting taste, but marketers have not figured out how to get consumers to buy them. By the way, we have found that 'stealth' vegetables in foods are an effective way to reduce energy density and to get kids to eat their vegetables. We recently published a study showing that we could add large amounts of vegetables to a variety of foods without affecting the palatability. Our problem with the stealth vegetables was with the baked goods – the children liked them better with more vegetables, probably because they were moister. By adding pureed vegetables to main dishes across a day, we got the preschoolers meeting their daily vegetable requirements [1]. If people like vegetables anyway, you don't have to go stealth, but why not try some more innovative ways to get vegetables into the day?

**Dr. Barclay:** The food industry is looking for ways to become increasingly part of the solution rather than only being considered part of the problem; however, we seem to be getting some mixed messages from the science. There is a recent paper from Duffey and Popkin [2] looking at the relative importance of portion size, eating frequency, and energy density. They found that energy density explained less of the increase in energy intake over recent decades in US adults compared to portion size and eating frequency.

**Dr. Rolls:** In that analysis of reported intakes in a population-based data set, a novel algorithm was used to compare the relative importance of those factors. We plan to revisit this issue using more conventional methods of analysis. In our controlled studies, energy density has more robust effects than portion size, but portion size also has significant effects on energy intake. It is clear that the pattern of eating and properties of foods such as energy density and portion size can affect intake, and the food industry should be applying this knowledge to product development.

**Dr. Goran:** I completely buy the energy density argument, but I was wondering if there is more research on the factors that drive choice at the moment of consumption. What are the contextual factors or the intrinsic biological factors that we know about or need to know about that drive individual choice at the moment of consumption?

**Dr. Rolls:** There is a large body of information on the determination of an individual's food choices that we don't have the time to cover. This brings us back to the issue of behavioral phenotypes and personalized approaches. Choice would be something that I would want to put into any weight management plan so up front we can figure out what kinds of foods people are going to be able to eat in a sustainable fashion. I dream of a computer program where people's food preferences are screened before they go into a program. You would then use that information to direct them towards a plan that will accommodate those choices. In the end, maintenance is the issue and that depends on liking the food.

**Dr. Drewnowski:** Designing food patterns based on linear programming in people's existing choices based on 7 days of records is being done by my colleagues in Marseille, France. So, this is something that's absolutely on its way.

**Dr. Rosenbaum:** I was wondering if people can learn to respond visually to portion size. If all foods were packaged so that people could see how much food they would get
for a particular amount or calories – like the 100-calorie packs, but for all foods – would they choose the bigger portions of less calorically dense foods and eat less?

Dr. Rolls: I wish we could find a real world setting to do that, but that's part of what we try to educate people to do. If you go lower calorie density you are going to get more food for your calories. But if you ask most people how many calories they should eat in any one occasion they have no idea. You also have the economics of food choice – some people want the most calories for their money.

Dr. Rosenbaum: But forget about the economics for a second. If you just walk into a store and you pay by the calorie and you have to buy 500 calories for a meal, if you can see that you would get a lot more food if you choose apples rather than a calorie-dense sandwich, would you buy differently?

Dr. Rolls: There is a chain in Britain that has a 'bundled meal' where you pay a flat rate for 500 calories for lunch. They have all kinds of different packages where you can mix and match your sandwich, drink, and snack. This could provide a wonderful opportunity to do research because people could buy items that were different in value as well as energy density and portion size for their 500 calories. Wouldn't it be interesting to look at what they choose?

Dr. St. Jeor: I am curious about what your recommendations are regarding high-protein drinks, some of them with as much as 60 g of protein that promotes their satiety-enhancing properties.

Dr. Rolls: We will always have a lot of choices, but this goes back to where I began. We don't want people basing their choices on the hope that they will get a boost of satiety that will help them to eat less with little effort. We want people to be eating a diet with a balance of nutrients. We need to think more about how to show people that they can use regular food to enhance satiety and eat less.

Dr. Drewnowski: One trend in children's nutrition is to try and replace juices with intact whole fruits. Would that make a difference in satiety or energy density?

Dr. Rolls: We have done studies and so have others showing that whole fruit is more satiating than juice even if you add the fiber back into the juice. There is a lot of interesting work on texture and thickness of beverages and how these properties affect satiety. This takes us back to the functional ingredients approach to satiety, which we should continue to pursue, but in the context of a healthier diet overall.

References


Targeting Adipose Tissue Inflammation to Treat the Underlying Basis of the Metabolic Complications of Obesity

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Abstract

The prevalence of obesity has increased throughout the last three decades due to genetic, metabolic, behavioral, and environmental factors [1]. Obesity in turn increases risk for a number of metabolic diseases including type 2 diabetes, cardiovascular disease, fatty liver disease and some forms of cancer [1]. Despite the well-known link between obesity and increased morbidity, the mechanism of this remains elusive. Thus, the question ‘why does increased body fat cause increased metabolic comorbidities’ remains unanswered. By understanding the underlying basis of obesity-associated metabolic diseases, different therapies could be designed to target relevant pathways. Although we lack a full understanding of the underlying mechanisms that result in disease, several putative explanations exist for why fat affects metabolic health. One such theory is based on the anatomic location of fat deposition and ectopic fat accumulation [2]. Specifically, current literature suggests that visceral, liver and skeletal fat accumulation affects organ function and contributes to the development of insulin resistance, fatty liver, and the metabolic syndrome [3]. However, even in individuals matched for body fat and fat distribution, significant differences can exist in metabolic outcomes, and the phenomenon of metabolically healthy obese has been well described [4]. More recent data suggest the alternative hypothesis relating excess adipose tissue to disease risk based on the metabolic function and morphological properties of adipose tissue. In this scenario, excess adipose tissue is hypothesized to contribute to a state of chronic inflammation which promotes development of insulin resistance as well as other metabolic complications by stimulating nuclear factor-κB and Jun N-terminal kinase pathways in adipocytes and the liver [5]. In this paper, we will review the hypothesis linking excess adipose tissue to increased disease risk through adipose tissue inflammation.

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Adipose Tissue as an Endocrine Organ

It was once believed that adipocytes were only involved in the storage of triglycerides, but recent studies have demonstrated that they also act as endocrine organs. Hotamisligil et al. [6] and Karasik's group first showed that proinflammatory cytokine tumor necrosis factor (TNF)-α was produced by adipocytes, induced insulin resistance, and increased with expanding fat volume. The concept of adipose tissue as a site for the production of cytokines and other substances has expanded to include leptin, interleukin (IL)-6, resistin, monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, visfatin, retinol-binding protein-4, and serum amyloid A. Adiponectin is also produced by adipocytes, but its release decreases with increasing adiposity. Leptin and adiponectin are adipokines that are produced only by adipocytes; while TNF-α, IL-6, MCP-1, visfatin, and PAI-1 are also expressed at high levels in activated macrophages. TNF-α, IL-6, resistin, and other proinflammatory cytokines participate in the induction and maintenance of the acute inflammatory response associated with obesity. Additionally, MCP-1 and other chemokines recruit macrophages to adipose tissue. These cytokines and chemokines activate intracellular pathways that promote the development of insulin resistance, type 2 diabetes and other metabolic complications associated with obesity [5]. Therefore, adipose tissue and macrophages within adipose tissue have been shown to play important roles in the regulation of metabolic pathways through the excretion of adipokines and cytokines.

Metabolically Benign Adipose Tissue

Despite the observed link between body fat, non-alcoholic fatty liver disease, and type 2 diabetes, some individuals exhibit ‘metabolically benign obesity’ and are protected from the metabolic consequences of excess adiposity, possibly due to differences in adipocyte tissue metabolism and macrophage infiltration. In a study aimed at identifying insulin-resistant individuals, 17% of the overweight and obese participants were found to be insulin sensitive [7]. Additionally, a review by Karelis et al. [4] determined that approximately 20% of the general population can be categorized as obese but metabolically healthy. In contrast to this, 18% of the population were found to have a normal bodyweight but suffered from severe metabolic abnormalities. In other studies among obese adults, the degree of adipose tissue inflammation was closely associated with increased metabolic risk for type 2 diabetes, cardiovascular disease and fatty liver disease, whereas obese adults without adipose tissue inflammation have metabolic risk factors in the healthy range [8, 9]. Despite the fact that most human research has focused on the links between fat distribution and metabolic risk, these findings suggest a role for adipose tissue inflammation. In a previous study among
obese young minority adults, we found that approximately 40% of subjects had subcutaneous abdominal adipose tissue with crown-like structures, indicating inflammation, whereas approximately 60% of subjects had no signs of adipose tissue inflammation. Despite the two groups being identical for overall obesity and subcutaneous abdominal adipose tissue volume, those with inflamed adipose tissue had approximately 30% greater visceral adipose tissue and 41% greater liver fat; 53% greater fasting insulin and 23% lower β-cell function, and 22% higher TNF-α. Additionally, adipose tissue from those with inflamed adipose tissue had upregulated nuclear factor-κB (NF-κB) expression activity and downregulation of insulin signaling [9]. Another recent study by Bremer et al. [8] demonstrated that, among overweight and obese adults, those with metabolic syndrome have significantly higher levels of infiltrating macrophages/crown-like structures in their adipose tissue compared to those without the metabolic syndrome. Given these observations, the disparities in metabolic diseases among obese individuals may be explained by the degree of chronic low-grade inflammation of adipose tissue. Therefore, targeting adipose tissue inflammation has become an important new strategy in treating the metabolic conditions typically associated with obesity.

**Weight Loss and Inflammation**

One of the few effective anti-inflammatory treatments for these metabolic diseases is weight loss [10]. Studies in diet-induced obese mice have shown that reductions in adiposity result in decreases in macrophage infiltration of adipose tissue as well as gene expression of pro-inflammatory markers [11, 12]. Specifically, Kosteli et al. [11] found that the murine immune response to weight loss was dynamic. Caloric restriction of high-fat diet-fed mice resulted in an initial increase in adipose tissue macrophages; however, the number of adipose tissue macrophages decreased following an extended period of weight loss. Vieira et al. [12] examined the effects of diet and exercise on inflammation among high-fat diet-induced obese mice. This study examined the effects of weight loss via a low-fat diet, exercise training, or a combination of low-fat diet and exercise on inflammation. All methods of weight loss resulted in a significant attenuation of high-fat diet-induced increases in systemic and adipose tissue inflammation. Additionally, all three interventions improved insulin sensitivity, reduced adiposity, MCP-1, and TNF-α gene expression. Among obese humans, caloric restriction to achieve weight loss also decreases markers of inflammation. For example, a 28-day severe calorie-restrictive diet (800 kcal/day) among obese females was found to reduce bodyweight by an average of 13 pounds as well as significantly alter markers of inflammation. Specifically, weight loss resulted in a decreased expression of proinflammatory markers (e.g. IL-12a, matrix metalloproteinase-9) in white adipose tissue and increased the
expression of anti-inflammatory molecules (e.g. IL-10 and IL-1 receptor antagonist) [13]. Studies using surgical methods to achieve weight loss also improve inflammation among obese patients. A study by Aron-Wisnewsky et al. [10] demonstrated that weight loss following gastric bypass surgery resulted in a mean weight loss of 44 pounds at 3 months. Among the 16 obese females in this study, the activation state of adipose tissue macrophages switched from mostly proinflammatory to anti-inflammatory after weight loss. However, since weight loss is difficult to achieve and maintain, alternative strategies aimed at adipocyte inflammation present a unique target in which to modify metabolic health.

**Diet and Inflammation**

Diets high in sugar and fat have been shown to increase systemic markers of inflammation [14, 15]. Given the link between diet and inflammation, it is not surprising that dietary alterations have been used to examine obesity and obesity-associated inflammation among obese humans [12]. Specifically, healthy adult males given fructose (40 or 80 g/day) or glucose (40 or 80 g/day) sugar-sweetened beverages for 2 weeks demonstrated significant increases in high-sensitivity CRP [14]. In addition to sugar intake, trans fat consumption is related to markers of inflammation. A cross-sectional analysis of 730 women from the Nurse's Health Study found that CRP levels were 73% higher and IL-6 levels were 17% higher among those in the highest quintile of trans fat intake compared to those in the lowest [15]. Among humans, a diet high in fiber (30 g/day), either through diet or fiber supplementation, has been shown to significantly reduce CRP levels [16]. Baseline examination of data from 406 participants from the Finnish Diabetes Prevention Study found that increases in fiber predicted decreases in CRP and IL-6. They also found that changes in fat and carbohydrate intake were either weakly or not related to reductions in CRP and IL-6 [17].

Studies using obese mice have found differing effects of diet composition on inflammation. For example, Wang et al. [18] used mice with high-fat diet-induced obesity to examine the effects of weight loss achieved by switching from high-fat diet to: (1) an ad libitum low-fat normal diet or (2) restricting the high-fat diet intake to match bodyweight of mice with low-fat normal-diet-induced weight loss. Weight loss by either of the two methods resulted in decreased fat mass and liver steatosis; however, effects were greatest among the low-fat normal-diet-induced weight loss than the high-fat diet restriction-induced weight loss. Interestingly, weight loss with the low-fat normal diet, but not the restricted high-fat diet, normalized blood CDC11c+ monocytes and attenuated hepatic inflammation. In contrast, the calorie-restricted high-fat diet significantly reduced chemokine levels and CDC11c+ cells in adipose tissue when compared to low-fat diet-induced weight loss and obese controls. Although
these studies demonstrate that changes in diet can affect systemic inflammation associated with obesity, the direct mechanism and critical dietary components are not known. Additionally, the dietary changes necessary to elicit weight loss and decreases in inflammation are likely to be too drastic to sustain over time.

**Anti-Inflammatory Treatments**

In addition to dietary interventions, studies have examined the effects of anti-inflammatory treatments on systemic markers of inflammation. For example, human studies examining omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation have shown mixed results in its ability to target systemic inflammation [19], while high-dose aspirin treatments have decreased plasma markers of inflammation [20]. Among adult men and women, a placebo-controlled, double-blind study used 3.5 g/day of fish oil (1.5 g/day n-3 PUFA) for 12 weeks to examine change in plasma markers of inflammation. Compared to placebo, the treatment group did not differ in the median CRP change over the course of the study. In fact, results suggested an increase, not a decrease, in CRP with n-3 PUFA supplementation compared to placebo [19]. Given the disparate findings among animal models and humans, it is not surprising that the potential therapeutic role of n-3 PUFA supplementation to target inflammation has been, for the most part, abandoned. Despite these lackluster findings, researchers have begun examining other potential anti-inflammatory treatments that directly target adipose tissue inflammation.

Studies using mice models have successfully used anti-inflammatory treatments, such as n-3 PUFA and resolvin D1 to target adipose tissue inflammation [21, 22]. Todoric et al. [22] treated diabetic mice with a low-fat or a high-fat diet [rich in either saturated/monounsaturated fatty acids (HF/S) or n-3 PUFA] and found that adipose tissue macrophage infiltration was increased and genes involved in inflammation were upregulated in mice fed HF/S compared with the low fat diet. The high-fat diet containing n-3 PUFA completely prevented macrophage infiltration induced by the high-fat diet as well as changes in inflammatory gene expression. Most notably, a recent study has demonstrated the therapeutic potential of resolvins. Resolvins are a newly discovered family of lipid mediators that are generated from n-3 PUFA eicosapentaenoic acid and docosahexaenoic acid. Resolvins have an anti-inflammatory effect by blocking leukocyte infiltration into tissues and decreasing the expression of proinflammatory cytokines. A recent study found that resolvin D1 significantly decreased adipose tissue macrophage accumulation and improved insulin sensitivity in male leptin-deficient mice [21]. Despite these promising results, to our knowledge, this is the only study examining the effects of resolvin D1 on adipose tissue inflammation. Further studies aimed at using resolvin D1 in humans are needed to fully understand the therapeutic potential of this agent.
Among animal models and humans, aspirin has shown promise for decreasing inflammation and improving type 2 diabetes. Aspirin is a non-steroidal anti-inflammatory drug that inhibits COX enzymes through the modification of the enzyme’s active sites and inhibits prostaglandin synthesis in a similar manner [23]. Specifically, high-dose aspirin studies in Caucasian adults have shown that aspirin inhibits JNK, IκB kinase, and the key enzyme of inflammatory transcription, NF-κB. Additionally, high-doses of aspirin (7 g/day) have been shown to improve peripheral insulin sensitivity and CRP [20]. In obese humans and mice, low-dose aspirin therapy was shown to inhibit systemic IL-6 and reduce IL-6 release from subcutaneous white adipose tissue [24]. In addition to aspirin, statin therapy attenuated increased mRNA expression of pro-inflammatory genes, MCP-1 and IL-6, in adipose tissue of obese mice [25]. Of these treatments, aspirin shows the most promise with regard to reducing adipose tissue inflammation associated with obesity; however, the therapeutic potential of high-dose aspirin is limited by bleeding risk.

Several recent studies, mostly in Caucasian adults, used the anti-inflammatory drug salsalate to address its efficacy and tolerability as a new treatment for insulin resistance and glucose control. Salsalate, unlike aspirin, lacks an acetyl group and does not effectively inhibit COX enzymes [23]; however, salsalate has been shown to inhibit NF-κB [26]. Four trials have examined the effects of salsalate treatment among obese adults. Studies by Fleischman et al. [27], Koska et al. [28], and Goldfine et al. [29–30], have demonstrated the viability of salsalate treatment as a means to decrease markers of inflammation and improve glucose control. Specifically, Fleischman et al. [27] used a double-masked, placebo-controlled trial of salsalate (4 g/day) for 4 weeks to examine inflammation and metabolic indices among 20 obese adults who were at risk for type 2 diabetes. After treatment, they found that salsalate reduced fasting glucose by 13%, glycemic response after oral glucose challenge by 20%, glycated albumin by 17%, and CRP by 34% [27]. Koska et al. [28] examined 54 obese adults using a randomized, double-blind, placebo controlled trial of 3 g/day of salsalate for 7 days. This shorter study found a reduction in fasting plasma glucose concentration and glucose area under the curve during an oral glucose tolerance test. Lastly, Goldfine et al. [29–30] completed two fundamental studies demonstrating the effects of a moderate and high-dose salsalate on insulin sensitivity as well as the effects of a longer-term clinical trial of salsalate [29, 30]. The first trial consisted of three arms: 4.5 g/day for 2 weeks, 3 g/day for 2 weeks, and 4.5 g/day for 4 weeks. The 4.5 and 3 g/day treatment lasting 2 weeks reduced fasting and post-challenge glucose, while the 4.5 g/day for 4 weeks improved fasting and post-challenge glucose levels and decreased NF-κB activity in peripheral blood mononuclear cells by approximately 65%. The second study by Goldfine et al. [30] included 108 obese adults in a randomized, double-masked placebo controlled trial using 3, 3.5, and 4 g/day of salsalate treatment for 14 weeks [29]. Hemoglobin A1c levels decreased and glycemic
control improved in all treatment groups. It is interesting to note that mild hypoglycemic events occurred in 22% of the 3 g/day, 30% of the 3.5 g/day, and 22% in the 4 g/day groups [29].

Overall, these trials noted improvements in insulin sensitivity, fasting glucose, CRP, and NF-κB activity with a 2- and 4-week high-dose salsalate treatment of 4.0 and 4.5 g/day [27, 28, 30]. These data support the hypothesis that utilizing a non-steroidal anti-inflammatory drug, such as salsalate, to target adipose tissue inflammation may provide a therapeutic route for treating obesity-related diseases. Coupled with the above-mentioned findings, and due to the fact that non-acetylated salicylates do not prolong bleeding times, salsalate may offer a relatively safe and effective treatment for the low-grade inflammation associated with obesity. However, it is important to note the limitations of salsalate treatment. Specifically, the moderately high dose needed to elicit improvements in inflammation has potential side effects that warrant concern. Participants in these trials experienced ringing in the ears, alterations in liver function tests, as well as hypoglycemia. These adverse effects highlight the need to understand the mechanism in which salsalate targets inflammation and improves metabolic indices.

Previous studies in obese individuals show that salsalate decreases plasma markers of inflammation and improves glucose control under conditions of weight stability. However, the mechanism of these effects is not known, and no prior clinical study has examined whether the improvement of metabolic complications is due to reduction in adipose tissue inflammation. Currently, our group is initiating a double-blind, randomized control trial, among obese Hispanic young adults, aimed at determining the effects of 4 weeks of salsalate treatment (4 g/day) on the number of macrophages in adipose tissue. This study will be the first to examine the effects of salsalate therapy, without weight loss, on subcutaneous adipose tissue inflammation. In particular, we will examine the notion that the improvement of metabolic risk after salsalate intervention occurs due to its effect on suppressing adipose tissue inflammation, and that without an improvement in adipose tissue inflammation there will be limited improvement in other metabolic risk factors. Findings from this study have the potential to elucidate the mechanism in which salsalate improves glucose control and decreases inflammation. Once the mechanism(s) is identified, safer and more effective therapies could be designed to target inflammation, and thereby treat the metabolic complications, associated with obesity.

Conclusions

Given the known link between chronic low-grade inflammation and metabolic health, it is becoming increasingly important to understand the biological processes that contribute to inflammation in adipose tissue. We have reviewed the
evidence linking dietary composition, physical activity, bodyweight, and possibly race/ethnicity to the inflammatory profile that is observed in most overweight and obese individuals. The effects of dietary interventions, dietary supplements, and weight loss have demonstrated mixed results in their ability to effectively treat the inflammation associated with obesity. Nonsteroidal anti-inflammatory drugs have been found to successfully target markers of inflammation and improve glucose control among obese participants. Studies in animal models, as well as humans, have highlighted the potential contribution of adipose tissue inflammation to metabolic disease risk. These studies underscore the need to examine treatments that have shown success in alleviating the metabolic complications associated with obesity, such as nonsteroidal anti-inflammatory drugs, in order to determine their effects on adipose tissue inflammation. Studies such as these would shed light on the mechanism in which these therapies improve systemic inflammation and metabolic health. By understanding the development of obesity-induced inflammation, as well as potential therapeutic targets, drugs can be engineered to alter the inflammatory process that occurs during obesity. These kinds of treatments may offer important clinical methods that can be used to prevent/treat insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease, and other metabolic conditions associated with obesity and inflammation.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the chapter.

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**Discussion**

*Dr. Lovejoy:* I question the accuracy of the term ‘healthy obesity’. If we take a diabetes-centric view, it might be possible, as you have shown here, to talk about individuals who are metabolically healthy versus those who aren’t. But when we look broadly, a big part of the public health burden of obesity are things like osteoarthritis and sleep apnea which require weight loss to reverse. So, there are other consequences of obesity in addition to metabolic ones. Furthermore, recent studies suggest that even ‘metabolically healthy obesity’ may be a temporary condition, as these obese individuals develop metabolic abnormalities over time at a higher rate than non-obese [1, 2]. The risk of using the term is the backlash we saw a few years ago when there was a lot of media attention around the notion of ‘healthy obesity’ that led many people to erroneously conclude that obesity is not a problem.

