Obesity pandemic: causes, consequences, and solutions—but do we have the will?

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Obesity has become pandemic owing to an obesogenic environment (inexpensive calorie dense food, technologies and structure of communities that reduce or replace physical activity, and inexpensive nonphysical entertainment) and excessive emphasis on low fat intake resulting in excessive intake of simple carbohydrates and sugar. Effects are greater for women owing to their smaller size and extra weight gain with each pregnancy, with 38% of American adult women being obese. Women are responsible for more than three-fourths of the more than 400 billion dollars of excess direct health care expenditures due to obesity. They are less likely to conceive naturally and with fertility treatments, more likely to miscarry, and have more prematurity and other complications with their pregnancies. We describe the many causes, including key roles that a dysbiotic intestinal microbiome plays in metabolic derangements accompanying obesity, increased calorie absorption, and increased appetite and fat storage. Genetic causes are contributory if these other factors are present but have limited effect in isolation. The numerous health consequences of obesity are discussed. The authors itemize ways that an individual and societies can mitigate the pandemic. However, individual will power, the will of society to enact change, and willingness of the public to accept outside intervention frustrate efforts to stabilize or reverse this crisis. The most promising strategies are education and efforts by individuals to make responsible choices several times every day to protect, most effectively by prevention, their most valuable asset. (Fertil Steril® 2017;107:833–9. ©2017 by American Society for Reproductive Medicine.)
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EPIDEMIOLOGY OF OBESITY AND THE SCOPE OF THE PROBLEM

The American Medical Association voted in 2013 to recognize obesity as a disease (against the advice of its Public Health and Science Committee). The AMA defended its action as a way to confer legitimacy to the condition, allowing for greater attention and better treatment. It also facilitates insurance coverage. Whether it is a condition that leads to disease or a disease itself, there is a strong world-wide consensus that obesity is pandemic and needs to be treated and more importantly prevented (especially in children) owing to its significant comorbidities, mortality, and costs.

Although there are several more accurate methods to measure the amount and location of fat tissue in the body, the body mass index (BMI) is most commonly used because of its simplicity. BMI is calculated by dividing body weight in kilograms by height in meters squared. A BMI of ≥ 30 kg/m^2 is considered to be obese (grade 1), with severe and morbid obesity defined as BMIs of 35 to <40 kg/m^2 (grade 2) and ≥ 40 kg/m^2 (grade 3), respectively. A well recognized problem with the use of BMI to define and detect obesity is its inability to differentiate dangerous adiposity (such as waist-line intra-abdominal fat) from potentially less harmful fat in other areas of the body or healthy "nonfat" body mass such as muscle. Recently, the concept of normal-weight obesity has been proposed [1] to allow for the identification of "at risk" individuals who do not meet the standard criteria according to BMI but have comorbidities associated with excess dangerous fat resulting in metabolic dysregulation (metabolic syndrome) and other sequelae. The World Health Organization defines obesity as excessive body fat accumulation that is associated with clear risks to health.

Obesity is considered to be largely preventable and mostly caused by recent changes in the so-called obesogenic environment [2] such as the highly processed and sugar-laden food supply (more calories in) and

automated technologies that reduce or replace physical activity (fewer calories expended). Genes and gene expression have been implicated as significant cofactors (3, 4).

The prevalence of obesity is increasing worldwide. The estimated U.S. prevalence in 2013 was 90 million obese in a population of 315 million (28.6%). In that year, 78 million were adults and 12 million were children. The U.S. incidence during the past two decades has been higher in women (38.3%) than in men (34.3%; HCHS Data Brief no. 219, November 2015), in part because of their smaller size (relative to meal portions) and excess weight gain with each pregnancy. Prevalence in the U.S. varies markedly by locale and is higher in black and Hispanic adults (www.cdc.gov/obesity/data/prevalence-maps.html). The prevalence of obesity varies widely among nations as well (www.worldobesity.org/resources/world-map-obesity). It has been projected (based on current incidence figures) that by 2030 nearly 40% of the world's population will be overweight and one in five people will be obese (5).

Recently there has been a leveling off of the incidence of obesity in children (6), owing in part to modifications of school lunch programs (including more nutritious foods and less sugary drinks) and increased physical activity. Unfortunately progress during the school season is lost during vacation time (6), showing that these healthful school measures are effective but must be sustained throughout the year. Persistent childhood obesity leads to an ever-increasing prevalence in adults, making efforts to reduce childhood obesity all the more urgent.