*Dr. Goran:* Good points, thank you for highlighting that. Most of what I have talked about relates to the metabolic dysfunction of obesity. The more correct term to use would be ‘metabolically healthy obesity’. The other aspects that you mention probably fall outside of the metabolic consequences of obesity.

*Dr. Oppert:* I have two quick questions. First, could it be that inflammation at the beginning is something beneficial or a normal reaction to enlarge the adipocytes? Second, could it be that there is a point of no return? For example, when there is inflammation and then fibrosis in the liver? Perhaps strategies to reduce inflammation would not be so beneficial at the beginning, and perhaps could be difficult to put in place when it’s fibrosis.

*Dr. Goran:* I think that’s a potentially very interesting point, and we don’t know a lot about the time course of when the process is established relative to the accumulation of body fat. It’s unclear whether this is an intrinsic property of adipose tissue or that it’s a normal reaction to adipocytes growth. I think those are questions that remain.

*Dr. Rosenbaum:* At the beginning, you are showing that adipocytes attract macrophages or macrophages come to adipocytes. I was wondering if you go back and look at the healthy versus the unhealthy obese, do you think the major difference is in whatever the adipocytes put out there to attract the macrophages, or in the macrophages themselves and in their aggressiveness in pursuing the adipocytes. Where is the original difference between those groups?

*Dr. Goran:* I don’t know who is calling whom, I think that’s a good question as to who is attracting whom. I don’t think we really know the answer to that.

*Dr. Finegood:* Is it not about the death of the cells themselves?

*Dr. Goran:* It is – but then what causes the death of the cells?

*Dr. Finegood:* Yes, but the point is that the macrophages are called to wall off the triglyceride that is sitting around presumably because the cells had died. What causes the difference in the death of the cells I think is important.

*Dr. Ochoa:* A recent paper showed that M2 responses prevented the insulin resistance and the hyperglycemia in mice from M1 responses. Do you know if when we do interventions, we are promoting M2 responses instead of just quieting down the whole system? Has anyone studied that?

*Dr. Goran:* I showed the surgical weight loss study where the M1 and M2 responses were different.
Dr. Ochoa: It’s interesting that any surgical intervention promotes M2 responses dramatically, and those in severe traumas may last for a month or more; so, it’s really fascinating that we are seeing that M2 response predominate in our patients.

Dr. Jakicic: When you look at this cascade and when you throw activity or fitness into this mix, what makes this pathway healthy? Can you really have a healthier obese person if you put activity into the mix? Is it necessary? And I guess you are thinking about at least doing some of that.

Dr. Goran: I wasn’t.

Dr. Jakicic: Are you sure? Have you thought about the issue when you talk about the GLP-1 and the blocking of the insulin that obesity may be blocking that if you are increasing insulin sensitivity on the other side with activity? Where does activity fit into this cascade?

Dr. Goran: We have published a few studies showing that exercise, or strength training can have variable effects on insulin and circulating cytokines for example, and there are some other studies like that, but I don’t really know what the mechanism is. It’s an interesting point, and I should probably think about it a bit more. Mostly, I have been disappointed with our studies with exercise as we have found mixed results. This was not just in different people but also in different studies that were done in the same way. We found one effect versus another, so our most consistent observation is that we can’t get a consistent effect of exercise.

Dr. Drewnowski: I have a question about sugar consumption. The consumption of added sugar in its many forms, whether solid or liquid, is often associated with lower incomes. Are there any racial or ethnic groups for whom this combination is particularly devastating? Can you answer that based on your research? I am saying the consumption of sugar varies as a function of socioeconomic status and is higher among lower income people than among the upper income people. Are there some low-income groups for whom sugar-fat mixtures would be particularly damaging?

Dr. Goran: Yes, in fact we have a paper in our Hispanic cohort, and this is a very specific example but it answers your question. There is some evidence to suggest that Hispanics have an increased liking for sugars. They have an increased prevalence of the PNPLA3 gene, though I don’t know why. The prevalence of this gene is almost 50% in Hispanics versus 20% in Caucasians. This gene promotes fatty liver disease. The substrate for fatty liver disease is sugar, possibly fructose, because fructose is lipogenic and promotes lipogenesis in the liver. So, I think this is a perfect storm among Hispanics who have a genetic predisposition and a liking for sugar. The issue of economics comes into the equation as well. If you consider the whole story of high fructose corn syrup, you see that the exports of corn sweeteners by the US are increasing dramatically as a result of a recent policy shift by the World Trade Organization. So, I think this is a very clear example of a specific subgroup of the population which is susceptible to the damaging effects of sugar.

Dr. Ard: How much of this has to do with energy balance in the context of intake of sugar or other things? Adipocyte biology can change with a bout of exercise or with the institution of calorie restriction or even bringing people into energy balance; so, how much of this do you think is related to that milieu of excess caloric intake that then continues to foster the inflammation?

Dr. Goran: There are limited data to answer this question, especially in humans which would require a fat biopsy. There are some animal studies that have looked at the
effects of positive overfeeding on the development of adipose tissue and the creation of adipose tissue inflammation.

*Dr. Rolls:* We would hypothesize that a low energy dense eating pattern would be a low inflammatory eating pattern, but I don’t know of specific data on that. Do you know of studies or do you agree with that hypothesis?

*Dr. Goran:* Yes I would. I think that’s a very interesting idea. The Zone diet for example has an anti-inflammatory element, and there are other diets that are promoted as anti-inflammatory. I would agree that the low energy density diet is also anti-inflammatory, but there is a lack of studies to show effectiveness in this regard.

*Dr. Finegood:* Did you characterize the subjects that you had in terms of their food intake and exercise levels? Do you know about differences in their eating patterns or exercise?

*Dr. Goran:* In our study that I showed you, the groups were quite small, and unfortunately we don’t have good dietary or activity data.

### References


Summary Discussion on Obesity Treatment: Challenges and Opportunities

Dr. Lovejoy: I would like to ask a controversial question that ties to what most of the speakers have talked about. Are there specific foods, for example those high in sugar or fat, that have effects on the brain or body that are parallel to those of addictive drugs? If that is the case, do we need to consider this in relation to obesity treatment and strategies for a healthy diet?

Dr. Rolls: I presume you are talking about addiction in a stringent way using a formal definition that includes withdrawal symptoms.

Dr. Lovejoy: I think that has been a part of the controversy. There are those who would argue that the stringent definition of addiction applies to food, including withdrawal. But others disagree and say that it's not truly addiction with food. But obviously certain foods are stimulating the same areas in the brain as addictive drugs. How do we come to grips with that as a field in a way that makes sense to the public?

Dr. Rosenbaum: Some of the brain areas that are more active in individuals following weight loss and are sensitive to leptin are the same ones that are more active in individuals who are additive, so there are certain parallels between addiction and the inability to sustain weight loss. I don't know if anyone has looked prospectively at who is going to gain weight along those lines. Could you identify someone early and say that he is going to be a food junky down the line? I don't know the answer.

Dr. Drewnowski: France Bellisle and I published a review entitled ‘Is sweetness addictive?’ in the British Nutrition Bulletin some years ago. It is worth noting that the former definition of addiction, as featured in the Diagnostic and Statistical Manual of Mental Disorders (DSM), is now gone. It used to be based on the criteria of tolerance and withdrawal. What we have now is something called substance dependence and the inclusion criteria are very soft. Just about anything fits. Substance use behaviors that are performed in private, that take precedence over other activities are now part of the definitions. So, conceivably, eating chocolate would fit the bill. We need to pay attention to the fact that the definitions of food addiction are changing. Our studies need to keep pace with the definitions. And then there are very few studies on food addiction or on the potential underlying mechanisms. Dr. David Kessler in his book, The End of Overeating, was referring to some studies performed by us at the University of Michigan.
Those studies, conducted with bulimic women used the opiate blocker naloxone to show that the opioid system was somehow involved in food preferences and the consumption of good tasting foods. However, that was a far cry from addiction. Now, 15 years later, there are still no new studies on selective opiate antagonists and their impact on food consumption. Instead, attention has shifted to dopamine and neuroimaging, but I am not sure that those studies have come to a consensus on whether or not foods are addictive. All we know is that something is going on in different areas in the brain following certain exposures. So, I think the issue of food addiction is still unresolved. I should note that in all of our research we have been very careful to note that foods were not truly addictive substances and that liking or even craving was not the same as addiction. We did not want to use the word addiction; we did not use the word addiction. Of course, our studies were interpreted in the popular press as a search for a drug that stops food cravings, which is not what we were all about. So, it's an interesting issue that many people raise all the time. There is a big difference between addiction and liking or preferring or even craving. I don't think that sugar liking is an addiction.

**Dr. Goran:** It doesn't matter what it's called. If you agree that there are those other properties that are not healthful, it doesn't matter whether it's technically addiction or not.

**Dr. Drewnowski:** We are kind of addicted to food since we eat it every day. But that is not really addiction, there are other factors that you need to very carefully consider as well.

**Dr. Goran:** Really, you think we are addicted to food?

**Dr. Drewnowski:** According to the definition of substance dependence in DSM-IV that I read very closely, eating food would actually fit.

**Dr. Rolls:** But really the issue is how we can shift people towards healthier foods and get them away from the foods that are pushing overconsumption.

**Dr. Drewnowski:** The economics plays a role too because the foods that you would identify as targets of cravings and addictions are energy dense, but also they are inexpensive.

**Dr. Rosenbaum:** In a rodent study that was just published, Yann Ravussin showed that if you take mice and overfeed them on the DIL diet, the nice diet that rodents and lab technicians love, they become obese. If they stay obese long enough, when you restrict their food, they behave like starving animals and they defend a higher bodyweight. That's an analogy to addiction in that somebody who abuses a substance develops a need for it, and they have a higher set point for how much of that stimulus they need. So, it's not a bad model, and perhaps if you sustain an elevated bodyweight long enough or at specific times in life, your tolerance level in a way that is similar to addiction is changed.

**Dr. Rolls:** But an interesting question that comes from your talk is can you ever reverse that? Can you reduce their weight long enough to get them back to where they were before the obese phase?

**Dr. Rosenbaum:** It seems from both the epidemiology and the evolutionary biology that you can probably jack this set point or whatever you want to call it up, but there is no way that we know how to jack it down.

**Dr. Rolls:** Do we really know that?

**Dr. Rosenbaum:** Animals that are sustained at reduced bodyweight for an extended period of time remain extraordinarily metabolically efficient, while animals maintained
at a higher level of bodyweight for an extended period of time will start to defend that bodyweight to some degree. Human beings are getting fatter and fatter, and whether you are fat or thin you make the same metabolic opposition to attempts to sustain reduced weight. I have studied people who kept weight off for 6 years so not everybody regains, but most people do.

*Dr. Rolls:* So once you are obese, that is it?

*Dr. Rosenbaum:* I would say that what is regulated is the relative level of body fat in the population. So it’s like baseball. If you were to move the back wall of every stadium back 20 yards, there would be fewer home runs, but the rank order of homerun hitters wouldn’t change. You would still have some pitchers at the bottom and other pitchers at the top. So, I think it’s the same thing. If the food environment were to be changed, people who are most obese in this environment would still be obese in the new environment. On an absolute basis, they would be less or more obese, but the relative distribution of obese people would be the same.

*Dr. Finegood:* What about the dynamic of that rise? How long do you have to be at a higher bodyweight to begin to defend it?

*Dr. Rosenbaum:* That would be an unethical study to do.

*Dr. Finegood:* In a controlled way, but what about in a less controlled way – there are people gaining weight all the time.

*Dr. Rosenbaum:* Again, I think it’s incredibly complicated. The things that influence the bodyweight you defend begin at the moment of implantation. That’s where the gene environment interactions begin. You get into all the ideas of the thrifty gene and the catch up growth hypothesis. Probably, there are specific times in life where you are more vulnerable.

*Dr. Finegood:* But you are suggesting that we also defend higher bodyweight if our bodyweight goes up.

*Dr. Rosenbaum:* I think that’s correct. If you maintain an elevated bodyweight long enough or at specific times in life or both, you may be able to jack that defended point up, but exactly what that time frame is and what influences it, I have absolutely no idea.

*Dr. Oppert:* That’s for Dr. Rosenbaum about the comeback of T₃ because this is about treatment; so, is this to counteract the adaptations in thyroid metabolism or is it the weight loss?

*Dr. Rosenbaum:* You ask about giving people thyroid hormone? The major factor for the decline in energy expenditure that occurs during reduced weight maintenance appears to be skeletal muscle, and the changes that occur in skeletal muscle could be due to the decrease in circulating T₃ that occurs as a result of weight loss. The MHC1 promoter region contains an inhibitory T₃ response element, and as T₃ falls the MHC1 expression should go up as it does in hypothyroid animals. So, the idea would be that if you replace T₃ to the levels that were present before weight loss, you might actually reverse the changes in muscle and only in muscle. You would then have an increase in energy expenditure, so at worst you could eat a little bit more and still match your energy expenditure. But it’s a physiology question. We are not at the point where it’s a treatment question, but it might be. The idea is that the weight-reduced person is very different from the weight-stable person. T₃ would not be the way I would promote weight loss, but it might be a good addition to reduced weight maintenance therapy for some people.
Dr. Oppert: But I thought that the decreasing T₃ was a kind of transient phenomenon.

Dr. Rosenbaum: Some people have reported that, others have not. We did not find that. The problem is that there are so many other things that influence T₃, sympathetic nervous system tone being a big one, so people can do other things that affect that.

Dr. St. Jeor: As Dr. Goran said, I think we might need a paradigm change mainly concentrating on obesity as a disease rather than the outcome of weight loss. We know the limitations of weight loss, and we know that the treatments are very complicated, and as Dr. Rosenbaum pointed out, the phenotypes and the assessment is really where we need to begin. We can see that obesity now is being classified as a disease by insurance companies, and a lot of progress needs to be made to understand the mechanisms of obesity. So, I would say that we just need a paradigm change, so we can pay a better attention to these mechanisms that affect not only the outcome of weight loss but weight loss maintenance to pull that field together. Having a more interdisciplinary understanding is really important because instead of just concentrating on weight loss or weight maintenance per se, I think we need to understand better the processes that are involved.

Dr. Jakicic: A lot of the discussions are around physiology and the gene and everything else. My concern is that people eat for a whole bunch of reasons that are not driven by physiology. They sit in front of TV for a whole bunch of reasons that are not driven by physiology. The physiology hasn't changed dramatically in my opinion in 30 or 40 years, so why is the obesity rate going up? We can continue to study what happens to the physiology, what drives fat metabolism, and these are really important questions. But at the end of the day we have to appreciate that there is a whole bunch of other drivers, these behaviors that actually are as important to this whole cascade that we have to appreciate. If somebody had a bad day, they may eat because food is comforting to them and not because some molecule told them to eat. I am just worried that if we make this all about the physiology, then we really are not going to solve the problem. If we make it about physiology, then we are going to create maybe pharmaceutical agents to address these issues. However, we also know people can override that decision, that the body is telling me I am not hungry but I am going to eat anyway. I am concerned that we have to keep that in this discussion in a major way, otherwise I don't think we are going to make much progress.

Dr. Rolls: You said that very eloquently, and it reinforces what I said.

Dr. Jakicic: I agree with you, and these are intriguing questions from a scientific perspective and from a clinical perspective: what molecule does this and what gene does that; but, if it was all physiologically driven, as soon as intake went off, energy expenditure would go up and it would be in pure compensation. That's not the case, the body is not truly compensating. So, I think we have to figure out how to do these interventions to prevent and treat and maintain and so on based upon a person's physiology. What we need to do is get people to eat fewer calories and get them to burn more energy. How do we do that, that's the major question.

Dr. Lampe: Along those lines, I was thinking during your talk Dr. Rolls that there used to be a day when a hamburger the size of a hockey puck was sufficient, and now we need hamburgers the size of dinner plates. Why can't we make the transition back, and what would it take to try to get us there? The world hasn't changed to the point that our needs require us to be eating hamburgers the size of dinner plates.
Dr. Rolls: Obviously consumer demand is there and it’s at least in part an economic issue. In America, we like value for our dollar and we put value on getting more food. This is going to be hard to change and must involve starting with parents and their children. Not only do people like big portions, but they are also a cheap source of calories. If you are in policy meetings and you say let’s cut back on the calories we are offering in triple hamburgers there are going to be people there who say that it’s going to discriminate against the poor people who are coming into this chain and relying on this food to sustain them. It’s going to be tough to change.

Dr.Finegood: As a colleague of mine, who was responsible for the food guide in Canada, says you practically have to have an eating disorder in the current obesogenic environment to be at a normal healthy bodyweight.

Dr. Bray: I don’t really disagree, but we need to make sure that we are aware that we are not eating the same food that we ate 20 years ago. We are ingesting a lot of chemicals and nutrients that affect DNA, things that affect our physiology and our brains at the molecular level. They may be a big part of why we are behaving the way we do because we are eating different kinds of things now.

Dr. Rosenbaum: I understand Dr. Jakicic’s point, but I think the idea of separating physiology and behavior and the environment is actually an unhealthy approach to this problem. The changes you want to make in behavior and the changes you want to make in the environment are on the template of a physiology that has not changed in the last few millennium, much less in the last 20 years. So, I think it has to be ‘the farmers and the cowmen should be friends’ approach, otherwise you are just on sort of a fishing expedition, let’s keep on trying things. If you can find the basis to predict what would work, if you can understand how the environment is interacting with the physiology that didn’t evolve in this kind of an environment, that’s how we are going to find a way to address this issue, not by going into separate camps and not working together.

Dr. Drewnowski: I have a comment on that as well. The point was to integrate those two approaches. There is now a great deal of work about who the obese people are, where they live, where they shop, where they eat, where their calories come from. Focusing on obesity rates in small area studies, we know that obesity rates can vary by a factor of 5 depending on the neighborhood, even if people shop at the same food stores. Some of the physiological models can accommodate those social and geographic disparities and other models cannot. The challenge is to select those models that can successfully integrate the social and the economic findings and see whether they provide some additional insight into the causes of obesity. Our task today is to determine what the best approach is and how it integrates the behavior, the physiology, and the environment.

Dr. Rosenbaum: We need a collaboration of geneticists, physiologists, behaviorists, and environmentalists.

Dr. Rolls: I think the either/or approach is not going to work, but what drives the either/or approach is the funding. There is just not enough money to go around, and so we all have to shout and say this is where all the action is, and that is going to stall the integrative research that we need.

Dr. Drewnowski: Interdisciplinary studies take a long time to establish. It can take years to become conversant with areas outside your primary area of expertise and to get your partners to join the research.
Dr. Oppert: If I may add something on the environment, it may well be that we are not so well advanced in our understanding of the relationships between attributes of the environment and the behaviors and even less advanced in what we should do.

Dr. Finegood: What is important is the interaction between physiology, genetics and the environment. Maybe the shift we have to start making is out of our siloed thinking. We need to start asking the hard questions about how these interact. The interdependencies are where the money is, so to speak.
The Gut Microbiome and Obesity

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Abstract
The composition of the gut microbiome is hypothesized to be an environmental factor that contributes to obesity. Results of several human studies suggest that obesity is associated with differences in the gut microbiota composition, reduced bacterial diversity, and altered representation of bacterial metabolic pathways. The obese phenotype is associated with increased microbial fermentation and energy extraction from non-digestible food components; however, until recently it was not clear how relatively small increases in energy extraction could contribute to the large and rapid weight gain observed in the animal studies. Mechanisms by which the gut microbiome may influence metabolism and energy homeostasis include regulation of energy uptake from diet, interaction with signaling molecules involved in host metabolism, modification of gut permeability, release of gut hormones, and low-grade, chronic inflammation, the latter being a hallmark of obesity-related diseases.

Introduction
Environmental and genetic factors play a role in determining energy balance and risk of obesity. The prevalence of excess adiposity and obesity-related factors has paralleled the rise in diseases associated with chronic low-grade inflammation, such as type 2 diabetes, cardiovascular disease, gall bladder disease and several cancers. The human gut microbial community has been identified as another possible factor that may alter host metabolism and adiposity and influence chronic low-grade inflammation [1, 2].

The composition of the gut microbiome (i.e. the collective genomes of the gut microbial community) is hypothesized to be an environmental factor that plays a role in the pathogenesis of obesity and associated diseases. This hypothesis has emerged with the advent of new technologies that have allowed for the generation of important new data related to the composition and characteristics...
of the gut microbiome. Recent application of molecular techniques to characterize intestinal bacterial species has allowed for more in-depth identification of gut microbial species and evaluating its relationship with human health and disease [3]. Much of the work has involved the sequencing of the 16S rRNA gene to determine which microbes are present in the gut, or more recently a metagenomics approach, measuring all of the genes in the microbial genomes, to identify the genetic potential of the bacteria present.

The gut microbiota colonize the length of the intestinal tract in varied cell densities, ranging from ~10^4 bacterial cells/ml luminal contents in the duodenum to 10^{11} cells/ml luminal contents in the colon and rectum [4]. The gut microbiota consist largely of members of five phyla, the Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia. The number of different species of bacteria is estimated to range from 300 to 1,000, with the majority of the species diversity distributed between the Firmicutes and Bacteroidetes [5, 6]. There is high interindividual variation in the composition of the communities, mostly at the species level [3], although recent work suggests that certain bacterial community composition patterns are identifiable within human populations [7].

Obesity and Gut Microbial Profiles in Humans and Experimental Animals

Results of several human studies, typically with small sample sizes, suggest that obesity is associated with differences in gut microbial profiles [2, 7–11], as well as reduced bacterial diversity [9], and altered representation of bacterial metabolic pathways [9]. It has been hypothesized that, at the phylum level, an increased ratio of Firmicutes to Bacteroidetes may contribute to the pathophysiology of human obesity [2, 12]; however, this hypothesis has not been supported consistently across studies [13, 14], even in the studies that detect obesity-associated differences in gut microbial community [7, 8, 10].

Recently, in a cross-sectional sample of 115 premenopausal women, we evaluated the association between adiposity and the gut microbial community. We measured percent body fat on these women by dual-energy X-ray absorptiometry and used several approaches to characterize the microbial community in fecal samples. First, using quantitative PCR and terminal restriction length polymorphism (TRFLP), we found that the abundance of Bacteroidetes was positively associated with percent adiposity (r = 0.20; p = 0.02) and that TRFLP peak 473 (indicative of the Bacteroidetes-Prevotella group) was statistically significantly associated with percent adiposity. Multiple regression testing of the relationship between adiposity and gut microbial community, adjusting for energy, carbohydrate, fat and dietary fiber intake, showed that Bacteroidetes explained 15% of the variation in adiposity in these women. In a subset of the women, we also compared the gut microbial community composition by
pyrosequencing the V1–V3 region of the 16S rRNA gene. In total, we analyzed 239,875 sequences. After trimming the sequences (no ambiguous nucleotides, homopolymer ≤8, primer mismatch ≤2, barcode mismatch ≤1, quality score ≥35 in 50 nt window), we aligned the sequences in SILVA (http://www.arb-silva.de) and found that out of 65,492 sequences 13,190 were unique. We found that the bacterial communities in the obese women (35–46% body fat; n = 35) were significantly less diverse than those of the women with average percent adiposity (25–32%; n = 27), a trend similar to that reported by Turnbaugh et al. [9] in a sample of twins. The phylogenetic composition and abundance of the microbial community were also significantly different between lean and obese individuals. Multivariate analysis of the pyrosequencing data, using non-metric multidimensional scaling (NMS), explained 75% variation in our data and NMS axis 2 was positively associated with percent adiposity. In addition, two *Prevotella* sp in the phylum Bacteroidetes were positively associated with NMS axis 2 and increasing adiposity. Given that the Bacteroidetes are a metabolically diverse group specializing in saccharolytic degradation, this suggests that increased efficiency of energy extraction from the diet may be associated with specific microbial metabolic pathways in a few groups of bacteria in obese individuals.

Studies in experimental animal models also support the hypothesis that gut microbes play an important role in energy regulation and adiposity. Colonization of axenic (i.e. ‘germ-free’) mice with a gut microbiota derived from conventional mice resulted in a 60% increase in body fat mass and development of insulin resistance [15], and the bacterial community composition of the inoculum influenced amount of fat stored [16]. These effects have been seen in the context of a chow diet and a semi-synthetic Western diet [17]; however, in a similar experiment conducted using a high-fat, semi-synthetic diet with the same overall proportions of macronutrients as the Western diet, but composed of different ingredients, axenic mice were not protected from obesity and gained as high or higher amounts of body fat as the conventional mice [18]. Bacterial community composition has also been shown to differ by degree of genetically mediated adiposity; obese ob/ob (i.e. leptin-knockout) mice had 50% lower abundance of Bacteroidetes and proportionally higher amounts of Firmicutes [1].

The results of the association studies in humans and the animal studies raise the question whether compositional change in the gut microbiota precedes the onset of weight gain and whether the microbiota plays a causative role [19]. Unfortunately, no prospective studies have been conducted in humans to examine this. In a retrospective study, Kalliomäki et al. [20] selected overweight and obese (n = 25) and normal-weight (n = 24) Finnish children, 7 years of age, and matching for numerous factors (e.g. gestational age, body mass index, BMI, at birth, etc.), and assessed gut microbial community by fluorescent in situ hybridization (FISH) and qRT-PCR in fecal samples collected at 6 and 12 months. They reported that, in infancy, bifidobacterial numbers were higher in normal-weight children, and *Staphylococcus aureus* was greater in overweight children. Some
work in mice supports a potentially causative role of the microbes; transfer of gut microbiota from genetically obese \textit{ob/ob} mice to lean, axenic mice resulted in greater body fat gain in these lean animals than in lean axenic mice colonized with microbiota from conventional lean mice [12].

Further, some, but not all, intervention studies of weight loss in humans also show changes in gut microbial populations. Studies report that obese individuals have fewer [9, 12], increased [8, 11] or no difference [7, 13] in the amount of Bacteroidetes compared to Firmicutes. Others have shown shifts at the genus level [10, 21]. Ley et al. [2] showed that weight reduction on either a fat- or carbohydrate-restricted weight loss diet resulted in a decrease in Firmicutes and an increase in Bacteroidetes; by 52 weeks, the distribution mimicked that in lean individuals, and the percentage bodyweight change was linearly associated with an increase in Bacteroidetes abundance. Similarly, administration of an obesity treatment program to adolescents resulted in significant changes in certain bacterial groups as monitored by quantitative real-time PCR; the changes were observed in the group of participants who lost >4.0 kg, whereas no changes were observed among the group who lost <2.0 kg [21]. Duncan et al. [13] monitored groups of fecal bacteria using FISH in obese and non-obese individuals under conditions of weight maintenance and weight loss on two different reduced-carbohydrate weight loss diets. There was no significant change in Bacteroidetes in the obese individuals after 4 weeks on the weight loss diets; however, there was a diet-dependent decrease in a group of butyrate-producing Firmicutes (\textit{Roseburia} + \textit{E. rectale}).

A recent weight loss study in mice examined the effects of weight loss on the gut microbiota in the context of high- and low-fat diets (60 and 10% of energy derived from fat, respectively) [22]. The design allowed for comparison of the effects of weight loss in lean and obese mice, as well as comparison of diet effects on gut microbial community composition independent of bodyweight. The investigators showed that the differences in diet composition had the largest effect on differences in the gut microbiota. When evaluating the effect of weight loss within diet category, in mice fed the high-fat diet, maintenance of a 20% reduced bodyweight influenced the composition of the gut microbiota. This effect was not seen in weight-reduced mice fed the low-fat diet. These differential responses and the findings of Fleissner et al. [18] speak to the complex interactions between diet, the gut microbiome, and host physiology (i.e. adiposity and associated metabolic parameters), and suggest that human studies designed to evaluate these relationships in weight reduction studies need to be stringently controlled to determine the individual impact of diet and fat mass loss on the gut microbiome.

Several technical factors may contribute to the varied reports on the relationship between microbial taxa and obesity in both human and mouse studies. Different methods used to characterize the microbial community may introduce different types and amounts of bias that could influence the strength of the
association and interpretation of the results. DNA extraction [23], PCR primer biases [24, 25], and accuracy of phylogenetic identification [26] are potential sources of variation. For example, oligonucleotide probes, used in FISH to identify shifts in microbiota associated with weight loss [10, 20], are hampered by cell permeability or probe mismatch issues [27]. In addition, on the adiposity side of the equation, relying on BMI rather than procedures that more accurately determine body fat percentage (e.g. dual-energy X-ray absorptiometry) may contribute to misclassification of individuals [28].

The potentially large, but often not considered, contribution of dietary and other lifestyle differences to some of the obesity-related findings of the cross-sectional studies is also a concern. Among those studies that evaluate diet, underreporting of diet, especially associated with studies of obesity, may be a source of bias [29]. Energy intake is, on average, underestimated, especially when using memory recall methods [30]. Several behavioral changes may influence the accuracy of self-report, such as: change in the true intake as a function of recording, lack of awareness of the amount of food consumed, and reluctance to disclose amounts or foods eaten. In addition, some studies have shown that, among dietary items reported, there is evidence for differential underreporting of certain foods [29], creating further bias in self-reported data.

**The Gut Microbiome and Obesity: Mechanisms of Action**

The obese phenotype is associated with increased microbial fermentation and energy extraction from non-digestible food components; however, until recently it was not clear how relatively small increases in energy extraction could contribute to the large and rapid weight gain observed in the animal studies. Mechanisms by which the gut microbiome influences human metabolism and energy homeostasis and subsequent obesity-associated disease risk include: regulation of energy uptake from diet [13, 31], interaction with signaling molecules involved in host metabolism [32], release of gut hormones [33, 34], and modification of gut permeability [35]. Some of the mechanisms appear to involve effects of products of bacterial metabolism of dietary constituents and others are direct effects of the gut microbes (fig. 1).

Fermentation efficiency and short-chain fatty acid (SCFA) composition can be influenced by the composition of the gut microbiota [16, 36]. Non-digestible carbohydrates (e.g. dietary fibers) are fermented by the gut microbes to produce hydrogen, carbon dioxide, SCFA (e.g. acetate, propionate, butyrate) and other compounds, such as lactate and formate. Estimates vary, depending on the substrates, the gut microbial community composition, and gastrointestinal transit, but fermentation accounts for approximately 10% of human’s daily energy intake [37]. Hydrogenotrophic methanogens (i.e. Archaea) and sulfate-reducing bacteria consume the hydrogen produced from the fermentation of polysaccharides.
and their rapid uptake of hydrogen helps to drive the process [38]. Thus, hydrogen transfer between hydrogen-producing bacteria and hydrogen-consuming Archaea is hypothesized to increase fermentation efficiency and SCFA production and contribute to increased adiposity – a relationship that has been shown in an experimental animal model [16]. In humans, the results of one study showed that higher numbers of Archaea and the order Methanobacterales were present in obese individuals (n = 3) as compared to normal-weight individuals (n = 3) [8]. However, in an earlier study of 1,293 individuals, obesity was statistically significantly less prevalent in methane producers than non-producers, when producer status was characterized by breath methane excretion [39]. It is likely that unaccounted dietary factors and other host exposures influence the observed relationships.

Fig. 1. The gut microbiome and its metabolites may influence metabolism and energy homeostasis through several mechanisms. SCFA, the products of carbohydrate fermentation, are substrates for lipogenesis, and also are signaling molecules for G protein-coupled receptors GPR41 and GPR43. The presence of the gut microbiota and SCFA modulate release of enteroendocrine hormones [e.g. glucagon-like peptides (GLP-1 and -2) and PYY], affecting hunger and satiety and suppress FIAF. Reduced FIAF in turn decreases hepatic and skeletal muscle fatty acid oxidation and increases lipoprotein lipase (LPL) activity and triacylglycerol storage in adipose. LPS translocation across the gut epithelium leads to higher circulating LPS concentrations and increased low-grade inflammation and macrophage activation in adipose tissue. Adapted from Bäckhed [31] and Delzenne and Cani [43].
In addition to providing energy, gut microbial metabolites, such as SCFA, also play a role as signaling molecules, interacting with receptors in pathways influencing energy uptake [31]. Acetate and propionate and butyrate bind to two G protein-coupled receptors GPR41 and GPR43, also known as free fatty acid receptors FFA3 and FFA2, respectively [40]. GPR43 is expressed in immune cells, adipocytes, and the distal ileum and colon, and Gpr41 is expressed in adipose tissue and several immune function-associated tissues, such as spleen, bone marrow [40]. Work in GPR41-deficient mice suggests that one aspect of the interaction between SCFA and GPR41 may be to increase levels of peptide YY (PYY), an enteroendocrine cell-derived hormone in circulation that reduces gut motility; reduced gut motility may aid in digestion and allow for increased absorption of SCFA – acetate and propionate are substrates for hepatic de novo lipogenesis and gluconeogenesis, respectively [32]. Activation of GPR43 by SCFA inhibits lipolysis and adipocyte differentiation and GPR43-deficient mice are less prone to high-fat diet-induced obesity and have lower macrophage numbers in their adipose tissue [41]. These findings would suggest that high intakes of non-digestible carbohydrate might be detrimental in weight control; however, prebiotic supplementation of animals overexpressing GPR43 and fed a high-fat diet has been shown to reduce adiposity [42].

The impact of gut microbial fermentation products, such as the SCFA, on release of enteroendocrine hormones involved in appetite and bodyweight regulation has been demonstrated in experimental studies in humans and animals. Fermentable carbohydrates from several sources, even though they modulate gut microbial community structure differently, have been shown consistently to decrease food intake and bodyweight and with concomitant increases in production and secretion of two anorexigenic peptides glucagon-like peptide-1 and PYY [reviewed in 43].

Gut bacteria have also been proposed to increase triacylglycerol storage in adipose tissue by suppressing fasting-induced adipocyte factor (FIAF) in the gut epithelium; FIAF suppression in turn stimulates de novo hepatic lipogenesis and promotes lipoprotein lipase-directed incorporation of triacylglycerol into adipocytes [15] and reduces fatty acid oxidation in the liver and in skeletal muscle [17]. In contrast, another study, also in mice, did not support a crucial role of the modulation of intestinal FIAF production in mediating fat storage [18]. Recent in vitro work using coinubcations of bacteria and cell lines showed that some bacteria increased and others decreased FIAF expression in intestinal cancer cell lines [44]. Further, incubation with propionate and butyrate, but not acetate, increased FIAF expression and cleavage in colon and hepatic cell lines, suggesting that the SCFA effects on FIAF may not be restricted to the gut epithelium, but that bacterial effects in vivo may be mediated by gut microbial metabolites at other tissue sites.

The gut microbiota also influences low-grade, chronic inflammation [43], a hallmark of obesity-related diseases. Gut microbiome composition has been
associated with altered concentrations of inflammation biomarkers, such as adipokines, C-reactive protein, monocyte chemotactic protein-1, and tumor necrosis factor-α, in circulation and in adipose tissue [45]. One microbiome-mediated pathway that may contribute to low-grade systemic inflammation is the presence of bacterial lipopolysaccharide (LPS; also called endotoxin) in circulation. Low concentrations of LPS in the blood (i.e. subsepticemic) have been linked to obesity and related metabolic disorders [46]. LPS stimulates the innate immune response by binding to toll-like receptors expressed by macrophages in adipocytes and epithelial cells [47]. A higher systemic LPS load accompanies increased translocation of LPS via chylomicron uptake and/or increased intestinal permeability [48]. Thus, diet, particularly high-fat diets, may contribute to the microbiome-inflammation relationship [18, 45]. In contrast, other end-products of microbial metabolism of diet, such as SCFA, have been associated with reduced inflammation through interaction with the TGF-β pathway [49]. Butyrate interacts with TGF-β to block the transfer of NF-κB to the nucleus thereby reducing transcription of inflammatory genes [50] and reducing inflammation.

In summary, the gut microbiome may contribute to altered energy storage and obesity through several mechanisms, including regulation of energy uptake from diet, interaction with signaling molecules involved in host metabolism, modification of gut permeability, and release of gut hormones. Further, the interaction of gut microbes with the host innate immune system influences inflammatory and metabolic processes associated with obesity and important to human health. The complex interplay between the gut microbial community, diet, and host physiology needs to be considered carefully in the design and interpretation of experimental interventions and population-based observational studies.

Acknowledgements

Supported in part by U01CA162077, R01DK084157 and Fred Hutchinson Cancer Research Center.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the chapter.
References


**Discussion**

*Dr. Birch:* My question is whether you have information about whether participants were breastfed or formula fed as infants?

*Dr. Lampe:* This was the study of Kalliomäki et al. [1]. Two groups of 7-year-old children, normal weight and overweight or obese, were selected for retrospective evaluation of their gut microbial communities in stool samples collected within the first year of life. The children were part of a follow-up of a cohort of Finnish children who had participated pre- and postnatally in a randomized trial of probiotics and atopic disease.

*Dr. Birch:* Do you know if obesity status at 7 years of age was associated with differences in infant feeding mode?

*Dr. Lampe:* There were no statistically significant differences in infant feeding mode between the normal weight and overweight children. The two groups were matched for several factors, including gestational age, BMI at birth, mode of delivery, duration of breastfeeding, use of antibiotics during infancy, intervention group, and frequencies of atopic diseases and atopic sensitization at 7 years of age. Other studies in breastfed and formula-fed infants show differences in gut microbial populations, which is why matching was important.

*Dr. Haschke:* The Finnish study was a secondary outcome study looking at allergies. All the infants were breastfed until 6 months of age, and there was some intervention in terms of giving mothers probiotics prenatally, so this study has been reported 3 times. It's from Erica Isolauri's group (Department of Pediatrics, University of Turku, Finland), and it could not be reproduced by any other group that there is some difference continuously there, so we have to wait for confirmation. The clinical data have been really weak until now. The hypothesis is attractive, but we still don't have a prospective study showing that certain microbiota could be preventive.

*Dr. Lampe:* Thanks for that clarification. I think you raise an important point, and that is that we really do not have any good prospective studies. We need to encourage cohort studies to collect and store stool samples, so that we can do the robust studies that are needed in order to answer these questions more effectively.

*Dr. Goran:* I always get a little confused with some of these aspects because short-chain fatty acids are being protective in some situations, so resistant starch for example is promoted as a vehicle to induce insulin resistance and it starts to act through short-chain fatty acids. Can you clarify whether there are positive and negative effects of some of these things, especially in the context of your study where you showed that fiber and starch were predictive of the biome? Are they predictive of a beneficial or a harmful profile?

*Dr. Lampe:* All of the individuals in our observational study of diet and gut microbial community were healthy, so we do not have information on differential relationships dependent on metabolic syndrome or other disease phenotypes. Although the dietary data are predictive of the microbiome, they cannot distinguish between physiologically positive and negative effects. Looking at the totality of the predictive value of diet, these diet components help to define different groups of individuals who have different microbiomes. Whether or not one is better from a health standpoint, we don't know in the context of this study. Intervention studies of dietary fiber and gut microbial community show shifts in different groups of bacteria and in directions that typically
have been thought to be beneficial. With regard to resistant starch and diabetes, I think that part of the effect of resistant starch in relation to glycemic load may be its influence on gut transit and absorption of sugars.

*Dr. Goran:* Were you able to look at in that study or did other studies look at subtypes of fiber, soluble versus insoluble for example, in different types of starches? And then the third factor that comes to mind is fructose, which in large amounts is poorly absorbed and may also contribute to the issue. Have you been able to dissect that?

*Dr. Lampe:* In this study, when we looked at soluble and insoluble fiber, it was really the insoluble fiber that was explaining most of the relationship between dietary fiber and microbial community. The contribution of soluble fiber was less apparent. Trying to measure resistant starch from a 3-day food record is not very accurate because it's really hard to quantitate it in observational studies. We didn't try to do that.

*Dr. Rosenbaum:* I don't fully understand, but you only can report relative amounts of different species, so we don't know if as people lose weight they are back to where one number goes up and the other one is coming down. Do you think that it's the balance between the different species or the absolute amount of one or the other, is this some sort of a functional assay that you could do that would determine the absolute amount, how they handle the starch load or something like that?

*Dr. Lampe:* In order to get at the absolute amount of bacteria, you would need to access the total contents of the lumen. Consequently, much of the focus has been on the relative amounts of different groups of bacteria. I think the ultimate goal is also to move towards measuring mRNA or even looking at protein levels of bacterial enzymes important in the various metabolic steps in the gut. This will give us information on the functionality of the gut community as compared to just what bacteria are there and in what relative amounts.

*Dr. Rosenbaum:* In the weight loss studies, was there a difference between dynamic weight loss and static weight maintenance, or they didn't look at that?

*Dr. Lampe:* The study was 52 weeks of a weight reduction intervention; there are no data to indicate that the participants were followed any further than that.

*Dr. Rolls:* Can you speculate a bit about whether you think this understanding of the microbiome holds some promise for either the treatment or prevention of obesity and how that might work? Could changing intake of a few foods help adults? Do we need to start prenatally or with maternal diets?

*Dr. Lampe:* It's very early days, but I think there may be some potential for both prevention and treatment. Given what we know so far, early life may be an important time to intervene. Crosstalk between the host and the gut microbial community is critical for development of the innate immune system and the body's ultimate comfort level with what microbes are present in the gut. The microbiota also interact with the adaptive arm of the host's intestinal mucosal immune system, modulating regulatory cells in the gut that are involved in maintaining immune tolerance. Related to this, we know from interventions in adults that it is difficult to get inoculations of probiotic bacteria to colonize and maintain a presence at detectable levels without constantly providing them. I think there will be opportunities for prevention and treatment of obesity, but we have a way to go to understand the basics and long-term consequences before we can effectively modulate the system.

*Dr. Drewnowski:* Is the gut microbiome established in the first year of life or even before that?
Dr. Lampe: As we saw from the one slide of the study of Koenig et al. [2] – and granted that this was just the example from one child – the gut microbiome is pretty well established by weaning. I think the estimate is that by age 2 or 3, the gut microbiome has the functional attributes of the adult microbial community.

Dr. Lovejoy: What would happen if you dramatically changed your diet, given the examples of children in Africa versus children in Italy? If somebody went from a largely meat-eating diet to becoming a vegan and staying a vegan, would their microbiome change and stay different or would they maintain the biome that they had since 2 years of age?

Dr. Lampe: Keep in mind that in that study, the children were born and raised to their particular environments and diets. Nonetheless, in adults, there would be changes to the microbiome as a result of what the person is eating and therefore what substrates are available to the bacteria. At the same time though, particularly at the genetic level, you are still likely to find those other bacteria that were part of the microbiome prior to the major change in diet. It’s just that there are going to be fewer of them, but they are still likely to be detectable unless there is some major perturbation as a result of antibiotic treatment or disease.

References


Abstract
Obesity prevalence among infants and young children has increased rapidly during the past 4 decades, a disturbing trend given early obesity’s association with later life obesity and its comorbidities. Fortunately, infancy is a period of great behavioral and metabolic plasticity offering numerous targets for preventive interventions. Modifiable factors that may affect early rapid weight gain and obesity risk include infant sleep duration, feeding to soothe infant distress, and the introduction of solid foods and transitional feeding. We discuss evidence linking these factors to weight outcomes, as well as results from behavioral obesity interventions in infancy, from our laboratory and others’. For example, in a recent pilot intervention, we focused on helping new mothers address three areas of infant behavior hypothesized to affect weight gain and early obesity risk: infant sleeping, crying, and feeding. First-time mothers were randomly assigned to receive either a Soothe/Sleep intervention, an Introduction of Solids intervention, both interventions, or no interventions. The interventions were delivered via home visits and showed positive effects on infant behaviors and weight outcomes at 1 year. Based on evidence from such pilot interventions, we assess the plausibility of targeting behavioral factors in infancy and suggest next steps for early prevention research.
life [3]. First, through prenatal influences (e.g. maternal pre-pregnancy weight, gestational weight gain, smoking during pregnancy), babies can be born large and stay large during the postnatal period. Second, babies with normal or low birthweights can gain excessive weight during infancy. Rapid weight gain during infancy predicts obesity and its comorbidities later in the lifespan, even after adjustment for prenatal factors. These two distinct pathways suggest two avenues for intervention: prevention efforts beginning during the prenatal period and targeting the diet and behaviors of the mother, and postnatal prevention efforts targeting infant factors linked to early weight gain. In this paper, the latter is our focus. However, it is important to remember that birthweight affects subsequent growth, and in general, infants who are born heavier are more likely to regress toward the mean and grow more slowly than those born at the lower end of the birthweight distribution.

Rapid weight gain during infancy is associated with increased risks of obesity and its cardiovascular comorbidities from early childhood [4] through adulthood [5]. In addition to the epidemiological evidence, research with animal models reveals that early rapid weight gain can have epigenetic effects that may alter developing metabolic systems to increase risks of obesity, metabolic syndrome, cardiovascular disease, and diabetes [6]. This evidence indicates that, contrary to popular belief, a chubby baby is not necessarily a healthy baby who will ‘grow out of it’ but may be more likely to ‘grow into’ obesity later in life. Despite extensive evidence that early rapid growth increases obesity risk, until very recently, few obesity prevention efforts have been focused on infancy [7].