Much is known about individual risk factors for obesity, but little about how they may be interrelated (7). Knowing more about the confluence of the risk factors may hold the key for the development of better treatments and prevention. Industrialization of food production, providing inexpensive and highly processed food, is a major environmental cause. Culture and socialization also play a role. In the past (and even today in some cultures), fatness was seen as a sign of wealth and "well-being." In more recent times the poor are at greater risk of being obese, with risk being inversely related to wealth and education (8). Social interaction seems to play a role with evidence of "contagion" as a result of direct human contact on social networks (9). When so many are overweight, one's perceptions of what is normal are altered. Even dress sizes are different: What used to be size 8 in the 1960s through 1980s are today listed as 00–2. A recent national poll in the U.S. found that although seven in ten Americans are overweight or obese, only 36% think they have a weight problem. Advertising of calorie-dense foods directly to children is a >10 billion dollars per year effort by industry to influence family diets and future consumers (10).

The role of genetics is much less than that of the environment. Rather than playing an independent role, genes seem to increase the risk of weight gain based on the way they interact with other risk factors, such as unhealthy diets and inactive lifestyles (11, 12). Bray et al. recently described the relationship between genes and the environment by stating, "genes load the gun—the environment pulls the trigger" (13). Tyrrell et al. (14) recently analyzed data from 120,000 adults in a large national data base using BMI as the outcome and genetics (a 69-variant genetic risk score for obesity) and self-reported estimates of nine behavioral measures, such as TV watching, Western diet, and physical inactivity, as exposures. More TV watching and less physical activity were strongly associated with a higher BMI. They reported a significant gene-environment interaction with self-reported TV watching ($P=.00007$) and physical activity (P value for interaction .000005). The interaction between genes and the environment persisted with the use of a composite measure of the obesogenic environment (P value for interaction .0002). The role that genes play in obesity has always been considered to be the only nonmodifiable risk factor. However, with increasing knowledge about the role of the epigenome, gene expression may be modifiable based on environmental factors during life and even before birth (15).

In the United States the additional annual direct cost of health care per adult obese male was calculated to be $1,152.00 and the additional annual cost per obese adult female was $3,613.00, more than threefold that of obese males. Very recently, the additional total direct cost in national health care spending was calculated to be $427 billion annually or >10% of total health care expenditures in 2014 (16). Employers are also burdened with extra costs. A company's annual health care cost and lost productivity (in 2012 values) in the highest versus lowest BMI groups was reported to be $6,313 versus $4,258, and days absent were 7.5 versus 4.5 days, respectively. Work place productivity was reported to be lowest in the obese group (17). The well documented prejudice of employers is understandable, resulting in lost income for the obese individual. A very recent study estimated the overall cost of obesity to the U.S. economy in 2014 to be more than $1.4 trillion dollars (16).

ENVIRONMENTAL CONTRIBUTORS

The prevalence of obesity was relatively low until the 1980s, when a significant rise began (18). This increase occurred about 8–10 years after significant and widespread changes in the so-called "built environment." The built urban environment has many physical features that reduce the need for physical activity, such as elevators, escalators and other labor-saving devices, along with passive entertainment such as video games, TV watching, and online news, socialization, and entertainment. Our "built environment" determines whether walking rather than driving is encouraged or discouraged, influencing whether physical activity is preferred or avoided. The built environment also includes the almost constant availability of inexpensive, highly processed, and sugar-laden food (19), which plays a predominant role in the increased prevalence of obesity (20). Before 1900, sugar was a rare treat. The average per-person consumption of sugar in the U.S. increased from 4–6 pounds per year in the early 1800s to 150–170 pounds today. Adding sugar is the least expensive way that the food industry can make everything tastier to increase sales. Environmental and behavioral factors act alone and in combination to create what has been referred to as the "obesogenic environment" of modern times.

In countries having the most obesity (U.S., Mexico, and increasingly parts of Europe and the Middle East),

inexpensive and highly processed food is almost constantly available. Restaurants are valued for their large portion sizes of food and giant-sized sugar-containing drinks (a Coca-Cola bottle in the 1950s held only 6 ounces, and a glass held just 4 ounces). Added sugar has been shown to be highly addicting (21) with both short- and long-term adverse health effects, including obesity (22). Governmental and policy efforts to control the large quantity of sugar and other highly refined carbohydrates in the American diet have been fought by industry as well as by some consumer groups. The sugar industry was reported to have paid Harvard researchers during the 1960s to downplay the role of sugar as a cause of heart disease and promote saturated fat as the main culprit (23). The unfortunate overemphasis on "low fat" intake in recent decades contributed greatly to the need to use sugar and other carbohydrates to enhance taste and caloric content and consequently exaggerated the subsequent epidemic of obesity and cardiovascular disease. Efforts to address the obesity epidemic as a public health issue in the U.S. have unfortunately been labeled by some as paternalistic, undemocratic, excessive, and inappropriate. The additional societal expenses of obesity are denied or considered to be acceptable as the cost of personal freedom and choice.