There are many reasons to consider obesity prevention during infancy. Obesity rates are high by early childhood, and epigenetic effects of obesogenic environments on early growth indicate that infancy is a period of behavioral and metabolic plasticity that can have life-long effects on health. The rapid dietary transition from an exclusive milk diet to a modified adult diet by age 24 months is one example of the flux and instability of infancy [8], highlighting this period as an opportunity to shape behaviors that affect growth and obesity risk. Basic research, in combination with a small number of pilot intervention studies, shed light on the efficacy of targeting behavioral factors linked to infant growth.

**Behavioral Factors Linked to Weight Outcomes during Infancy**

The current state of obesity research in early life suggests that moderating early rapid growth could be a successful first step in preventing obesity. What infant factors should be targeted in order to achieve this goal? In a recent review, Paul et al. [9] identified several modifiable factors, implicated by basic research as predictors of early rapid weight gain and obesity risk. These factors were infant feeding mode (breastfeeding or formula feeding), infant sleep duration, parental use of food to regulate infant distress, the timing of the introduction
of solid foods, sweetened beverage consumption, the age of weaning from the bottle, and the introduction of solids and table foods. Recently, the Institute of Medicine released a report on ‘Early Childhood Obesity Prevention Policies’, which focuses on the period from birth to age 5 and includes brief reviews of the evidence for some of these factors influencing early growth in infancy and early childhood [10].

A consistent and growing evidence base implicates infant sleep, parental regulation of infant distress, and the introduction of complementary foods and transitional feeding as promising early behavioral targets and suggests potential possibilities for interventions (table 1). What about breastfeeding? Breastfeeding is indisputably the ideal infant feeding mode for many reasons, including immunological benefits, but the evidence is not consistent regarding the extent to which breastfeeding protects against childhood obesity. Although meta-analyses show a modest, protective effect of breastfeeding [11], exclusively breastfeeding for long durations seems to confer the greatest benefit. While promoting exclusive and long durations of breastfeeding is a goal in the US, and rates of breastfeeding initiation have increased, with the majority of new mothers in the United States breastfeeding in the hospital, it is rare for an infant to be exclusively breastfed for durations that have been shown to result in reduced obesity risk. In addition, the effects of breastfeeding decrease in magnitude after adjusting for maternal and socioeconomic confounders that are also related to offspring obesity [12]. A recent study comparing longitudinal data on breastfeeding and later obesity across cultures in which the social patterning of breastfeeding differs adds to the evidence that part of breastfeeding’s apparent protective effect is due to residual confounding: In the UK, where breastfeeding is associated with a higher socioeconomic status, breastfeeding was inversely associated with child BMI, but in Brazil, where such social patterning of breastfeeding is not observed, breastfeeding was not associated with child BMI [13]. These findings do not support a causal effect of breastfeeding on BMI but do support possible causal links between breastfeeding and IQ and between breastfeeding and blood pressure as positive associations between breastfeeding and these outcomes were noted across samples differing in the social patterning of breastfeeding. Although breastfeeding is an important public health goal for multiple reasons, the lack of clear evidence that breastfeeding reduces obesity risk and the challenges of promoting exclusive breastfeeding for long durations have led us to focus on other factors.

Although evidence regarding causal mechanisms is still emerging, short sleep duration has been linked to a higher weight status in all age groups, including infants [e.g. 14], with only a few published studies failing to find this relationship [e.g., 15]. Short sleep may affect hormones regulating hunger and satiety and/or may lead to more feedings in infants who are awake for longer durations. To teach infants that hunger leads to feeding, feeding should be reserved for when the infant exhibits hunger cues. Feeding as an indiscriminate response to
<table>
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<th>Opportunity</th>
<th>Possible intervention</th>
<th>Evidence from pilot studies</th>
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| Infant sleep | Educate parents on methods to lengthen sleep duration and soothe at night without feeding as a first response to nocturnal crying | + Intervention infants had greater increases in nocturnal sleep compared to controls, as well as greater reductions in settling time and night-time waking [23]  
Breastfed intervention infants showed increased nocturnal sleep duration [24]; effect not seen in infants transitioned to formula before 16 weeks |
| Parental regulation of infant distress (i.e. use of food to soothe or change behavior when child is not hungry) | Respond quickly to crying in early infancy, but use alternative methods to soothe than feeding | + Intervention infants were less likely to be given food as a reward [22]  
− Intervention did not affect maternal beliefs about using food to calm baby or responsiveness to satiety cues [23]  
+ In [24], fussing/crying episodes were more likely to be followed by awake/calm (as opposed to feeding; [27]) |
| Introduction of solid foods | − Delay introduction of complementary foods until at least 4 months of age  
− Avoid placing cereal in a bottle  
− Use repeated exposure to healthy foods as a response to normal infant neophobia | + Intervention group introduced solid foods later [21, 22]  
+ Intervention group introduced solid foods later [23]  
+ Tended to introduce solids later (trend level) and were more likely to accept novel foods [24] |
| Transitional feeding (i.e. introduction of developmentally appropriate foods and beverages) | − Emphasize healthy dietary choices  
− Use low-fat cow’s milk after introduction at 1 year  
− Do not any give juice to children <6 months; then, limit daily consumption of 100% fruit juice to <6 oz  
− Give juice only in a cup; do not allow children to easily transport juice  
− Completely avoid fruit drinks/soft drinks | + Earlier introduction of cup [21, 22] in intervention group  
+ Less juice feeding in intervention group [21]  
+ Less likely to be put to bed with a bottle [22]  
− No effects on maternal intake of healthy foods [23] |

1 Intervention targets selected from Paul et al. [9], based on the existing evidence base from pilot interventions targeting infants.

2 This column shows whether these variables were affected in the pilot studies of three groups whose studies were reviewed herein [21–24]. If one of the studies is not mentioned in a given row, then that behavior was not targeted in that study.
infant distress is another possible risk factor for obesity, and focus group data suggest that this practice is likely in low-income groups already at heightened obesity risk [16]. Fussier infants tend to be heavier, and researchers have speculated that this is because these fussy infants tend to be fed more as an attempt to soothe them. Recent research shows that highly negative infants and young children who are fed to soothe have increased BMI-for-age z-scores [17].

Fussier infants may also receive complementary foods sooner [18]. Early introduction of complementary foods has been linked to obesity risk, as have other inappropriate transitional feeding practices, such as offering sweetened beverages to young children [9]. While the evidence on early introduction of complementary foods is mixed, with many but not all studies indicating that early introduction increases obesity risk, there is also the possibility that the associations noted are the result of residual confounding or reverse causality (i.e. infants who grow faster are given solid foods earlier because they are hungrier). There is evidence that formula-fed infants receive complementary foods earlier than breastfed infants, and that early introduction of solid foods is associated with obesity risk in formula-fed but not breastfed infants [19].

As indicated above, there are many other differences between breastfed and formula-fed infants that make interpretation difficult. Causal manipulations of the timing and process of the introduction of solid foods can shed light on these issues, and initial evidence shows that the introduction of solids is an opportunity for infants to learn to like the foods that are offered and can have long-term effects on food acceptance [20]. Early periods of dietary transition offer unique opportunities to shape subsequent food selection and diet quality, an important goal given that the transition to the modified adult diet begins before the end of infancy, is relatively complete by 24 months [8], and is currently characterized by a high intake of sweets and grains and low intake of fruits and vegetables.

Taken together, sleep duration, feeding to soothe, and the timing and process of introducing new foods and beverages are all potentially modifiable behavioral factors that seem to predict weight status, providing the evidence base needed to attempt to causally manipulate these factors, alone or in combination, in pilot studies and efficacy trials aiming to prevent rapid growth during infancy and subsequent childhood obesity.

Results of Initial Intervention Research during Infancy

In a recent review of inventions designed to prevent obesity in 0- to 5-year-olds [7], most studies focused on preschoolers; only 6 of the 23 studies enrolled participants during the first year of life. Of these, only 2 enrolled participants in early infancy, when early measures of rapid growth could be obtained, and another was designed to focus on high-risk infants, based on infant weight status (≥95th percentile weight-for-age) or maternal obesity (BMI ≥30). Despite
the paucity of empirical evidence, this research area is growing, as evidenced by a number of publications describing protocols designed to prevent rapid growth and obesity during infancy. To date, many of these studies are in progress, and a few have published results.

In a feasibility pilot study conducted on an Australian sample, home visitors delivered an intervention that centered on feeding recommendations in the first year [21]. The intervention resulted in a lower proportion of mothers introducing solids before 4 months, a lower rate of juice feeding, and a higher proportion of cup use at infant age 12 months. The intervention group also had a higher proportion of mothers still breastfeeding at 12 months, but there were no differences between treatment and control on duration or proportion of exclusive breastfeeding. Nevertheless, these results are promising, and in a subsequent larger trial targeting socially and economically disadvantaged families, results were consistent with those from the pilot study [22].

Similarly, a pilot intervention in the US demonstrated promising effects on some early behaviors linked to rapid growth and obesity risk [23]. In this study, intervention messages were delivered to parents in primary care practices and via phone calls and targeted domains of sleep, TV viewing, feeding, and physical activity in infants and their mothers. Positive intervention effects were observed in the infants, including later introduction of solids and greater increases in reported night-time sleep duration from infant age 2 weeks to 6 months. There were no effects on breastfeeding duration, maternal beliefs about using food to soothe a crying baby, or on maternal responsiveness to infant fullness cues. Intervention and control infants did not differ on weight status at age 6 months, but there was a trend such that intervention infants were less likely to be in the highest weight status quartile.

In our own pilot research, we also reported promising effects on infant behaviors and weight status in a US sample [24]. We focused on helping new mothers to develop parenting skills to address three areas of infant behavior hypothesized to affect weight gain and early obesity risk: sleeping, crying, and feeding. First-time mothers who intended to breastfeed at infant birth were randomly assigned to receive either a Soothe/Sleep intervention, an Introduction of Solids intervention, both interventions, or no interventions. The interventions were delivered via home visits at ages 2–3 weeks and 4–6 months. One hundred and ten mostly White, higher income mothers residing in central Pennsylvania and their infants completed the one-year study. The Soothe/Sleep intervention focused on strategies to lengthen infant sleep and taught parents soothing strategies to use rather than indiscriminately feeding in response to infant fussing and crying. At age 2–3 weeks, dyads randomized to this intervention were instructed on alternate soothing responses, including swaddling, side or stomach position, shushing, swinging, and (non-nutritive) sucking. Parents were also taught to emphasize day/night differences and to respond to night waking with alternate soothing and care-taking responses. The Introduction of Solids intervention focused on
‘when,’ ‘how,’ and ‘which’ foods to introduce to infants and provided systematic experiences with new foods between ages 4–6 months. All participants were given a standard infant parenting book, and nurses answered questions about general infant care. Mothers reported on infant behavioral states (sleeping, fussing/crying, awake/calm, and feeding) in 15-min intervals over 4 days at infant ages 3 and 16 weeks. At age 1 year, infant weight and length were measured.

Infants receiving both interventions had significantly lower weight-for-length percentiles at 1 year compared to other groups. This result is depicted in figure 1, where the y-axis depicts weight-for-length percentiles using the World Health Organization (WHO) growth charts, in accordance with the recent CDC recommendation to plot the growth of American children younger than 2 using these charts [25] and in contrast with our previously published results, which were plotted relative to the CDC growth charts [24]. The WHO charts depict optimal growth of breastfed infants living in families with adequate resources, so that infant growth was not limited by food availability. These growth standards are appropriate for our sample where all mothers intended to breastfeed.

Breastfed infants who received the Soothe/Sleep intervention also slept longer at night and had fewer nightly feedings from 3 to 16 weeks compared to infants who did not receive this intervention [24], and there was evidence that mothers in this group were less likely to indiscriminately use food to soothe.
infant distress. Because the Soothe/Sleep intervention aimed to help parents use adaptive soothing techniques, it was hypothesized that this intervention would increase infants’ likelihood of transitioning from a fussing/crying state to an awake/calm state, as opposed to transitioning from a fussing/crying state to feeding. To assess this aspect of the intervention, the data from the daily behavior diaries were analyzed using a statistical technique called Markov modeling [26], which enabled an examination of the transitions between behavioral states. Consistent with our hypotheses, the Soothe/Sleep intervention significantly increased the likelihood of transitioning from fussing/crying to awake and calm at 16 weeks. In other words, when intervention group infants were fussing and crying, it was more likely that they would move to an awake/calm state next, compared to controls. There was also evidence that transitions from fussing/crying to feeding predicted subsequent weight status [27].

These results provide initial evidence that behavioral interventions designed to modify parenting practices can decrease early weight gain through changes in parenting and in infant lifestyle, including sleeping, crying, and feeding. For the most part, these factors were parent reported, although the observed effects on measured weight status suggest that positive effects are not due to reporting biases. While this is an encouraging start, additional research is needed to determine the generalizability of these findings. Our pilot study showed effects on behaviors and weight outcomes, but our well-educated sample of mothers who intended to breastfeed at infant birth can be considered low risk. It is not clear if these results would be replicated in a more heterogeneous population or a population at increased risk of childhood obesity.

Conclusions

Obesity interventions in infancy can be viewed as controversial as traditional parenting and medical care have focused on ensuring sufficient growth rather than preventing its excess, and intervening with at-risk populations, although a natural next step brings its own controversial issues. One example that was mentioned is breastfeeding. Observational studies suggest that infants may be ‘protected’ from early obesity if they are exclusively breastfed for long durations. Breastfeeding also has demonstrated benefits in numerous other domains of child development; thus, it is the ideal infant feeding mode. Yet, there are marked sociodemographic differences in the prevalence of breastfeeding in many societies [see 12, 13], such that low-income and minority families are less likely to meet breastfeeding recommendations and also are at increased risk for obesity. Is it more practical to promote breastfeeding in these families, or is it more practical to give them information on the ‘best practices’ within the context of what they are already doing (formula feeding, and later, feeding solid foods and table foods)?
We have argued that there are a number of logical behavioral targets for early obesity prevention, but another caveat that must be added is that early obesity prevention efforts will not inoculate children against obesity. The initial evidence suggests that early behavioral interventions could help young children and their families to acquire healthy behaviors and growth healthfully, but in our current obesogenic environment, the efforts cannot stop there. Perhaps if coupled with early prevention efforts, school-based obesity interventions will be more effective. Perhaps early interventions will need to be supplemented with later family-based interventions. Perhaps some aspects of the broader environment will need to change. There are many questions and controversies to address as we build upon the existing pilot research.

In sum, current obesity rates suggest that prevention efforts are needed as early as infancy, a period of rapid transitions and developmental instability. Basic research implicates behavioral targets in different domains, including infant sleep, feeding to soothe, and the introduction of solids and transitional feeding, and there is initial evidence from pilot studies in home or pediatric contexts that it is possible to modify each of these. Next steps will be to expand upon this research by examining: (1) the pathways through which these efforts have their effects, (2) which factors seem to have the largest effects on weight, (3) whether effects are sustained in larger efficacy trials and effectiveness trials, (4) the generalizability of findings across different populations, including those at high risk, (5) the generalizability of findings within populations (e.g. are certain effects moderated by infant temperament?), (6) longitudinal data on the long-term effects of early interventions, and (7) ways to build on infancy interventions in childhood and beyond. The research on obesity prevention during infancy is off to a promising start, but this is only the beginning.

**Disclosure Statement**

The authors declare that no financial or other conflict of interest exists in relation to the content of the chapter.

**References**


Discussion

*Dr. Rosenbaum:* In my experience as a teacher and as a pediatrician, I find that a lot of the things you learn when you are young you forget in adolescence and then recall in adulthood. Is it possible that this is the case with early interventions? Perhaps the effects appear later on in life?

*Dr. Birch:* Yes, I think that's quite possible, but longitudinal data in humans are limited. In addition, although evidence shows early effects on outcomes later in life, as in studies of 'fetal programming,' there is typically no information about what occurs between the early life exposures and subsequent outcomes in adulthood. For example, with respect to the effects of breastfeeding on later obesity risk, no one has investigated whether diets during childhood and adolescence of breastfed children differ from those who were formula fed, although this seems likely.

*Dr. Goran:* I was wondering if you had done any analysis in your new data or other studies looking at the effect of other maternal exposures. When we have looked at our Hispanic cohorts, we found that breastfeeding is protective, but interestingly in kids who are exposed in utero to gestational diabetes that effect is practically wiped out. What might be responsible for this?

*Dr. Birch:* Animal model research has shown that maternal obesity, excessive gestational weight gain, and gestational diabetes can all interact with postnatal exposures to affect offspring growth and obesity risk. There are also data indicating that the composition of breast milk and success of breastfeeding are altered in women with diabetes. Finally, gestational diabetes is often accompanied by elevated maternal weight status, and excessive weight gain during pregnancy, factors that would predispose the infant to overweight and increase obesity risk, and these factors could offset any protective effect of breastfeeding.

*Dr. Ard:* This is anecdotal, but being a parent of young kids and having their friends around I am often struck by how parents project their liking or not liking of certain foods on their children. I wonder, in your studies, are you going to look at the introduction of new foods? If the mum doesn't like peas then she is not going to introduce the peas, and then the next time they are around someone eating peas she is probably going to say he doesn't like peas because he has never had peas and she doesn't like peas.

*Dr. Birch:* Your observations are consistent with some of the findings from our early research on the use of repeated exposure to promote acceptance of new foods. In general, foods that become familiar become preferred over those that are unfamiliar. If parents don't like a food, they are probably less likely to have it around, to eat it, or to offer it to the child, and early experience with tasting foods such as vegetables is essential to acceptance of these foods. With respect to mothers' reports of children's food preferences, nearly all of the very early research on children's food preferences relied on maternal reports. The first thing I did when I began doing research in this area was to develop a procedure for obtaining preference data directly from young children. As a part of this work, we looked at the validity of children's food preferences, and as a part of this validation, we compared children's reported preferences with maternal reports of children's preferences. We also asked the mothers about their own food preferences and the results were consistent with your suggestion that mothers may project their own food likes and dislikes on the child. We found that mothers' own food preferences correlated with mothers' reports of their child's preferences, but these maternal reports
of their children’ preferences were not related to children’s reports of their preferences. It was children's reports of preferences, not mothers’ reports that predicted children's food intake.

*Dr. Lovejoy:* I think that intervening in pregnancy is incredibly important, particularly given the epigenetic changes that can occur. But although pregnancy seems a great time to intervene because the woman is highly motivated and concerned about the health of her baby, the kinds of effects from behavior change interventions you’d expect to see are often not observed. For example, we have anecdotal evidence that since pregnant women know that smoking is bad for their baby, they may simply lie about their smoking behavior rather than actively seek cessation support. So, although I think we need to intervene early, I am concerned that if we provide information on food as well as on smoking and alcohol use during pregnancy, we are just going to get behavioral suppression, and lack of compliance.

*Dr. Birch:* You make an excellent point about compliance, and in recent discussions on the design of interventions, Tom Robinson suggested that to promote compliance, behavioral interventions need to be inherently motivating and include short-term incentives as well as more distal incentives, such as reducing obesity risk later in life. Robinson has had a lot of success in his research on obesity prevention and treatment in children using this approach. We are trying to do something similar in an RCT that we are beginning with first-time mothers and infants. Rather than talking about preventing obesity in their infants, we are promoting the intervention to new parents on the grounds that it can teach them the parenting skills they need to become effective, responsive parents. Short-term effects of responsive parenting can include positive effects on parents and infants. Based on the results of our pilot study, effects include increased parent self-efficacy, infants who tend to sleep longer, take fewer feedings at night, and who are less likely to gain excessive weight in the first year of life. The intervention teaches parents to be appropriately responsive to their baby’s needs, in particular, to learn to identify infant hunger and to use feeding to soothe only when the infant is hungry, and to use alternative soothing techniques in response to other distress. I do think that pregnancy and new parenthood are ‘teachable moments’. However, although excessive weight gain in infancy is a risk factor for obesity, most new parents are not particularly concerned about their infant becoming obese. They have more immediate challenges to deal with! Most are motivated to be good parents, who are able to soothe and care for their infant, and we think this will help to motivate compliance; time will tell. There is a large body of evidence that responsive parenting is associated with positive cognitive, emotional, and health outcomes in children. We are hypothesizing that another benefit of responsive parenting will be to prevent excessive weight gain in infancy.

*Dr. Talamini:* You mentioned that your pilot study with mothers and infants provided mothers with soothing strategies. In your current study, will you offer age-appropriate soothing strategies for alternatives to food?

*Dr. Birch:* Yes, that’s right; the idea is during the first 3 months to teach them swaddling and use of white noise, which are effective approaches to soothing and calming young infants. However, for older infants and young children, swaddling is no longer effective and other strategies are needed. It’s easy and effective to use palatable foods to soothe infants and to use food to control older children’s behavior, and parents need guidance on effective alternatives to the use of food to soothe or control behavior.
**Dr. Rolls:** There must be huge cross-cultural differences in these early practices. Has anybody been exploring those and tried to tease out what effect they have on eating behavior?

**Dr. Birch:** There are a few classic anthropological studies that have described cultural differences in feeding practices, but they have not tended to focus on effects on eating behavior. I am not aware of current research on the topic. In his classic anthropological work, Robert LeVine reported on differences in parenting practices among cultural groups in Africa. One of the major points he makes is that parenting practices differ across groups to the extent that perceived threats to children's health and well-being differ. Parenting practices are attempts to protect children from perceived environmental threats to children's health. So, for example among groups who experience periodic famine or food scarcity, parents are concerned that children get enough to eat when food is available, and they may deliberately ignore hunger and fullness cues in their children, and overfeeding is common and may include offering food in response to any infant distress, force-feeding, and offering preferred foods when available. However, although a major threat to children's health these days is too much food or too much of the wrong foods, these traditional feeding practices persist, particularly among low-income groups at high risk for obesity. In ongoing research, we are finding that these traditional feeding practices are reported by Pennsylvania WIC mothers, many of whom have probably lived in environments where food is scarce, at least periodically. If parenting practices are a response to parents' perceived threats, then to change these traditional overfeeding practices, we need to change parents' perceptions. Simply telling them to use different strategies won't be sufficient.

**Mrs. Wangsgaard:** Have recommendations changed over the years concerning the order in which solid foods should be introduced? Does it matter in terms of their gut?

**Dr. Birch:** This is still an area of controversy, perhaps because guidance on order of introduction of solid foods is not evidence based. However, there is an ongoing multisite trial that should provide evidence soon.

**Dr. Goran:** Dr. Rolls, I think you mentioned a good point in terms of cultural differences. There is pretty good evidence, I think it's from a national longitudinal study of growth that the separation of obesity by ethnicity occurs early. We have shown in our WIC population that an increase in obesity is occurring by age 2 years in Hispanic children, whereas the increase occurs later in African-American populations.

**Dr. Birch:** The patterns of early obesity seen in NHANES data differ by gender between Hispanic and African-American children. To me, this suggests that differences between Hispanics and African-Americans in feeding practices may be responsible, but NHANES doesn't provide any direct evidence on differences in feeding practices. In particular, among African-Americans, girls are heavier than boys but among Hispanics, boys are heavier than girls. To me, this seems unlikely to be genetic; it's very likely that this difference is culturally driven.

**Dr. Finagood:** What is your sense about the impact of social media and the Internet on people's practices? Is it actually helping or is it creating more confusion? Are people adopting better practices?

**Dr. Birch:** In terms of impact, I don't really know. However, in doing our own search of what's out there, we found an amazing number of websites, blogs and YouTube videos related to infant care and feeding, and these varied greatly in information provided and in the extent to which they were evidence based. All this information could be very
confusing to new parents; being a new parent is challenging, and parents are looking for information. We found lots of information on some topics but little on others. For example, while there is conflicting guidance across sources about introducing solids, there is very little guidance on bottle feeding. We found limited guidance on how much to offer infants of various ages or on how to select appropriate bottles and nipples for infants of different ages/stages. Choosing appropriate bottles and nipples is important because although breastfeeding requires that the infant is an active participant, a bottle-fed infant can be more passive, and it is easy to overfeed a bottle-fed infant. Parents need guidance to recognize hunger and fullness in their infant, and to use these infant cues during feeding.
The Economics of Food Choice Behavior: Why Poverty and Obesity Are Linked

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Abstract

Obesity in the United States does not affect all segments of the population equally. It is more prevalent in deprived neighborhoods and among groups with lower education and incomes. Inequitable access to healthy foods is one mechanism by which socioeconomic factors can influence food choice behaviors, overall diet quality, and bodyweight. Having a supermarket in the immediate neighborhood has been linked to better diets and to lower obesity rates. However, the affordability of healthy foods may have more of an impact on food patterns than does distance to the nearest store. Grains, added sugars, and added fats are inexpensive, good-tasting, and convenient. Their consumption has been linked to lower quality diets, lower diet costs, and lower socioeconomic status. By contrast, the recommended healthier diets not only cost more but were consumed by more affluent groups. New techniques of spatial analysis are a promising approach to mapping obesity rates and linking them with measures of socioeconomic status based on diverse social and economic aspects of the built environment. Low residential property values predicted bodyweights of women better than did either education or incomes. Shopping in low-cost supermarkets was another powerful predictor of bodyweight. Bodyweight gain may be best predicted not by any one nutrient, food or beverage but by low diet cost. Higher obesity rates in poor neighborhoods may be the toxic consequence of economic insecurity. Alleviating poverty may be the best, if not the only, way to stop the obesity epidemic.

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Introduction

The obesity epidemic in the United States has been linked to the changing food environment. Studies have linked rising obesity rates with a growing consumption of energy-dense foods, sweetened beverages, and selected dietary ingredients [1, 2]. Much research attention has focused on the consumption of added
sugars and fats and on the role of snacks, beverages, fast foods, large portion sizes, and eating away from home. However, pinpointing which dietary factors are directly responsible for obesity has proved difficult. Food patterns are the result of complex interactions between the person and the social and economic environment [3]. Although individual behavior is clearly involved, diet quality is reliably predicted by education, occupation, incomes and by other, often unobserved, indices of social class.

Obesity rates in the US are not equally distributed across all social strata [4]. Instead, higher rates are observed among some minorities and groups with lower education and incomes [1, 4, 5]. Minorities and the poor are clearly at a disadvantage when it comes to the adoption of healthier eating habits [6]. Local disparities in access to healthy foods may be one problem. Studies on ‘food deserts’ [7] have shown that lower income neighborhoods attracted more fast-food outlets and convenience stores as opposed to full-service supermarkets [8]. By contrast, wealthier areas had access to better restaurants, fresher produce, and more opportunities for physical activity.

Socioeconomic variables, including those in the built environment, have a profound impact on bodyweights and health [9, 10]. Yet, greater distance to the nearest supermarket may not fully explain why obesity rates are much higher in poor neighborhoods [7]. That explanation may involve food affordability and food cost. Simply put, on a per calorie basis, grains, fats and sweets cost less, whereas many healthier and more nutrient-dense foods cost more [1, 11]. In recent analyses of US federal data sets, higher quality diets were associated with higher per calorie diet costs, and were more likely to be consumed by wealthier and better-educated persons [12]. In other studies, the observed influence of socioeconomic status (SES) variables on diet quality, so often attributed to nutrition education, was partly explained by diet cost [13].

Obesity research in the US has steered clear of the complex issues of poverty and social class, preferring to deal with individual-level genetics, metabolism, physiology, or behavior. One concern has been that if obesity becomes a problem of the disadvantaged and the poor, it will no longer command national attention. However, effective obesity prevention and treatment strategies critically depend on knowing the environmental context of the national obesity epidemic. Knowing who is most likely to become obese, where and why, is an essential prerequisite to designing effective strategies for obesity prevention and treatment.

**Poverty and Obesity Are Linked**

Obesity rates in the US are linked inversely to education and incomes [4]. However, the observed socioeconomic gradient has not been very steep and, other than for white women, not always readily apparent. Some researchers
have emphasized that obesity trajectories were similar for all groups, with obesity rates increasing steadily in both sexes, across all ages and races, and at all incomes and educational levels [4]. By contrast, others have noted divergent trajectories and a growing social gap in obesity rates among children. Whereas obesity rates among children from the highest SES group declined between 2003 and 2007, children from the lowest SES group continued to gain weight [5].

Measuring the social gradient in health and bodyweight presents many challenges. Whether past education and current income measures adequately capture the multiple aspects of SES is unclear. Several researchers believe that these two measures are insufficient to explain the observed influence of social position on long-term bodyweight [14, 15]. Some have tried to supplement the existing measures with new metrics of economic insecurity and with measures of area-based deprivation versus long-term wealth.

Geographic mapping of obesity rates at a sufficiently fine geographic scale offers new insights into the social and economic determinants of health [16]. Existing approaches to mapping obesity rates by state, county, or metropolitan area tend to obscure SES distinctions by neighborhood. Whereas state- and county-level obesity maps issued by the Centers for Disease Control are well known, fewer studies have mapped obesity rates by political districts, health planning areas, zip codes, census tracts or by neighborhoods. Where such data do exist, the link between high-obesity and high-poverty census tracts becomes more apparent.

Figure 1 shows the joint distribution of obesity and 150% poverty by census tract for Seattle King County. Although King County is reputed to be healthy overall, the local disparities in obesity rates by census tract ranged from 5 to over 30%, a 6-fold difference. The map also makes it clear that high poverty and obesity rates shared the same geographic location.

One problem with area-based data is that the links between obesity and the built environment depend on the type of geographic aggregation and may require complex multilevel analysis. Whereas data on poverty and wealth at the census tract level can be readily obtained from the US Census, health and weight data at that level of geographic resolution are exceedingly rare. As a result, we still have an imprecise understanding of the spatial distribution of obesity and its links to poverty and social disadvantage.

New techniques of spatial analysis may help remedy this problem. The geocoding of addresses of health survey respondents allows for more sophisticated spatial analyses of obesity at the individual level [16, 17]. For example, the addresses of participants in the Seattle Obesity Study (SOS) were geocoded to the centroid of the home parcel using the 2008 King County Assessor parcel data. Geocoding followed standard methods in ArcGIS, version 9.3.1. Spatial cluster detection analyses were then used to identify significant obesity clusters in lower income neighborhoods. Relevant neighborhood features included
residential property values, residential density, traffic volume, density of fast food and quick service, intersection density, density of broad-selection food stores and access to parks and trails. SmartMaps, created by the Urban Form Lab, transformed these neighborhood features into spatially continuous values for each study participant, without any need for geographic aggregation.

Fig. 1. Joint geographic distribution of obesity (BMI >30) and 150% poverty rates in Seattle King County by census tract.
In other words, studies of the impact of neighborhood variables on bodyweights and health can now be conducted at the individual level.

Residential property values became the variable of most interest, given that home equity for most Americans represents the bulk of their wealth. Obtained from county tax rolls, property values for study respondents may be a more accurate measure of individual socioeconomic position than provided by either education or income [16]. Based on objective tax data, rather than on self-report, residential property values provide an additional link to neighborhood resources, including access to food sources and local opportunities for physical activity.

Spatial analyses, based on individual-level metrics of the built environment offer a new way to map the geographic distribution of obesity and health behaviors across neighborhoods [17–19]. Such methods also permit a new look at the social, economic and environmental determinants of obesity and self-reported health. In the SOS, consistent inverse associations were obtained between obesity and low residential property values [17]. In analyses based on standard regression models, residential property values were the best predictor of bodyweight of women, adjusting for individual-level education and incomes. In contrast, and consistent with other data, property values had no impact on bodyweights of men.

The disparity in obesity rates among women by property values was more than 3-fold (300%). By contrast, the observed disparities in obesity rates by race/ethnicity, education, or incomes are normally in the order of no more than 20–50%. Property values are a potentially useful and novel metric of wealth for health studies. These new measures point to a strong social gradient in obesity rates across neighborhoods.

**Access to Healthy Foods: Proximity or Price?**

Having a supermarket in the immediate neighborhood is reported to affect diet quality, bodyweight, and other health outcomes. Studies have noted that people living in low-income or minority communities had limited access to full-service supermarkets and to grocery stores selling healthful foods. Some of those studies were conducted in Detroit, Philadelphia, New Orleans and Los Angeles county, areas often characterized by racial segregation, poor housing and inadequate food supply.

Much of the existing research on obesity and access to healthy foods has relied on two assumptions, both of which may hold for some cities but not others [20]. Lacking data on where people actually shopped for food, researchers were forced to assume that most food shopping was done within the immediate neighborhood. Studies on the food environment and heath were then able to correlate the density of supermarkets or fast food restaurants in a given area with
measures of diets and health in the same area. Some studies used the street network distance to calculate the distance between the nearest supermarket and the participant’s home. In many such studies, physical distance between the home and the nearest supermarket was associated with healthier eating, lower body mass index values, and with lower rates of obesity and diabetes. Those studies became the principal research underpinning for many policies related to obesity prevention at the community level. Although the assumption about local food sourcing may have been correct, especially for people lacking transport, none of those studies had any information as to where people actually shopped for food.

There was a further reason why distance to the nearest full-service supermarket was the presumed predictor of diet quality. Here, the underlying assumption was that only supermarkets offered healthful foods, including fresh produce, at affordable prices. Even though supermarket prices can vary across store chains, as do client demographics, few studies looked for differences within the supermarket category by food quality or price.

The SOS was the first to address food shopping destinations and to identify those supermarkets and grocery stores that study participants reported as their primary food sources [20]. First, the locations of all food sources, including supermarkets were geo-coded, as indicated in figure 2. The geocoding of home addresses and food shopping destinations permitted the calculation of network distances between the participants’ homes, the nearest supermarket, and the supermarket that was their primary food source.

First, only 1 in 7 study respondents shopped at the nearest supermarket. Second, the distance from home to the nearest supermarket had no impact on obesity rates. Distance to the supermarket identified as the primary food source was also unrelated to obesity rates. These Seattle-based findings ran counter to the previous research consensus that physical proximity to supermarkets had a major influence on diets and health. That was clearly not the case in Seattle, where most people, admittedly, shopped by car [20, 21].

Characterizing supermarkets by price can help provide additional insights into the economic mechanisms behind the observed disparities in bodyweight. The Seattle supermarkets were assigned to three price categories, high, medium and low, based on the average cost of the market basket of 100 representative foods. The question asked was whether supermarket proximity or price would be more strongly associated with obesity rates, adjusting for individual-level demographics, education and income.

The results were dramatic. Shopping at low-price supermarkets was associated with far higher obesity rates (27%) than shopping at high-price supermarkets (9%), another 3-fold difference. The supermarket effect was significant even after adjusting for the standard individual-level SES variables, education and incomes [20]. The data suggest that supermarket selection, driven by food prices, may be another understudied aspect of SES.
The SOS data run counter to the overwhelming consensus is that physical proximity to supermarkets has a major influence on diet quality and health. In the SOS sample, most people did not shop in the immediate neighborhood, such that mere physical proximity to a store was not an accurate index of exposure. Furthermore, it appeared that the poor and the wealthy shopped farther than absolutely necessary, going up to three miles beyond the nearest store. The interpretation was that lower income groups drove farther in search of food bargains, whereas the wealthy drove to more expensive destination stores more commensurate with their SES.

These Seattle-based data need replicating in cities with different patterns of food shopping. Arguably, communities may be vulnerable to obesity and chronic disease not because the nearest supermarket is more than a mile away, but
because healthy food choice is not always the most affordable choice. Systematic efforts to improve diet quality by improving access to healthful foods will need to take economic inequalities into account.

The Economics of Food Choice Behavior

Food choices are made on the basis of taste, cost, convenience, health and variety [22]. Taste refers to the sensory appeal of foods, such as palatability, aroma, and texture. The concepts of taste and energy density are intertwined, since the most energy-dense foods are usually the most palatable and vice versa. Energy density of foods is defined as energy per unit weight or volume (MJ/kg) [23, 24]. Cost refers to the purchase cost per unit of energy (USD/10 MJ) or the purchase cost of a daily diet (USD/day). Convenience refers to the time spent on buying, preparing, and cooking food. Variety refers to the innate drive to secure a varied diet, whereas health refers to concerns with nutrition, chronic disease, and bodyweight.

The low cost and high palatability of energy-dense foods could help explain why higher obesity rates are found among lower income groups [23, 24]. Grains, fats and sweets are good-tasting, satisfying, accessible, and convenient. In general, grains, fats and sweets cost less per calorie than do lean meats, vegetables and fruit (fig. 3). Clinical and laboratory studies suggest that energy-dense foods have a lower satiating power, and may lead to passive overeating and weight gain.

For those reasons, rising obesity rates have been blamed on the food environment. Energy-dense diets, increasing portion sizes and the consumption of

Fig. 3. Relation between energy density (kcal/100 g) and energy cost (USD/100 kcal) denoting the relative positions of the different food groups. Median data by group are from US Department of Agriculture Food and Nutrient Database for Dietary Studies (FNDDS 2.0).
fast foods, snacks and beverages have all been linked at one time or another to obesity risk. Again, physiological mechanisms regulating food intake were generally thought to be at fault. Whereas some studies suggested that humans failed to compensate for calories in liquids, other studies invoked incomplete compensation for solid energy-dense foods.

By contrast, there has been relatively less research emphasis on the obese persons’ *economic* environment. With the exception of studies on healthy food patterns conducted by the US Department of Agriculture [25], US-based research on diet cost in relation to health outcomes is very limited [11, 12, 26]. Existing studies, some based on econometric modeling, do suggest that constraints on food expenditures may contribute to the obesity epidemic, especially among lower income groups. One hypothesis, grounded in the economics of food choice behavior, is that individual weight gain is best predicted not so much by the consumption of any one food or any one nutrient but by low overall diet cost.

**The Cost of Eating Healthy**

Diet quality, both in the US and elsewhere, is a function of SES. It is well known that older and wealthier consumers have higher quality, healthier, and more varied diets, with more high-quality meats, seafood, vegetables and fruit [24]. In contrast, lower income households tend to select diets with lower cost meats, inexpensive grains, and more added sugars and fats. The observed influence of SES on diet quality may be explained, in part, by diet cost.

In the SOS, usual dietary intakes of a representative sample of 1,295 adults in King County (WA) were assessed based on a food frequency questionnaire [13]. Energy density (kcal/100 g) was calculated using food composition tables. The monetary value of individual diets was estimated using local retail supermarket prices for 384 foods. A column of prices in USD/100 g edible portion was added to the nutrient composition database. Local prices were attached to 384 FFQ component foods. Prices were obtained for those foods that were most frequently consumed and for the lower cost options, including frozen and canned foods. The underlying assumption in calculating diet costs was that all foods were purchased at retail and then prepared and consumed at home. Analogous assumptions are made by the US Department of Agriculture in calculating the cost of healthful diets, including the Thrifty Food Plan [25].

Mean cost per edible portion of food was calculated, after adjusting for preparation and waste, and was used to estimate the cost of daily diet. Nutrient quality of the diet was based on nutrients of concern as identified by the 2005 Dietary Guidelines: fiber, vitamins A, C and E, calcium, magnesium and potassium. The more costly diets were associated with a higher consumption of fruit and vegetables and with lower consumption of grains, fats and sweets, after adjusting
Regression analyses showed that intakes of the 7 nutrients and the overall nutrient density of the diet were significantly associated with higher diet costs.

Both diet quality and diet cost were then directly linked to the participants’ SES. Overall diet quality, as measured by nutrient density scores, was significantly higher for the highest education group than for the lowest education group. However, higher quality diets were also more expensive. Estimated diet cost for the highest education group was USD 1.09/day higher than for the lowest group (USD 9.28 vs. USD 8.19, p trend <0.001). Similar cost trends were observed across income strata. These SES-related differences in diet quality were attenuated once diet cost was introduced into the model.

The impact of SES on weights and health is thought to be mediated by diet quality [26]. One interpretation of the observed social gradient has been that higher SES groups have more nutrition knowledge. The present findings shifted the focus from education to the affordability of healthy foods: the observed disparities in diet quality by SES were partly explained by the fact that healthier diets cost more. The higher cost of adopting a healthy diet may pose a barrier to dietary change and may contribute to the observed social disparities in body-weights and health.

Such profound disparities may not be remedied by small shifts in income or by minor manipulation of food prices. A USDA study showed that low-income households spent about USD 1.43 less per person per week on fruit and vegetables, as compared to higher income households. Whereas higher income households did increase fruit and vegetable consumption following an increase in income, lower income households did not. One interpretation is that fruit and vegetables were not a priority and that low-income households chose to spend limited resources on more essential items such as meat, clothing, or rent.

### Why Poverty and Obesity Are Causally Linked

A systems approach that incorporates diets, lifestyles and environmental factors is clearly required to deal with the obesity epidemic. To date, obesity prevention and treatment strategies still focus on the individual [27]. Food-seeking behaviors of obese persons continue to be viewed through the prism of physiology and medicine. Excess consumption of added sugars and added fats has been explained using such concepts as satiety deficits and passive overeating. The consumption of sweets and desserts has been explained in terms of an addictive personality, stress, depression, and seeking comfort in high-fat foods. Frequent consumption of palatable sweets and fats has been explained through the mechanisms of ‘cravings’ and neurotransmitter imbalance.

The present hypothesis is that the observed links between poverty and obesity are largely economic. What refined grains, added sugars and added fats have
in common is their low cost. Diets of lower income households provide cheap, concentrated energy from fat, sugar, cereals, potatoes and meat products – but offer little in the way of whole grains, vegetables and fruit. Low-income consumers are more likely to live in areas with limited access to healthier foods and to be users of fast-food as opposed to full-service restaurants. The failure to select healthy diets has been explained in terms of economic conditions that include limited physical access to supermarkets and grocery stores and the time spent commuting to work.

There is accumulating evidence that obesity tends to cluster in poorer neighborhoods. Going beyond education and incomes, the SOS examined the influence of neighborhood type, property values, and supermarket choice on the participants’ bodyweight. Preliminary analyses suggest that SES variables were extremely powerful and were more strongly linked to obesity than were diet-related variables. In other words, the new measures of SES accounted for more variance in obesity rates than did energy density or the macronutrient composition of the diet.

Adopting a healthy diet may pose an economic as well as a behavioral challenge. Some of the current strategies for obesity prevention do not recognize that healthier diets can cost more. Some years ago, the NIH Obesity Education Initiative advised obese patients to look for guavas, persimmons, star fruit, kiwi, and papaya as opposed to bologna and American cheese. Dietary Guidelines 2010[27] recommended a healthful assortment of foods that included vegetables, fruit, whole grains, low-fat milk products, and fish, lean meat, poultry or beans. The 2010 Guidelines further emphasized foods that were unprocessed, fresh, and contained little sodium and no added sugars and fats. It is a matter of some concern that those obesity prevention strategies are largely based on recommending high-income diets to low-income people.

Studies conducted in Australia, Canada, and the EU contrast with the prevailing US view that healthful diets do not represent any additional expenditure to the consumer. In a French study, diets with a higher content of vitamins and minerals were associated with higher diet costs. In fact, lower energy density and higher nutrient density were each independently associated with higher energy adjusted diet costs. In other modeling studies, based on linear programming, attempting to reduce daily diet costs without taking diet quality into account led to energy-dense diets composed of grains and sweets that were similar to those already consumed by lower income groups. Although spending more does not assure a good diet, reducing diet costs below a certain minimum virtually assures that the resulting diet will be energy rich but nutrient poor.

Based on recent analyses of federal data sets, evidence is emerging that higher quality diets as measured by the Healthy Eating Index (HEI) cost more. Higher HEI scores were associated with higher diet costs, higher incomes, more education, and with lower rates of obesity.
The Economics of Obesity

Economic and food policy interventions at the national and international levels are the most promising approach to obesity prevention. The UK Foresight Report [28] outlined a multisector multilevel strategy that involved all branches of government. However, stemming the obesity epidemic cannot be separated from stemming the tide of poverty. The rising obesity rates may reflect the increasingly unequal distributions of incomes and wealth [29]. Evidence is emerging that obesity in America is a largely economic issue.

Acknowledgements

This work was supported by NIH grants DK076608 and DK085406.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the chapter.

References

Discussion

Dr. Finegood: I think the take-home message I just got is that if I am poor, I should still try to own a home and shop at Whole Foods so I don't have the money to eat, is that it?

Dr. Drewnowski: No.

Dr. Finegood: Obviously, I am being a bit facetious.

Dr. Drewnowski: We found that people's attitudes towards healthy food were the most important predictor of diet quality. If people wanted their diets to be healthy, then they had more nutrient-dense diets, regardless of where they shopped. In other words, it is possible to select nutrient-dense foods even within a low-cost supermarket. We are now doing second-level analyses trying to determine whether or not health-related attitudes determine food choices within the supermarket at all levels of income.
**Dr. Finegood:** There are a couple of things that are interesting here, such as the 8-fold difference in obesity rates by supermarket. But there is not an 8-fold difference in the cost of food in those supermarkets. The question is: now that you have this detailed ability to look at the spatial relationships, have you tried to look at low-income neighborhoods that are in closer proximity to high-income neighborhoods versus the ones that are not? Even if you do not have money, but live in proximity to a high-income neighborhood, will you be in better shape?