NEWER CONCEPTS REGARDING UNDERLYING CAUSES

The human body is composed of trillions of individual cells. It is estimated that ∼30 trillion belong to the body genetically and that at least an equal number are genetically unrelated to their human host in the form of bacteria, viruses, and other organisms, most of which reside in the intestinal microbiome (24). This important collection of microorganisms, often referred to as the gut flora, is involved in immune function and metabolic processes and plays a role in inflammatory disorders, including obesity (25). The role of the gut flora has been studied in both human and other animal models, and knowledge about its role in health and disease has increased rapidly in the past decade.

Colonization of microbes in the human gut begins at birth. Babies who are delivered vaginally generally have greater bacterial cell counts than those delivered by means of cesarean section (26). Some studies show that a baby's microbiome is generally similar to that of their mother's (25). This early immune system programming is thought to have long-lasting effects helping to establish healthy functioning of the intestinal microbiome throughout life. Other factors such as genetics, diet, and antibiotic consumption can affect the gut flora.

The relationship between host and microbiome is complex and has been described as symbiotic, commensal, and pathogenic. The symbiotic relationship affects and supports the human immune system, allowing it to differentiate the bacteria that are harmful to the host versus those that are helpful. The extent to which the body is influenced by its intestinal flora is just now being realized as an environmental cause of obesity. Although quite complex, there is now emerging clarity about its association with the development of obesity and metabolic disorders, the risk for type 2 diabetes, and cardiovascular disease. The gut microbiome is seen as a

separate endocrine organ involved in the body's homeostatic process and is thought to affect metabolic disease processes through stimulation of low-grade inflammation. Excessive calorie intake, increased fat accumulation, and lipotoxicity activate the production of cytokines and cells that are primarily involved in immune function but are also inflammatory. It has been shown that inflammation contributes to desensitizing insulin-signaling pathways, which increases the risk for diabetes.

Figure 1, from a comprehensive review on the topic (24), illustrates interactions between the gut microbiome and the body's metabolism. A high-fat diet appears to increase gut permeability, resulting in increased levels of lipopolysaccharides in the body's systemic circulation. Lipopolysaccharides are endotoxins that have been shown to be associated with inflammation-related processes such as obesity and insulin resistance. By influencing gut epithelium and motility, certain bacterial species in the gut microbiome extract more calories from food, thus increasing calorie absorption and fat storage. The gut microbiota is hypothesized to inhibit fasting-induced adipose factor, resulting in an increased deposition of triglycerides in adipocytes. Gut microbiota also affect many other regulatory processes in the body, such as mitochondrial fatty acid oxidation, ketogenesis, glucose uptake/insulin sensitivity, insulin secretion, increased lipogenesis, and cholesterol and triglyceride synthesis. These processes all contribute to metabolic disease and obesity (24).

Conversely, more diversity of bacteria in the gut is associated with a greater antiinflammatory response and less oxidative stress (Fig. 1). Probiotics (live bacteria and yeasts) may supply a healthier and more diverse population of microorganisms. Prebiotics are substances (foods and supplements) that can enhance the positive effects of probiotics. "Fecal transplants" are increasingly being successfully used to restore or improve the gut microbiome so that it can function normally. It is therefore hypothesized that reduction of diversity of the microbiome by behavioral changes, including diet and the use of antibiotics (27), could be an important driver of the obesity pandemic.

A promising new treatment/preventive intervention for obesity may come in the form of pharmaceutical agents that beneficially change the microbiome. An early example is metformin, the most commonly prescribed medication for diabetes. Recent studies have found that metformin favorably changes the way gut bacteria function, increasing their ability to create healthful short-chain fatty acids that lower blood sugar. Gut flora of those taking metformin also had many more coliform bacteria, which could explain the increase in healthful short-chain fatty acids as well as some of the adverse symptoms associated with metformin (28). Newer drugs and or biologics will likely be developed to treat or prevent metabolic disorders such as diabetes and obesity by altering the gut microbiome.

In a very recent study (29), mice fed a high-fat diet were found to have changes in their gut flora that resulted in increased acetate conversion from fat. The increased circulating acetate caused the brain to stimulate release of insulin from the pancreas via the vagus nerve, and the excessive amount of insulin led to fat storage and obesity. The acetate