**Dr. Drewnowski:** We have a grant from the National Institutes of Health to set up a longitudinal cohort for a study of food shopping, obesity, and weight gain. We are doing address-based sampling stratified by ranges of property values. That will allow us to look at residential locations that are of comparable value but far apart, and those that are close together in space but very different in value. In Seattle, people of different SES who live in homes with different property values can live in neighborhoods in close proximity to each other. They may even be using the same neighborhood shops and other resources. We plan to attach GPS tracking devices to 400 people in our longitudinal cohort to flag where people shop and where they eat. We want to find out where in the neighborhood the calories are coming from on a regular basis. We want to know where our subjects get their food, how they schedule their supermarket trips, and whether they eat or shop on the way to or from work or school.

**Dr. Bray:** Do you have any information about their history of SES? For example, if someone grew up poor, but is now educated and wealthier, will they still have the profile of a poor person?

**Dr. Drewnowski:** We do not have enough power in our sample to test this hypothesis. We have data on length of residence at the current address, age, and education, so we might be able to figure it out. We found that the leanest people in our sample were women who lived in expensive homes and did not work. We are trying to figure out how SES variables affect food choices.

**Dr. Warshaw:** You have this sample of Seattle, but how generalizable do you think this is?

**Dr. Drewnowski:** Seattle is not typical of the US, but neither is Detroit or New Orleans, where a lot of the data on food deserts came from. We are conscious of the potential differences between the cities, because in Seattle people even from low-income households had access to a car, even those living in a food desert. Our subjects mostly shopped in a supermarket once a week; that supermarket was 10 min drive or less. Some people went much farther to big wholesalers, but they went once a month. So, we do have data on the frequency of grocery shopping and distance to the store; we have the demographic profiles of the shoppers, and we know who goes to wholesalers versus high-end grocery stores. There is so much more to know about food shopping and the local context. Even though our data are for Seattle and not the US, our techniques could be applied to other cities in the US. For example, I would expect to find similar distributions of obesity rates in rich versus poor neighborhoods. We are also doing studies of food shopping in Seattle versus Paris.

**Dr. Ochoa:** Is the individual of a high economic class more obese now than 30 years ago or 60 years ago? We know that there have been changes in different geographic regions of the world in what people eat, how they live, and what they die of.

**Dr. Drewnowski:** The patterns of obesity and disparity are different as well. It is the lower income groups in the US who are more obese and the higher income groups who
are less obese. This pattern is reversed in developing countries. For minorities in the US, things become more complicated because in some cases the more affluent minority numbers are more likely to be overweight or obese. There is also the issue of obesity trajectories, and here opinions vary. In the US, obesity data seem to show that all SES groups are getting obese at the same rate, so that all the trajectories are rising in parallel. Data from Europe suggest, to the contrary, that the social disparities are actually increasing. So whom do you believe? In France and in other countries, the poor are becoming obese but the rich are not, or not nearly as fast. So the divergence by SES between the US and the EU is interesting, I am not sure what the final word is. The consensus in the US seems to be that everyone is getting more overweight at the same rate.

Dr. Johnson-Askew: Have you had an opportunity to look at those people in your region that are poorer, or look at those who own their home versus those who do not? The other question is whether you have adjusted for fast food density in your study.

Dr. Drewnowski: We have data on lower income groups. Lower income households live in areas with lower property values, and we can track those by their geographic location. Seattle is not particularly segregated, so that low-income areas cannot be associated with any particular race or ethnicity. We do have geocoded data on the locations and the density of fast foods. We can also distinguish between the fast food restaurants that were closest to our participants’ homes and the ones that they actually went to on a regular basis. The two were not the same. The fast food restaurants that were actually frequented were not even in the immediate neighborhoods. So that is very interesting from the standpoint of public policy. The current strategies to build more supermarkets and take fast foods away are all based on the premise that people shop and eat near where they live. That may not be the case. People make shopping and eating decisions for many reasons. Physical proximity is just one of them.

Dr. Oppert: If I understand correctly, you don’t believe in the food desert concept.

Dr. Drewnowski: No, I don’t believe in food deserts in Seattle. I am prepared to believe that the concept of food deserts is very real in places like New Orleans after Katrina or in Detroit, especially if people have to walk to get the food. It’s just that in Seattle, with our distribution of food sources and our study population, we did not see that. We have submitted a manuscript where we added the transportation component and car ownership to the definition of food deserts – currently thought of as census tracts with low income and distance of more than a mile to the nearest supermarket. We added the mode of transportation: food deserts expand or shrink depending on whether you walk, bike, take the bus, or drive. So, if you walk, there will be places where the nearest supermarket is more than 10 min away. But if you bike, take public transport or go in a car, then pretty much every residential address in Seattle can access a supermarket within 10 min. It may not be the right supermarket but there is a supermarket.

Dr. Oppert: You also showed that some fast food outlets were clustered.

Dr. Drewnowski: Driving influences development.

Dr. Oppert: So, don’t you feel that we are just following what people have done when they have built these food outlets along the major roads?

Dr. Drewnowski: Most of the fast food restaurants were clustered along big arterial roads in a ribbon pattern and did not necessarily target middle schools or low-income areas. Restaurants, including fast foods, tend to locate where the people are, which is something that people in the business world already know about. The location of food
sources depends on traffic patterns and on arterial roads. I should mention that we in Seattle are very lucky. We do have a number of low-cost ethnic restaurants and some local food markets, so the food supply is good. From that standpoint, Seattle is not a typical place, but we think it is representative of the US.

Dr. Rolls: Do you know if food assistance programs have any impact on these relationships?

Dr. Drewnowski: That’s what we hope to address in the follow-up study. In our first sample, we didn’t have enough people on food assistance to be able to come to any conclusions. I can’t answer that question based on existing data from the Seattle Obesity Study.

Dr. Rolls: Do you have food intake data?

Dr. Drewnowski: Yes we do. We have food frequency questionnaire data for everybody. We have also attached food prices to the food frequency questionnaires so that we can estimate diet cost.

Dr. Rolls: So, the people who want to eat a healthier diet are choosing healthier foods. Are they spending more, and if they are spending more where are they getting the money?

Dr. Drewnowski: Our estimates of diet cost showed that healthier diets did cost more. People who wanted to eat a healthier diet had higher quality diets, and those diets did cost more. So, it was just a relative change in spending on food.

Dr. Rolls: So, you don’t know where they would get the money to spend more?

Dr. Drewnowski: These were relative differences across SES strata. Some people did not mind spending more money to get better foods. In fact, spending more money on food is not a bad idea, given the high cost of medical care and other consequences of poor diets. Another thing is that although healthier diets are normally more expensive, they don’t have to be more expensive. There were people in our sample who were eating nutrient-dense diets at low cost, and we are trying to find out who they were and what they were doing right. That is because the relation between nutrient quality and diet cost is highly variable; whereas some people seem to get good nutrition value for their dollar, others do not.

Dr. Jakicic: It’s interesting that you know the different grocery chains. We have all been in these various chains, and we know their different layouts as you go in. Is it the food selection, is it what they offer, or do you think there are major differences in how Safeway is laid out compared to Whole Foods? There may be differences in terms of what is at the end of the aisle, what is at the eye level versus what is on the bottom shelf. I know that, at least in our place, the brands pay the grocery chain to have their products in a better location. I wonder: is there a difference in marketing that may help to explain some of this?

Dr. Drewnowski: Usually supermarkets are laid out in the same way, with processed foods in the middle and fruits and vegetables and meat and dairy on the perimeter. The dietary strategy to: ‘shop the perimeter’ is deservedly popular, because that is where the most nutrient dense foods are. We are actually doing a project with the art school to map the nutrient density of foods by supermarket aisle. If you want cheap sources of potassium, which aisle do you go to? Do you go toward the aisle with the canned fish or toward the vegetables, or the fruits, or the potatoes? We need to know how shoppers use the supermarket layout once they are inside.

What’s interesting here is that some supermarkets were shopping destinations whereas other were not. People would drive for miles to go to a specific supermarket,
bypassing many others on the way, so there must have been something special about those stores. I think that every supermarket would like to distinguish itself in some way and become the preferred shopping destination for people coming in from all over the place. We were able to create some interesting shopping polygons to map each supermarket's service area. We found that adjoining supermarkets could serve customers of very different SES.

Dr. Barclay: I am trying to understand why low-income populations are choosing not only cheaper but also less healthy foods. Is it about education? Should supermarkets help people to monitor their health? Should the processed food industry focus on improving the nutritional quality of lower cost foods?

Dr. Drewnowski: It was not all about money. There were people who were going to low-cost supermarkets but who were still selecting a nutritious diet. There are other aspects of culture, lifestyles and attitudes that affect food selection. Whether the answer lies in education, health promotion, price interventions, supermarket interventions, or food fortification, I can't tell you at this point.

Whatever the best solutions to obesity prevention are, they need to come from the ground up and be a part of a systems approach. Grassroots initiatives are better than government-imposed taxation, prohibition, or legislation. Something has to happen to shape consumer behavior for the better. In our research, we are just beginning to delineate food shopping behavior. I know that the easy answer is to build more supermarkets, but bringing a supermarket half a mile closer may not affect shopping or eating behavior all that much.

Dr. St. Jeor: This is fascinating data, and how it comes together is quite complex. I was just curious if you are working with the food industry. What about commercial development done by city planners because they must be ahead of this in one way or another? And finally, how do you plan to interpret your findings to benefit the obese or the non-obese population?

Dr. Drewnowski: We have not worked with a supermarket chain on this research project, but I think that will come. We do work with researchers in architecture and in urban planning and with the local transportation people and with the Seattle city planners. That is our new audience in the area of obesity prevention. We are interested in working with supermarkets and grocery stores as potential partners in fighting the obesity epidemic. National statistics show that 62% of calories in the diet of adults were purchased in a grocery store. By contrast, the amount of calories supplied by fast foods or vending machines is very small. National statistics also show that 72% of added sugars are purchased in a grocery store. Supermarkets and grocery stores are the main sources of calories for obese and lean people.

Dr. St. Jeor: But do you have a plan? How can you put some of your findings into action to help with this problem?

Dr. Drewnowski: Our research relates to food systems and food policy. It tells us that looking at food retail is very important. Showing where the calories are coming from is an important and overlooked component. The environmental and socioeconomic factors can also supplement the data on the physiology of obesity that we already have. In the systems approach, everything is interconnected. There are many leverage points that can be used to improve diets.

Dr. Finegood: I am still stuck on that 8-fold difference in obesity rates by supermarket chain, and I am wondering whether the obese people who live in high-income...
neighborhoods go out of their way to find a grocery store where they are going to feel more comfortable because there is a social norm for obesity?

Dr. Drewnowski: We can look at that. We have data on obese persons in lean neighborhoods and lean persons in obese neighborhoods. You may think that an obese person in a lean neighborhood may be more stressed because their bodyweight does not correspond to the norm for their census tract or their immediate neighborhood or zip code.

Dr. Finegood: Do they go out of their way to shop where they are going to feel more at home?

Dr. Drewnowski: That could be. But in Seattle, upper income people lived farther away from any kind of food store and were thinner. So, the distance to the store was not a major determinant of bodyweight.
The Importance of the Food and Physical Activity Environments

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Abstract

There is increasing interest in identifying characteristics of neighborhood environments (physical, social, economical) that might favor unhealthy dietary and physical activity patterns leading to excess weight at population level. Measurement of characteristics of the physical environment in relation to food and physical activity has greatly improved in recent years. Methods based on assessment of perceptions by residents of their neighborhood or on objective assessment of the actual built environment (such as provided by Geographic Information Systems tools) would benefit to be combined. A number of recent systematic reviews have updated our knowledge on relationships of food and physical activity environments with relevant behaviors and obesity. Available evidence appears to show more consistent evidence of association between built environment characteristics related to physical activity ('walkability' indices, land use mix, variety of transports. . .) with physical activity behavior than with weight status. In contrast, built environment characteristics related to food habits (accessibility to different types of food outlets, availability of healthy foods. . .) would be more consistently associated with weight status than with eating behavior. The need for data from different countries and cultures is emphasized, as much as the importance of transdisciplinary research efforts for translation of these findings into our living environment.

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Introduction

The development of socioecological models of health behaviors in the last two decades [1] has promoted environmental factors as key players in our thinking about obesity prevention and treatment [2]. For example, integrated maps about
obesity development emphasize the potential role of ‘activity environment’ alongside ‘individual activity’ as major clusters of interest in systems thinking on obesity [3]. There is therefore increasing interest in identifying the characteristics of neighborhood or local environments (physical, social, economical) that might favor unhealthy dietary and physical activity patterns leading to excess weight and obesity at the population level.

Our focus in this paper will be on the potential influence of the characteristics of the living environment (social, built), with a special emphasis on physical and infrastructural aspects. Dietary behavior may indeed be modified by spatial accessibility to food items through the patterns of implantation of various types of food outlets and services. Similarly, physical activity behavior may be influenced by access to recreational or sports facilities, green spaces or parks as well as transport infrastructures and land use [4]. Access has been recognized however as a complex construct that associates different dimensions such as availability (number, density of outlets), proximity (referring to distance and travel), diversity (referring to the types of services available) as much as affordability [5]. This applies to the concept of access in general but also to access to services related to eating or physical activity habits.

In the following text, we would like to briefly address some issues related to (1) the measurement of food and physical activity environments, (2) the current knowledge on the relations of attributes of the environment with behaviors and weight status, and (3) the possible implications for interventions and prevention.

Assessment of Relevant Attributes of the Food and Physical Activity Environments

Measurement of characteristics of the physical environment potentially related to eating and physical activity habits has greatly improved in recent years. A number of methods are currently used, based either on assessment of the perceptions by individual residents of their neighborhood, or on an objective assessment of the actual environment [6, 7].

Objective measures mainly rely on preexisting inventory databases and business directories or, in some cases, on environmental audits, which consist of sending trained raters with checklists to document specific aspects of the physical environment. Among objective approaches, spatial analysis methods based on geographic information systems (GIS) have opened up a new era of research in the field of public health nutrition [8]. GIS are computer-based methods and tools which, via different information sources, enable organizing, managing and combining spatial and thematic data, and representing and analyzing results according to geographic location [9]. Using GIS tools, analyses can be carried out to model spatial interactions between different types of information.
In the framework of a research project ongoing in France – the ELIANE (Environmental LInks to physical Activity, Nutrition and hEalth, www.elianeproject.eu) study – we recently performed and published a systematic review of the literature to investigate which GIS methods had been used to define the food environment and what type of spatial measurements were generated [8]. In total, 29 papers were included in the review. The aim of these studies was either to compare food outlet spatial accessibility between different neighborhoods or to investigate relationships between characteristics of the spatial accessibility measures and individual food behavior. Two main approaches were identified. A first approach was focused on availability of facilities with the aim to quantify the number of food outlets using the buffer method, kernel density estimation or spatial clustering. The second approach was focused on proximity with the aim to assess the spatial accessibility to food outlets by measuring distances or travel times.

Based on this literature review [8], it was concluded that only some among many GIS methods available had been used, while other GIS methods combining availability and proximity, such as spatial interaction models, had not yet been applied to this field. As recently discussed by Salze et al. [10], spatial interaction models allow to compute access to facilities (such as food outlets or sports equipments) according to an inverse function of the distance from the resident home or work address (gravity-based models). Using such models makes it possible to overcome the limitations of the most frequently used indices such as the count of opportunities within a given neighborhood. Another way forward is to extend these models in order to take into account both home and work-based accessibility for a commuting population. This seems to be relevant to study the influence of environmental factors on eating habits in general, including food purchase and consumption.

Another conclusion from this methodological review on GIS measures of the food environment was that future research would benefit from a combination of GIS methods with survey approaches to describe both built and social environmental characteristics as important determinants of individual food and physical activity behaviors [8]. In particular, access to food outlets and physical activity resources may be limited by the subject's perception of the environment in one's neighborhood [11]. Therefore, the availability of healthy foods and physical activity opportunities as reported by residents (perception) and their availability as measured by GIS application (density) provide complementary information for characterizing the local food and physical activity environment. To better understand how features of the environment related to eating and physical activity behaviors are perceived, techniques such as asking residents to draw themselves maps of their neighborhood may help define their living space as seen by the subjects themselves. Information obtained by such (mental) maps can then be linked with physical activity measurements (e.g. accelerometers [12]) and/or GIS data. This field of research combining objective and subjective assessment seems particularly promising.
Recent systematic reviews have updated the status of knowledge regarding relationships of food and physical activity environments with relevant behaviors and obesity [13–15]. For the food environment, in the review by Giskes et al. [13] focused on obesogenic dietary intakes in adults (≥18 years), 28 original studies (from 2005 to 2008) were reviewed. Number of participants ranged from 22 to 1,000. Most studies originated from the US (n = 16), followed by Australia (n = 6), Japan (n = 2), the UK (n = 2), The Netherlands (n = 1), and New Zealand (n = 1). All but one were cross-sectional studies. Interestingly, among a total of 18 accessibility factors assessed, 16 were objective measures. An important finding emerging from this review is that current literature in adults appears to show more consistent evidence of associations between environmental factors and weight status than between environmental factors and obesity-related dietary intakes. Greater accessibility to supermarkets and lower access to takeaway outlets were found associated with lower BMI or prevalence of overweight/obesity. No consistent association was found between fruit and vegetable consumption and access to supermarkets or takeaway outlets, or availability/shelf space of fruits and vegetables. In contrast, area-level socioeconomic status was more consistently associated with healthier dietary behaviors. In children, based on objective measures of environmental factors, available evidence suggests that weight status is positively related to spatial accessibility to convenience stores, but findings with other food retail outlets and restaurants appear mixed [14].

For the physical activity environment, Ding and Gebel [15] performed a review of reviews on associations between built environment characteristics, physical activity behavior and obesity based on reviews published between 1990 and 2011. Among 37 reviews included for examination of their key characteristics, a vast majority (n = 27) dealt with physical activity and only a few with obesity (n = 5) or both physical activity and obesity (n = 5). Most reviews focused on youth (n = 12), and only 5 targeted adults and 2 senior residents. Very few reviews considered specific populations such as African-Americans, low socioeconomic or rural residents (n = 1 each) pointing to the need for more data in these groups.

Another recent review also emphasizes the fact that fewer studies have assessed associations of physical environment attributes with weight status than with physical activity [16]. In this latter review by Durand et al. [16], 5–10 times more studies assessed relations with walking behavior compared to BMI/weight status for environmental characteristics such as ‘walkability’ (composite indices usually including residential density, street connectivity and land use mix), mixed land use, variety of transports available, or density of built space. Moreover, if 30 to about 60% of associations between built environment characteristics were found in the expected direction with walking behavior, this...
proportion was reduced to only 10–20% for associations with BMI. Positive associations between accessibility to green space and both physical activity and weight status are also increasingly being reported [17]. Finally, in older adults, current literature appears inconsistent on the relation between walkability indices and physical activity [18].

Altogether, available evidence more consistently shows an association between built environment characteristics related to physical activity with physical activity behavior than with weight status, whereas built environment characteristics related to food habits would be more consistently associated with weight status than with eating behavior (table 1). The importance of combining perceived and objectively determined aspects of the environment has again been recently emphasized. Gebel et al. [19] observed that residents who perceived neighborhoods to be less walkable than objectively determined (through GIS) were less active, more obese and more likely to decrease physical activity and to gain weight over time than those with a more accurate environmental perception.

### Implications for Intervention Strategies and Future Research

Significant advances have been made in recent years regarding the theories and methods used to study the food and physical activity environments. However, we have to acknowledge that major challenges are ahead to better understand the complex pathways through which attributes of the built environment may impact weight status, in conjunction with neighborhood and individual socio-economic characteristics.

In terms of measurement, defining the size of the neighborhood in which the relation between environment and behavior operates remains a methodological issue, as much as ways to combine refined objective spatial measures (such as GPS) with assessment of how residents perceive their environment. The combination of data from multiple sources and obtained with different types of sensors will require the development of new data platforms for integration and analysis. Designing and implementing longitudinal studies are on the list of priorities,

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Table 1. A tentative synthesis of current knowledge on relationships between food and physical activity environments, corresponding behaviors and weight status.
as much as evaluation of ‘natural experiments’ such as re-location studies or opportunistic evaluations (including cost-benefit) of environmental interventions [20]. Wider use of refined analytical methodologies, including multilevel modeling, will be needed in attempts to identify causal relationships.

Regarding generalizability, it is likely that the effects of environment factors differ greatly across countries, cultures and climate. Since most studies were performed in the US, the UK or Australia, there is clearly a need for data from other regions and settings. Finally, to integrate findings about the physical activity and food landscape in a global picture including the social and policy environments appears very much in line with the current thinking on the prevention of non-communicable diseases [21]. The translation of findings from such trans-disciplinary research will not be possible without the input from all potential stakeholders, to assist in creating environments that are more conducive to regular physical activity, healthy eating and maintenance of a healthy bodyweight.

Acknowledgments

Part of the work of the authors reported in this paper is from the ELIANE study. ELIANE is a project supported by the French National Research Agency (ANR-07-PNRA-004, coordinator J.M. Oppert).

Disclosure Statement

J-M. O serves on scientific advisory boards for Vivus, Tanita, Institut Benjamin Delessert and has received funding from Fondation Le Roch (France).

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Discussion

**Dr. Drewnowski:** I was very interested to see the major differences in urban form between Berlin, Shanghai and New York. Context can be very important, and what we see in Seattle may not apply to Shanghai or to Paris. We need to do this kind of transdisciplinary transcontinental research to figure out which features of the food environment are common and which are unique to specific cities. It's an interesting question.

**Dr. Oppert:** Right, but you have to convince the funders.

**Dr. Finegood:** It seems that all this work on the causal mechanisms of obesity is not going to get us very far because it's not terribly transferable from one place to another. Shouldn't we get more focused on solution-oriented research which isn't worried about the causes of the problem but is more focused on what solutions are going to work in Shanghai versus New York versus another place? Your argument about causality – I would say forget it and move on.

**Dr. Oppert:** Yes, of course we emphasize cultural specificity; however, we can anticipate that some associations will be transferable from one place to the other, or at least this is what we are trying to do with Dr. Drewnowski, comparing shopping in Paris with Seattle supermarkets.

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15 Ding D, Gebel K: Built environment, physical activity, and obesity: what have we learnt from reviewing the literature? Health Place 2012;18:100–105.
Dr. Drewnowski: In Paris, people live about 400 meters away from the nearest supermarket. In Seattle, shops are farther away. There will be huge differences in distance, and of course Parisians will walk to shops as opposed to drive and will shop much more often. But there will still be communalities in how people access food sources; that’s what is interesting to us.

Dr. Barclay: Is it possible to obtain data from supermarkets about what is in the shopping basket and the cost? With what they call fidelity cards, they have a very good record of what people buy.

Dr. Drewnowski: We haven’t done a project in collaboration with supermarket chains, but we have collected study participants’ grocery store receipts for at least 2 weeks, if not 4 weeks, to confirm what foods they bought. This was to validate self-reports of what people ate and how much they paid.

Dr. Finegood: There is a huge data base on what people purchase, but academic researchers don’t usually have an access to it because it’s expensive. Yes, supermarket chains have tons of data that would be very useful, but it’s hard to access.

Dr. Drewnowski: The data are available from consumer market research companies such as the NPD group.

Dr. Finegood: For how much?

Dr. Drewnowski: For free if they are interested in research. But the point is that health researchers need to go to commercial data sets and start looking at commercial suppliers. The problem is that with national surveys, the number of people in any one location will be small. For example, I would expect the number of Seattle residents in any national database to be under 100. However, we are interested in data that can be geocoded where the data set is national. Is there anything like this in Europe, there are a number of consumer research suppliers?

Dr. Oppert: Yes, there are directories or databases where you can get some of these data. I would think that the firms would be interested in working together with researchers. One reason is that the market is evolving. For example, in France and in some parts of Europe it is not supermarkets but mini-markets that are getting back into town. I think that the companies would be really interested. We have good contacts with some of them.

Dr. Rolls: I have been at meetings in the UK where it has been made clear that supermarkets have information that is proprietary. Stores know a lot about how food choices are affected by price, labels, and positioning, but they are reluctant to share their data. Such data would be very useful to try to figure out how to change food choices.

Dr. Oppert: Designing an audit method to assess exactly what is in a shop is very complicated. In one of the large-scale EU projects that was performed in the last several years on prevention of obesity, a big part of the project was dedicated to this, and they found that it was really complicated to make a complete audit of store contents. So, I think that perhaps photos taken with a camera would provide more information than a store-by-store checklist of what products are being sold.

Dr. Klassen: Do you have data on the person that purchases the products? The person who shops may be different from the person who consumes the food. For example, in urban areas you might find more singles or students, which consequently may lead to a different purchase pattern in Paris than in rural areas.

Dr. Drewnowski: Dr. Oppert has those exact data for Paris. In Seattle, we looked to see who went to large warehouse stores, such as Costco, which can be farther away. It
was as you would think. People who went to Costco had large families and went there less often compared to the average Safeway shopper.

Dr. Oppert: Sometimes you have those details but you don't know where the people go, so currently we have to admit it's very difficult to have all the relevant questions in the same study.

Dr. Warshaw: I would imagine that even shopping patterns are different from Paris to Seattle or other US cities.

Dr. Oppert: What do you mean by shopping patterns?

Dr. Warshaw: Frequency, value purchase per time shopping, maybe that's my perception in Paris.

Dr. Drewnowski: You are right, I think in Seattle the shopping pattern was to go by car once a week; in Paris that was clearly not the case, so yes, absolutely.

Dr. Finegood: I will just be a little bit more challenging here, and say that part of the reason why we think we need to work out the causality is that we believe we will find solutions in the causes of the problem. But in this big domain of the food and physical activity environment, the changes will need to be big. My impression is mostly anecdotal and I apologize for that, but the experiments that have been done to change the food environment and the physical activity environment haven't worked out very well. I wonder whether you can comment on that. Proposed changes to the environment can be very expensive, but we haven't seen the results that people were hoping for.

Dr. Oppert: I think there have been a few so-called natural experiments that have been performed especially in the UK, and these were not so positive. The results were really mixed; I mean having a new supermarket in a neighborhood may lead to changes in food purchasing behavior. But I think there are many new ongoing studies on this, especially physical activity. New projects are looking in great detail into changes in the physical environment and the effective impact on physical activity habits. I think there are new studies and new designs ongoing at the moment, so I would try to be positive.

Dr. Lovejoy: I think we do need to know causality, and I think the challenge, as Dr. Drewnowski pointed out earlier, is that we haven't looked enough at it at a micro-level. We have been making assumptions about things like food deserts and how people shop and how people engage in physical activity based on macro-situations when there are so many exceptions. One common assumption is that easy access to green spaces in parks will be associated with more physical activity. But researchers found that in some places that is not true because green spaces in parks in the US anyway are sometimes used only for little league fields. So if your children are not playing in little league, they are not using the park and they are not engaging in any more physical activity. So that's an example of a micro-level. You need to know that causal piece of it in that unique situation in order to be able to do an effective intervention.

Dr. Oppert: But this is why you have to complement the objective data with subjective data using interviews to assess the perceptions of residents about the environment they live in. The use of a place can be completely changed from its initial purpose, and this appears especially true for physical activity.

Dr. Rosenbaum: You have to distinguish between intervention and prevention. You can't do prevention if you don't understand causality. If I don't know why people are getting fatter, I can't do anything to prevent it.

Dr. Oppert: There are good guesses, however, which would not prevent us from action.
The Importance of Systems Thinking to Address Obesity

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Abstract

Obesity is clearly a complex problem for both the individual and for society. Complex or ‘wicked’ problems have common characteristics such as heterogeneity, nonlinearity, interdependence, and self-organization. As such they require solutions appropriate for complex problems, rather than a reductionist search for the causes. ‘Systems thinking’ provides new ways to consider how to collectively address complex societal problems like obesity, where biology interacts with social, cultural and built environmental factors in infinite permutations and combinations. The systems that give rise to the obesity epidemic function at multiple levels, and there are important interactions between these levels. At any given level, individual actors and organizations matter and system function is optimized when individual and organizational capacity to respond is well matched to the complexity of individual tasks. Providing system supports to help networks of individuals become ‘communities of practice’ and ‘systems of influence’ may also help to accelerate the pace of effective action against obesity. Research efforts need to move away from the relentless search for the specific isolated causes of obesity and focus on solutions that have been shown to work in addressing other ‘wicked’ problems.

Causality, Complexity and the Need for a Paradigm Shift

For many years, the obesity ‘problem’ has been framed within the paradigm that people need to be individually responsible to eat less and move more [1]. While public discourse remains mostly rooted in this paradigm, academic literature has shifted to include recognition of the importance of many social, psychological and physical environment variables in causing obesity. This has helped to move the dialogue somewhat from individual to societal responsibility [2], but
blame is still ascribed in the tone of moral panic which supports the notion that people must be individually responsible for their weight [3].

Obesity research is usually based on conceptual models that have focused more on working out the causes of obesity than on developing solutions, especially solutions appropriate for complex problems. Biological and physiological mechanisms associated with obesity were the exclusive focus of obesity research when the first journal devoted to obesity was introduced in the late 1970s [4]. The deeply held belief of this biomedical focus is that working out the causes of a problem will lead to solutions. This paradigm remained dominant until the late 1990s when papers on population and public health began to appear in the three obesity research journals that existed by that time [4]. The rise in population level research helped to increase the number of identified causes and has opened the door to a discussion of societal level responsibility, but has not yet led to a shift from the basic paradigm that solutions need to be rooted in an understanding of the causes [5].

In the last few years, obesity has been labeled a complex or ‘wicked’ problem [6]. Characteristics giving rise to this complexity include the heterogeneity of our genes and environments, nonlinearities in processes like weight loss, the importance of triggers to sustained behavior change, and the many reinforcing feedback loops that drive individuals towards less healthy behaviors (table 1). Current scientific approaches, especially those rooted in an understanding of the causes, are better suited to problems that are simple or complicated, not ones that are complex. Simple problems have simple solutions based on the causes of the problem and sometimes complicated and complex problems can have simple solutions (or a set of simple solutions), but these solutions need to be based on a systems approach and not necessarily on the causes. As Wagner [7] points out, causality can only be meaningfully defined for systems with linear interactions.

Rittel and Webber [8] suggest we need a different way to approach wicked problems. They suggest that scientific methods have been developed to address

<table>
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<tr>
<th>Simple/complicated systems</th>
<th>Complex systems</th>
<th>Examples/relevance</th>
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<tbody>
<tr>
<td>Homogeneous</td>
<td>Heterogeneous</td>
<td>Genes, environments, etc.</td>
</tr>
<tr>
<td>Linear</td>
<td>Nonlinear</td>
<td>Exposures, life course</td>
</tr>
<tr>
<td>Deterministic</td>
<td>Stochastic</td>
<td>Triggers for behaviour change</td>
</tr>
<tr>
<td>Static</td>
<td>Dynamic</td>
<td>Weight loss/maintenance</td>
</tr>
<tr>
<td>Independent</td>
<td>Interdependent</td>
<td>Food production and consumption</td>
</tr>
<tr>
<td>No feedback</td>
<td>Feedback</td>
<td>Mostly missing</td>
</tr>
<tr>
<td>Not adaptive or self-organizing</td>
<td>Adaptive and self-organizing</td>
<td>Makes causality mostly irrelevant</td>
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<tr>
<td>No connection between levels or subsystems</td>
<td>Emergent</td>
<td>Current obesity trends</td>
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‘tame’ problems, not ones where the problem cannot be definitively described, where there are no ‘optimal’ solutions, and it is impossible to define a ‘stopping rule’, or to know when the problem is solved [8]. Solutions appropriate for complex problems tend to be more process (as opposed to outcome) oriented and focus on the interactions and interdependencies between individuals, organizations or levels in the system [9].

New streams of research rooted in systems thinking are needed to build novel and effective approaches to address obesity and other complex health and societal problems [6]. But achieving this goal will require several fundamental paradigm shifts. We need to focus on solutions rather than the causes of the problems [5], be holistic and integrative rather than reductionist, focus on processes rather than outcomes, and understand both our collective and individual roles and responsibilities.

New Places to Look for ‘Simple’ Solutions to the Obesity Problem

The introduction of the Foresight Obesity System Map in 2007 [10] helped initiate a dialogue about the complexity of obesity and how systems thinking and systems science can help to change the way we approach looking for solutions [6]. The Obesity System Map is a causal loop diagram which helps communicate the complexity of the system as a whole and emphasizes the importance of feedback loops and interdependencies to the development of obesity [10]. The map, a product of a stakeholder engagement process, illustrates many possible connections between important subsystems including food production, social psychology and physical activity environments [11]. The map was built both on available evidence and the experience of the stakeholders involved in its construction; specific linkages may only be relevant to some individuals in the contexts in which they live, learn, work and play.

Common responses to complex problems include despair, retreat, believing the problem is beyond hope and assigning blame [9]. But accepting complexity does not mean we need to give up, rather it means we need to turn to solutions appropriate for complex problems. When viewing solutions from a reductionist paradigm, the natural tendency is to think solutions for complex problems need to be multi-level and comprehensive [12, 13]. There is evidence that comprehensive interventions are more effective, but comprehensive interventions can also overwhelm the systems that support them, the resources available and they are difficult to evaluate [14].

Can accepting complexity help us identify new ‘simple’ solutions? Many systems thinkers, researchers and writers articulate ‘simple’ principles that underlie systems approaches. Bar-Yam [9] reminds us we need to look for solutions in the interactions between a system and its environment, such as the capacity of actors to act relative to the complexity of their tasks. He also suggests that
interdependencies between processes like cooperation and competition can be used to create the conditions for more collaboration [15]. Meadows and Wright [16] provide insight into solutions appropriate at different levels within a system such as feedback loops, information flows and the goals of the system. Wheatley and Kellner-Rogers [17] suggest that all organizational structures can be considered as networks, and to have impact we need to act locally, connect regionally and learn globally.

**Matching Capacity and Complexity**

Although complex systems often involve multiple subsystems with a myriad of actors and the organizations they work for, one simple principle is that each individual still matters [9], be they the individual at the centre of the Foresight map struggling with weight control or the CEO of a large food company balancing shareholder profits against a growing demand for a healthier food supply. As Bar-Yam [9] points out, what matters is matching an individual or organization’s capacity with the complexity of their environment and specific tasks. If the capacity of an individual is less than is needed to deal with the complexity of their tasks, they are more likely to fail (fig. 1). In contrast, if a person or organization’s capacity exceeds the complexity of their task, they are more likely to succeed. For a large system to function well, a focus on matching capacity and complexity may help.

![Fig. 1. Matching capacity and complexity. When the capacity of an individual or organization is greater than the complexity of their environment (or tasks), the individual or organization will survive. When capacity is less than complexity the individual or organization will fail.](image-url)
While this idea that capacity and complexity need to be well matched is a theoretical construct, it also makes sense intuitively and can be applied directly to thinking about solutions. Rather than asking ‘what are the various biological, social and environmental factors causing obesity?’ it suggests that research should focus on where in the complex system (described for example by Foresight Obesity System map) there are mismatches between capacity and complexity. More importantly, it leads us to consider interventions that reduce complexity (rather than increase it) or increase capacity.

One could argue that the dominant focus on educational approaches to addressing obesity has been an attempt to increase people’s capacity for healthy eating and active living. Yet, the fact that education has largely failed to halt or reverse the epidemic suggests either that the marginal increase in capacity that might derive from an educational approach is insufficient, or that the focus of most educational programs is not actually helping to increase capacity. Different educational targets may be better able to increase capacity, but it is also likely that education is not sufficient to overcome other drivers that make it more complex to act according to what we know [18].

The need to match capacity and complexity also suggests we need to reduce the complexity of healthy eating and active living. Many environmental approaches and the notion that ‘we need to make the healthy choice the easy choice’ are consistent with reducing complexity, but some changes may inadvertently increase complexity. Consider for example the impact of increasing the availability of healthy food choices. Behavioral economists have shown that as the number of choices increase, we are less likely to actually make an active choice and instead will make our decisions by default [19]. For this reason, it is not enough to make the healthy choice an easy choice; we must also make unhealthy choices more difficult or non-existent.

Lastly, when we consider variables like our capacity for behavior change and the complexity of the change, it is not enough to only consider the rational components of behavior. Emotional drivers can easily outweigh rationality [18]. As such, it is not enough to make the healthy choice the easy choice; we must also make it the desirable choice [20]. Having more desirable defaults when choices are being made will reduce the complexity of making healthy choices and ensure more individuals have the capacity to succeed.

**Leverage Points in Complex Systems**

Systems operate at many different levels. With respect to obesity, these levels range from the microscopic (genes and proteins), to the individual (physiology and life course) to the population (local, national, global). Meadows articulated the levels of complex systems in terms of their common characteristics across different kinds of systems and with a specific focus on their potential for changing system behavior, i.e. their potential as leverage points. At one end of the spectrum her leverage points include: (12) numbers (constants and parameters
such as subsidies, taxes and standards) and (11) buffers (the size of stabilizing stocks relative to their flows, e.g. the number of people on earth relative to the number who are born and die each day). Other leverage points include (7 and 8) balancing and reinforcing feedback loops, (4) self-organization, (2) the paradigm or mind-set of the system (the deeply held beliefs) and (1) transcending the paradigm (letting go of beliefs and assumptions about the system). As Meadows points out, the leverage points with the higher numbers are relatively easier to implement, but also are less effective, whereas changing the deeply held beliefs under which a system operates is much harder, but also more effective.

While the 12 leverage points Meadows described provide a helpful framework for a systems approach to complex problems, with 12 levels, this framework was difficult to translate into a tool for planning and/or analyzing intervention approaches [21]. We collapsed the 12 levels into a 5-point intervention level framework (table 2). The 5 levels are paradigm, goals, structure (as a whole), feedback loops/delays, and structural elements, and include all 12 of Meadows levels [22]. With only 5 levels, this framework has the potential to be applicable to a variety of challenges associated with complex problems including understanding how a system operates to assessing the compatibility of actions at different levels of a system and across a range of goals.

Our first application of this framework was to a set of materials provided as pre-conference reading for a meeting on food systems and public health [23]. The actions recommended within these readings that spoke to making food systems healthy, green, fair and affordable were sorted into the intervention level framework [22]. This analysis suggested that some actions to achieve all four goals are compatible, including broad public discussion and implementation of policies and programs that support sustainable food production and distribution. At the level of paradigm and goals, however, the challenge of making healthy and green food also affordable becomes apparent as some actions at some levels may be in conflict.

Current and future uses of the intervention level framework include other analyses of qualitative data, supporting reflective practice to enable cross-sector dialogue, program planning, research and evaluation. As Meadows points out

<table>
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<tr>
<th>Level</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Paradigm</td>
<td>Deepest held beliefs</td>
</tr>
<tr>
<td>Goals</td>
<td>What trying to achieve</td>
</tr>
<tr>
<td>Structure</td>
<td>Information flows, connectivity, trust</td>
</tr>
<tr>
<td>Feedback and delays</td>
<td>Self-regulation, reinforcement and adaptation</td>
</tr>
<tr>
<td>Structural elements</td>
<td>Subsystems, actors, operating parameters</td>
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Table 2. Intervention level framework
in her ‘guidelines for living in a world of systems’, it is very important to ‘get the beat of the system’ and to ‘expose your mental models to the light of day’. Recognizing the multiple levels at which a system of interest operates and where the changes are needed is an important step to tackling a complex problem for the good of the whole. Asking questions about what is happening and what needs to change at each level of a system and in the interaction of the levels is a good place to start.

**Influencing Emergence**

Emergence refers to the arising of novel structures, patterns, and properties during the process of self-organization in complex systems [24], and is often thought of as ‘the whole is greater than the sum of the parts’. Bar-Yam [25] defines multiple types of emergence depending on the nature of the relationship between the parts and the whole. ‘Weak’ emergence is the difficult to understand micro-to-macro relationship between the parts and the whole, whereas ‘strong’ emergence can arise either through system constraints or from a global-to-local causality. The Foresight Obesity System map suggests that obesity results from weak emergence of a large number of factors. The map illustrates how more than one hundred different ‘micro’ level variables and their interdependencies give rise to obese individuals. It is also likely that strong emergence contributes to the epidemic of obesity. For example, globalization of the food supply clearly has an effect on local food environments. A better understanding of system constraints and global-to-local relationships could provide new insights into how to influence the emergence of obesity.

Wheatley and Frieze [26] suggest ways to influence emergence even in the absence of a deeper understanding of system constraints or causality. They consider that networks are the only form of organization used by living systems and since they are mostly interested in social systems, this frame works well and enables them to describe emergence as ‘the fundamental scientific explanation for how local changes can materialize as global systems of influence’ [26]. They suggest that as a change theory, this approach offers methods and practices to influence emergence and accomplish system-wide changes.

Networks are defined as the first stage in the life cycle of emergence. They tend to be based on self-interest, are self-organized and have fluid membership. The next stage is ‘communities of practice’. These can spring from networks, are also self-organized, but motivation for participation goes beyond self-interest. In communities of practice, people participate to serve their own needs, but also to serve the needs of others; there is an intentional commitment to advance the field of practice and to share learning with a wider audience. The speed with which people exchange knowledge, learn and grow can be rapid in a community of practice. The last stage in the life cycle of emergence is the ‘system of influence’ where efforts and ideas that were expressed by a few suddenly become the norm. Practices developed by courageous communities suddenly become the
accepted standard, and there is no hesitation about adopting these ideas and approaches. This process is illustrated by the rapid rise in smoke-free space legislation following the ‘emergence of passive smoking as a scientific fact’ [27].

Wheatley and Frieze [26] argue that emergence always results in a powerful system that has many more capacities than could ever be predicted by analyzing the individual parts. They suggest that to influence emergence we need to ‘act locally, connect regionally and learn globally’. Given the variable influence of the various factors identified as causally important to obesity [10], the need to act locally makes sense. Only local actors have sufficient knowledge to consider what is important in their community/context and how to implement policies and programs to address obesity and chronic disease prevention. We could influence the emergence of healthier communities by supporting local actors in learning from each other. By creating system supports which enable knowledge exchange of what works in local contexts, we could accelerate the pace of learning and enable networks to become communities of practice and ultimately systems of influence. But emphasizing the value of local knowledge and expert opinion will require a paradigm shift from an evidence-based medicine approach in which the ‘best’ evidence comes from carefully controlled experimental paradigms that do not exist in the real world.

Conclusions

The dominant reductionist paradigm of biomedical research has served us reasonably well for many years in tackling many complicated problems such as diseases caused by single-gene defects. But most of today’s ‘wicked’ problems are complex problems with characteristics that make the reductionist approach, including highly controlled experimental conditions and a search for the causal relationship that stands out even in multiple contexts less helpful. Instead, we must turn to systems thinking and the science of complexity in our search for appropriate solutions. The characteristics of complex systems and the features that are common across most complex problems provide new avenues for obesity research. By shifting the paradigm from a ‘problem orientation’ to a ‘solution orientation’ and by considering the interdependencies between actors and their environments and the possibilities for influencing emergence, we should find more effective solutions to complex societal problems like obesity.

Acknowledgements

The author wishes to gratefully acknowledge feedback on the manuscript from Dr. Carrie L. Matteson, Philippe Giabbanelli, Lee Johnston and Penny Deck and grant support from the Canadian Institutes of Health Research.
Disclosure Statement

The author of this chapter does not have any relationships to disclose.

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Discussion

Dr. Drewnowski: Let me begin by asking you a question about your experience at the Canadian Institutes of Health Research (CIHR) and the emerging interdisciplinary networks in the area of obesity.

Dr. Finegood: Networks and teams are helpful ways to advance obesity research because they create an interface where different disciplines can learn about each other and can bring complimentary skill sets together to work on a problem. At the CIHR, we created several opportunities for multi- and transdisciplinary teams to form and to enable both basic research and research on natural experiments. By creating a competition for funding, we enabled the cooperation of researchers across their usual silos. By supporting research on natural experiments, where the researcher does not have control over the intervention, we have begun to learn more about policy level interventions like the return of PartipAction and the implementation of a physical activity tax credit. Those projects have been fairly effective at emphasizing the value of intervention and interdisciplinary research and giving it a foothold so that it could grow.

Dr. Drewnowski: Our experience was similar in that our work with urban planners and geographers was sparked by a planning grant from the National Institutes of Health for a transdisciplinary exploratory center for obesity research. Putting money on the table is the best way to promote interdisciplinary research between people who would never talk to each other otherwise.

Dr. Finegood: By creating competition at the right level, you create cooperation at the next level down. Think sports teams and leagues, the most competitive team in the league has the most cooperative players. This systems idea can be used in the research funding domain to stimulate cooperation, but also elsewhere in government.

Dr. Bray: We had a program in place, briefly, where we had the police department, the university system, and government people with all of us donating our time. The mayor was actually quite engaged in community wide health. The program was really comprehensive, but the problem was that it wasn't self-sustaining. There are a lot of people who acknowledge that obesity is a complex problem and there are people who want to participate. But those of us, who want to do it, can't do it endlessly without some sort of support and somehow that self-sustaining component is often not there.

Dr. Finegood: Many of us understand that obesity is a big complex problem, and we need to address many different facets of it. Our reductionist mindset has led us to huge and comprehensive solutions and those are very hard to self-sustain. But if we shift our mindset a little bit and zero in on integration and integrative structures, without trying to be comprehensive in everything we do, then we can be more self-sustaining and
adaptable. This is where supporting emerging networks can be helpful; by taking people who are on the ground doing things separately and making strategic connections, you enhance the ability of the structures to function. You do not necessarily make people do more, but by making strategic links you begin to move from a network to a ‘community of practice’ and ultimately to a ‘system of influence’. These are things that we can do if we get away from the mindset that everything has to be done together in one big effort. Does that make sense?

Dr. Bray: Yes it does, and I also think that sustainability has to also be part of the plan.

Dr. Finegood: If we are thinking that the solution to a complex problem lies in working out the reasons for the problem, linking these causes to their specific outcomes and then intervening at the cause, then we are ignoring the potential for intervention through integrative approaches. The path to workable solutions through working out the causes of a problem is slow and very costly due to its complexity. I believe that simple, more sustainable solutions can be developed within whatever resources the actors bring to the table if the focus for the group is problem solving around their shared goals and integrative processes.

Dr. Rosenbaum: But doesn’t the importance of working out causality depend on what your goal is? Isn’t it different when your goal is ‘health improvement’ as compared to ‘reducing body fatness’, not that the two are necessarily separate? Isn’t causality important to work out treatment as compared to prevention? It’s like looking for ways to treat measles or for ways to prevent it, that’s the question. I guess the official topic of this session was prevention, so I was thinking that causality is very important. Prevention and treatment are completely different problems.

Dr. Finegood: There probably are differences in the importance of working out causality for prevention and treatment. Tom Robinson argues that we will speed up the finding of effective solutions if we test hypotheses not about the ‘causes of the problem’, but instead we focus on the ‘causes of the solutions’. Both health improvement and reducing body fatness are complex problems and chasing causality in both cases isn’t necessarily all that helpful. And yes, there probably are differences between prevention and treatment outcomes for variables like physical activity or the nature of the food environment.

Dr. Rosenbaum: The relationship between food and physical activity is very different in someone at their usual weight than in somebody who is reduced weight. I like your idea of capacity and complexity because I think that the kind of physical activity that is necessary to lose weight may well be beyond the capacity of most of us. We just can’t do it, we don’t have the time, and we don’t have the capacity.

Dr. Finegood: This really strikes me as being a view about the individual. The difference between prevention and treatment may apply to an individual. But the same argument about capacity and complexity also applies to the food environment. I don’t think that the changes that we need to make in our food environment are going to be different for obesity prevention and obesity treatment necessarily. So, in that sense I don’t think they are different. It depends on what level you are at as to whether that distinction is important or not.

Dr. Rosenbaum: I would say that they are very different. In one case, your body is fighting against you in terms of treatment; there are a million things that fight against
you. In the case of prevention, your body has not yet begun to fight, so it’s a different arena.

**Dr. Finegood:** I personally understand that relationship and dynamic completely having lost 35% of my bodyweight and kept it off for more than a decade now. What I would argue is this. If I had started being more physically active and eating a healthier diet before I gained the weight, I probably would not have gained it. I am not sure that the behaviors that I needed or would have undertaken would have looked that different to me. Yes, I have to work harder at it now because I gained the weight, but the behavior changes that I need to make are not necessarily different from those that I could have started earlier. Perhaps I would not have had to work so hard at it. I apologize for this being an anecdotal response.

**Dr. Goran:** The real challenge here is how to convey what we know about this very complex problem in simple terms. How do we provide relevant information to the Mayor of Houston to address obesity locally? What this demonstrates is not only that obesity is a complex issue but that the solution is going to be very specific to the contextual factors of a community, and you alluded to that slightly. It seems like the next step would be to come up with strategies for communities to seriously address the obesity problem rather than just apply a simple band aid which is typically what happens. So what do we need to do to make that move?

**Dr. Finegood:** That is about influencing emergence, which is an important point. What is coming out of this conversation is that the action needs to be at the local level. Hopefully we are starting to understand the importance of contextual factors. When we get to community-based participatory research, the community becomes incredibly important in determining what is going to happen next. If you talk to anybody who has done this kind of community engagement research, you will find that they often go in there with their own preconceived notions about what changes need to be made based on the best available evidence, and they come out doing something very different. Sometimes, the community accepts projects that increase physical activity, or the community isn’t ready to talk about physical activity depending on where they are. Instead, they want to talk about the fact that they can’t afford to exercise, they have got to work 3 jobs, and they don’t have time.

A part of the argument here is that we set aside causality for a moment and recognize that what we have to do is act locally and learn and figure out the best ways to engage with people. We can help to guide their solutions, but they are the ones that are going to generate them, and all that data that we have collected are not necessarily going to be all that helpful. We already know a lot. Maybe if we didn’t know anything about the causes, I might not be standing up here being a bit provocative. But we do know a lot, and we could apply a fair amount of what we know already to help communities take action in their own environments. And there are some other major problems; for example, lots of us don’t live in places where we even perceive that we are in a community, we don’t know our neighbors.

**Dr. Drewnowski:** I have a comment here about the use of data. I think local communities want local data. Although we do know a lot, local communities don’t know enough about themselves. The moment you present them with maps saying this is the extent of problem, this is where you live and this is where the supermarket is, things change. Maps are very telling and local politicians prefer to use local data from 5 miles down the road as opposed to national statistics.
Dr. Finegood: I didn’t tell you anything about the CAPTURE Project, which is another half of my life at the moment. CAPTURE stands for a CAnadian Platform To increase Usage of Real-world Evidence. It is an effort to build a system to support the collection, sharing, and use of practice-based or real-world evidence. It is intended to support communities and people on the ground. The goal is to figure out what data would help them and then use that data to figure out what they want to do. If we were better at doing that kind of work, then we could solve some of these problems without necessarily spending huge amounts of money. It is the people on the ground that need to explore the diversity of ideas and come together to figure out what is possible with the resources they have and the context that they are in.

Dr. Drewnowski: One way to provide helpful data is to aggregate obesity statistics by political district. The moment you do that, it becomes somebody’s responsibility. It’s just another way of analyzing geographic data but everything changes because now it can be brought to the attention of politicians and policy makers. So, it’s one way of making best use of local data.

Dr. Bray: There is no way that obesity prevention or intervention projects can depend on an endless flow of money. They have to be community oriented, it has to be something intrinsic to the program itself, and it probably will need to arise from the community.

Dr. Barclay: I think there has been at least one reasonably successful multisectorial collaboration which started in France (EPODE: http://www.epode-european-network.com). Although it hasn’t been able to reverse obesity, it has been able to stabilize obesity in children. The program brings together players from government, education, and industry, etc.

Dr. Finegood: Funded if I am not mistaken by Nestlé, is that correct?

Dr. Barclay: Nestlé is one of the co-funders.

Dr. Finegood: It’s a good example of what can happen if you can engage people at multiple levels and in multiple sectors.

Dr. Drewnowski: I have a question for you based on your experience as a former head of a research institute. We have heard about various aspects of science at the individual level and environmental level; we have heard about the microbiome, inflammation, the brain, and the environment. Based on the people in this room, who would you put together with whom and why to create an emerging network?

Dr. Finegood: What I would say to that is it’s not up to me because it’s not a command and control kind of problem. If I can create the competition that stimulates cooperation then it’s up to the people in the room to figure out who they can work with and what makes the most sense. I have led enough multidisciplinary research teams to know that it’s a challenging thing to do. It takes time for people to learn each other’s language. The important thing is to create the opportunity and to give them the time and maybe financial support. But there are some multidisciplinary questions and problems that we do need to resolve.

Dr. Drewnowski: I think you are right; it’s a question of time and trust. At one point granting agencies had a list of bullets saying that you must have one person from this area and one person from that area.

Dr. Finegood: Forcing it doesn’t work that well. People have to know each other. This was a technique used at CIHR over the years. Sometimes what you get are researchers going to people in government on the day that the grant is due saying: will you sign this letter of support. That is not what I call authentic engagement. But at other times, you
will get people who have already spent time engaged with collaborators in different sectors and want to bring the shared experience to the funding table. But it's hard to do. Money helps and leadership helps, and after that you have got to let people self-assemble.

**Dr. Rolls:** Can you think of examples where competition has created cooperation that has given us better food?

**Dr. Finegood:** The problem on the food side is that there is such a negative atmosphere for cooperation right now. If you follow any social media and you follow the people who are well connected like Marion Nestle and others, then you get the idea that collaborating with the food sector is dangerous.

**Dr. Rolls:** What about within the food sector?

**Dr. Finegood:** Within the food sector, I probably don't have enough knowledge. I don't have a good example that comes to mind. But I am going to be debating this topic about collaboration with the food industry next week at The Obesity Society with Dr. Yoni Freedhoff who feels that it's wrong to collaborate with the food industry because you give them the credibility of your academic or your organizational brand and all they are doing is making more money based on your credibility. I will tell a quick story about collaboration on physical activity in Canada. We had the 2010 Olympics in Vancouver, and Coca Cola had the rights to the 2010 torch relay. Coca Cola wanted to get kids engaged and get them physically active and they could have just gone out and developed the program by themselves, not that they have any expertise about what works. Instead, they partnered with ParticipAction, a not-for-profit organization to develop this program. Maybe they did that because ParticipAction had the expertise to help them develop something that was evidence based, but outsiders assumed that the only motive was to get the credibility of the ParticipAction brand. It's very hard to collaborate, and that's the reason why I have held three meetings to have this discussion around how to build trust to address obesity.

**Dr. Rolls:** I wonder if within a food company you could have scientists competing to come up with the best-selling and profitable healthy products and so leverage that kind of development.

**Dr. Finegood:** So, a competition to create the healthiest product – that's an interesting idea. I wonder to what extent that might be going on in Pepsico for example which is trying hard to shift its portfolio. It must be challenging for the CEO of a food company that wants to shift their portfolio to healthier products. If the products don't sell, the shareholders will not be happy. We consumers are an important part of this feedback loop. If we don't shift our eating habits and actively make healthy choices, then we cannot expect them to be available in the marketplace.

**Dr. Drewnowski:** That goes to the heart of the sustainability issue because those changes need to be sustainable, which means consumers have to work with the food industry and with food environment to make changes in the long-term. Together, the consumer and the supplier need to both understand what is both healthy and desirable.

**Dr. Finegood:** I wonder how many companies went broke during the Atkins craze because a lot of companies shifted their food portfolio to sell low carbohydrate food and now few people are buying it. It's quite conceivable that a lot of companies went broke because they responded to consumer demand.

**Dr. Bray:** I think that I shouldn't say this in a meeting sponsored by a nutrition company, but there may be depending on the company as much effort at developing the
image of a healthy food as there is developing the actual healthy food. Subway has done an excellent job of marketing themselves as a supplier of healthy food and created a health halo for their products, but not all of their sandwiches are in the same healthy category.

Dr. Finegood: I am not going to stand up here and defend the food industry for its practices because many of those practices are questionable, and yet I would defend them for wanting to sell their food. If we want to stay in our corners and not have conversations about this, how can we support the shift that the companies need to make, the iterative gradual shifts that they need to make in order to deliver a much healthier food supply that is honestly healthy and is not just capitalizing on the apparent demand for healthy food? One of the things that we need to do is to get our government policies to change.

Dr. Johnson-Askew: I would like to know what role you think systems modeling has as we approach this very complex problem of obesity.

Dr. Finegood: One thing systems modeling can do is to help us integrate the data we do have so as to create a better understanding of the big picture, although there is a part of me that thinks it’s just the way reductionist scientists need to go about addressing a complex problem. Josh Epstein answers the question of ‘why model?’ with many different points about how it improves the rigor of our consideration of fact and assumption, helps us test predictions, and can illuminate core dynamics and uncertainties.
Summary Discussion on New Directions for Prevention

Dr. Lovejoy: I wanted to bring up something that we haven't talked about much today, which is the role of stress. As we are thinking about obesity treatment and prevention, we should look at the physiological effects of stress, which certainly impact the brain, the gut, and inflammation, and at the behavioral effects which impact people's desire to eat different foods and their willingness to engage in physical activity. Research has been done showing that the built environment contributes to stress and lack of sleep, so I think that stress is the often overlooked third leg of the obesity story. We talk about diet and physical activity all the time, but we need to consider that stress may be just as important in terms of the big picture.

Dr. Drewnowski: I am glad that you mentioned stress. People who work on the relation between the built environment and obesity have been using the stress hypothesis a lot. Living in a low-income neighborhood with no access to facilities and resources can increase stress levels and alter work patterns, sleep patterns, and food choice. So, the stress hypothesis has been quite prominent, and there is increasing literature on that. We did not talk about it today, but that is not to understate its importance, it's a major factor.

Dr. Warshaw: Building on this, I want to introduce another topic that relates both to treatment and prevention – the importance of support. Study after study suggests that support has to be a critical issue. In the national diabetes prevention program which is a CDC project from the affordable care act, they are going to be using some community health workers. There is a lot of interest in using community health workers and paraprofessionals as supporters since they are less expensive than trained professionals. Such support seems particularly important for weight loss maintenance. We tend to support people intensively during the weight loss phase and then there often is withdrawal of support, but yet so much research suggests that's when people need support. We need to communicate to the public just how hard it is to keep weight off and that they likely will continue to need support.

Dr. Drewnowski: I agree with you. There are two important issues related to social support. Having spouse, family, or peer support during the weight loss phase is critical to its success. The other issue is having sufficient social support to prevent weight gain in the first place. The latter is sometimes called social capital as distinct from income and material resources. Basically, it's who you know that can provide you with support and
with social resources. Even if your income is low, but you still have parents, family, neighbors, a house and some assets, you will probably do okay. But there are people who are completely on their own, without a social support network. Such issues are not picked up in studies on obesity and SES because many just focus on incomes and nothing else. There are other aspects of social context and social capital which are very important, and we need a better handle on those.

Dr. Finegood: We heard lots of good data this morning that would argue that it is more important to support people after the first 6 months of weight loss than it is during the first 6 months. You can do almost any treatment in those first 6 months, and people will lose weight. It is after the first 6 months that people are struggling and need support. I have often thought that the challenge, in my experience, is that weight loss gets harder, not easier. But if you get that idea out there, it may prevent people from ever starting weight loss – so what will that do? In my own experience, very small behavior changes at the beginning were the easy ones. I could start off by parking my car far away and taking the stairs. Those are things that I have now incorporated in a sustainable way in my own behavior. But now, 10 years later, I am at that point where I am at a steady state. I can’t find anything else to do that is easy enough and that I am capable of doing to bring my bodyweight down further and to sustain that weight loss. And yet, the social norm and my knowledge drive me nuts because I am still obese. So I think you are right, our strategies are backwards. We need to focus a little less on our initial weight loss interventions during the first 6 months and put more emphasis on maintenance.

Dr. Oppert: Going back to prevention versus treatment, I think that obesity treatment is more of an individual topic but that prevention should be more properly focused at the population level. For example, obesity treatment in Europe is managed by national health systems but prevention issues can be addressed at an international meeting at the European level. So, I agree that there are similarities between prevention and treatment, but there are also major differences. However, I think it is an interesting issue that prevention efforts aimed at changing the environment will also affect the environment of obese patients. So, prevention initiatives apply not only to the whole population but to obese patients and may help with treatment.

Dr. Rosenbaum: Would you say that it’s harder to engage politicians in prevention than in treatment? In my experience, working with the public schools in New York City, if you say you are going to do something now that is going to decrease the prevalence of obesity 10 years from now, they say that’s very nice but I am not going to be here in 10 years. They want something that before the next election is going to change this. It’s much easier to get the powers that you alluded to on board with something that they can see right now. That’s a big barrier to some of the changes that we need to make.

Dr. Finegood: That is a fundamental challenge in terms of getting government regulation. The way I would think about it is that the things that we might do around prevention tend to be at the higher levels. They are less about genes and proteins or even individuals per se, and they are more about systems and structures. And the things that we do at the higher levels can be helpful in both prevention and treatment. But it’s true that treatment occurs at the individual level, particularly with the morbidly obese who need individual attention. For example, there are some people for whom bariatric surgery may be the best solution. So yes, treatment can be individualized, but the prevention step is going to apply to everybody.
Dr. Drewnowski: Let me do a quick summary. This began as an anti-consensus workshop featuring cutting-edge research, but in fact we have identified a number of common themes. Our discussions included biology, behavior, economics, and the environment. We liked the idea of transdisciplinary networks and a system’s approach. Sustainability is certainly another key issue that found support. We also agreed on the importance of research at the local level that could influence policies and environmental changes that may prevent obesity.
Concluding Remarks

Based on workshop discussions, the disease model of obesity needs to be better placed in its social and environmental context. On one hand, there is clear evidence for the direct involvement of the brain, the adipose tissue, and the gut microbiome in weight loss and weight regain. On the other hand, the broader social, economic, and environmental contexts may help explain why some people become obese whereas others do not. Energy balance behaviors and access to resources and services may further predict why some people are successful in losing weight whereas other people are not.

The systems approach to obesity treatment and prevention recognizes that biology, behavior, and the food environment are connected in a myriad of ways. The many social and economic determinants of health and weight and their interconnections are all prominently featured in systems maps such as the one produced by the UK Foresight Report. Given its strong inverse links to multiple measures of socioeconomic status (SES), especially among women, obesity does not fit the standard model of a genetic or a metabolic disease. To the contrary, the geographic distribution of obesity suggests a pattern of poverty and social disparities. Some population groups and some neighborhoods are more vulnerable and more affected than others. The targets for prevention and intervention are becoming increasingly clear.

What is to be done? First, new approaches to obesity treatment and prevention need to take advantage of the latest scientific discoveries. As demonstrated during the workshop, research on the gut microbiome, the adipose tissue, and the brain is on the cutting edge of biological science. Studies suggest that the gut microflora in obesity is less diverse and may be metabolically specialized to extract maximum calories from the diet. Gut bacteria can affect energy uptake, gut permeability, and gut hormones and can produce proinflammatory molecules. Fat accumulation in the adipose tissue can also contribute to inflammatory response, leading to insulin resistance and metabolic disease. Strong biological forces promote return to former bodyweight following weight loss. Brain reorganization during weight loss means that neuronal activity encourages greater energy intake and reduces energy expenditures. Brain physiology
conspires against maintaining the new lower bodyweight. However, biological drives can be countered by behavior, including physical activity.

Achieving a convergence between biology and the full spectrum of food-related behaviors is the second of the new directions. We live in an obesogenic environment with ready access to many good tasting, energy-dense, inexpensive foods. A food-based treatment approach would be to eat foods that help control hunger and promote satiety. Consuming larger portions of lower energy-dense foods would permit consumers to eat satisfying portions while limiting calories. Not incidentally, lower energy-dense diets tend to be nutrient rich. Yet much research in this area has focused on the macronutrient composition of the diet, often with disappointing results. We need science-based strategies which will lead to more effective advice than the simple injunction to eat less and exercise more.

Third, behavioral strategies for obesity prevention need to have a developmental component. One new direction in research is to understand the early determinants of food-related behaviors so that behavioral training can start during pregnancy and the immediate postnatal period. Behavioral targets may include parental eating behavior, infant feeding mode, infant sleep duration, soothing strategies, and the introduction of solid foods. Shaping the early development of food preferences and eating patterns is likely to lead to a healthier diet later in life.

Fourth, prevention and treatment strategies need to acknowledge the economics of consumer food choice behavior. Many palatable energy-dense foods are inexpensive and appeal to lower income groups. By contrast, some of the recommended nutrient-dense foods tend to cost more per calorie. In general, diets lower in energy density but higher in nutrient quality are more expensive, although they do not have to be. The selection of nutrient-dense foods and the creation of high-quality diets involve a number of economic decisions. Nutrient density and affordability indices are among the tools that can help consumers select diets that are nutrient rich, affordable, and appealing.

Finally, new directions in obesity prevention should include measures of the built environment collected using Geographic Information Systems approaches. Such studies have helped map the geographic distribution of obesity rates in relation to neighborhood characteristics, showing beyond doubt the links to SES variables. In particular, obesity rates among women were better predicted by low residential property values than by the standard measures of education and income. One puzzle is that location appears to be associated with bodyweight but less consistently with measures of diet quality. The explanation may be that the social gradient is stronger for bodyweight than for the existing measures of diet quality. One provocative idea put forward during the workshop was while obesity rates are predicted by neighborhood characteristics, dietary choices and diet quality are not. Health-related attitudes and beliefs are an important component of dietary choices and the social gradient in diet quality appears to be less strong.
Given the influence of geography, economics, and the food environment on bodyweight, it is essential that obesity research extends its focus beyond the individual. A better understanding of how people of diverse bodyweights interact with their food environment on a daily basis will help develop new and better targeted prevention strategies. It is becoming increasingly clear that such strategies will need to involve food production and distributions systems, retail, transportation, and other aspects of the built environment. All these factors are among the socioeconomic determinants of weight and health and all are interconnected.

Acknowledging this connectivity is the essence of systems thinking. The systems approach has challenged the deeply held belief that direct causes need to be uncovered before effective interventions can be put in place. Previous studies on the causes of obesity have variously sought to link the consumption of a single food, beverage, macronutrient, or dietary ingredient with obesity and weight gain. In general, the contribution of dietary factors has been viewed through the lens of physiology and metabolism, with much attention devoted to the consequences of high-fat or high-sugar diets. Less attention has been paid to the fact that both added sugars and saturated fats tend to lower diet costs, making energy-dense diets more attractive to lower income persons. Further, the impact of SES variables on bodyweight can extend beyond dietary factors and may involve inactivity, sedentary lifestyles, stress, depression, disturbed sleep patterns, and anxiety. Opportunities for physical activity are also sharply limited in lower income neighborhoods as is access to a range of affordable healthy foods.

In addition to new directions, the workshop identified some questions for the future. Given that new technologies permit the tracking of food-related behaviors in time and space, what do we need to know about the patterns of food purchases in obesity, food choices and portion sizes? Are some groups vulnerable because they put too much emphasis on taste, cost and convenience? Would studies of energy density and satiety, including anticipated satiety, help us develop new ways to feel more satisfied on fewer calories? Should we change the entire food supply or modify the behaviors of vulnerable persons?

Demonstrating causality may not be possible in complex systems, but should not hinder the development of appropriate solutions. It may not be possible to link obesity with any one food or beverage or any one pattern of behavior, given that much of the behavior is not under individual control but is constrained by social and economic circumstances. On the other hand, likely prevention strategies at the individual and population level suggest themselves, and they involve behavior, lifestyles, and the environment. The challenge is to create a food and physical environment that better suits our collective biology.

Adam Drewnowski
Barbara Rolls
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