FIGURE 1
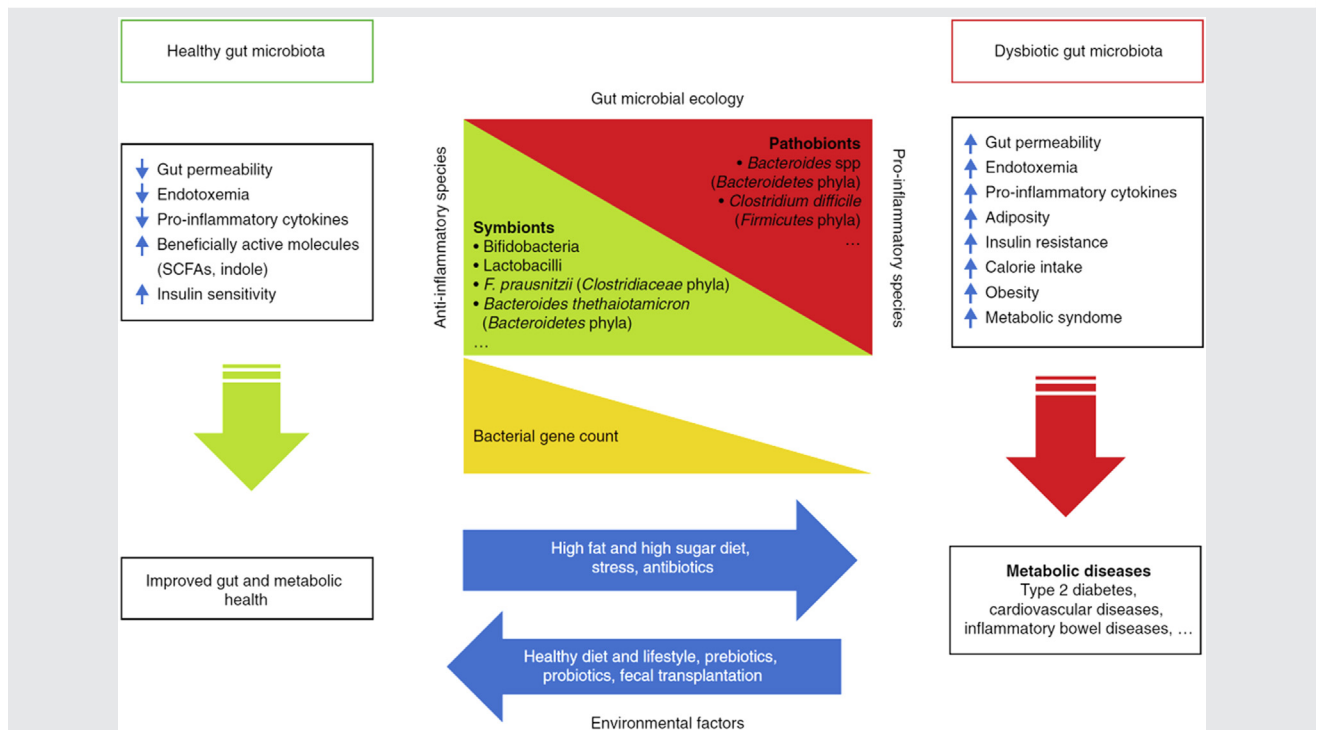
Effects of a healthy gut microbiota and dysbiosis on the gut and metabolic health of the host. A healthy microbiota comprises a balanced representation of symbionts (bacteria with health-promoting functions) and pathobionts (bacteria that potentially induce pathology). A shift toward dysbiosis results from a decrease in symbionts and/or an increase in pathobionts and is likely to be triggered by environmental factors (such as diet, stress, antibiotics, and infections). Low bacterial gene counts (indicating fewer distinct species) have also been associated with altered gut microbial functions and dysbiosis and have been linked to increased fat accumulation, lipopolysaccharide-induced inflammation, insulin resistance, obesity, and the metabolic syndrome. Individuals with these characteristics are more likely to develop metabolic diseases (such as type 2 diabetes, cardiovascular diseases, and inflammatory bowel diseases). Both pre- and probiotics may help to maintain and restore a healthy gut microbiome. SCFA = short-chain fatty acid. From Boulange et al. (24).

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also increased the release of ghrelin, which stimulates hunger, resulting in more food consumption. The findings must be duplicated in humans, but they serve to demonstrate the complexity of the biome/diet relationship and the confluence of multiple factors that are involved in metabolic dysfunction and obesity.

THE HEALTH CONSEQUENCES OF OBESITY

Many chronic illnesses and conditions are directly caused or adversely affected by obesity. These include diabetes mellitus (particularly type 2), a number of cancers, cardiovascular disease, hypertension, and osteoarthritis. These and other comorbid conditions directly related to obesity decrease longevity and quality of life. The metabolic syndrome of dyslipidemia, insulin resistance (IR), and central adiposity is strongly associated with obesity. Oxidative stress (OS) and chronic inflammation are the principal causes of IR (30). Obesity increases OS by increasing substrates for mitochondrial energy production (30) and the excess energy production necessary to support a larger mass of tissue. Like a furnace, the greater the energy production, the more noxious byproducts (free oxygen radicals) are produced. Central

obesity also causes systemic release of adipose-derived inflammatory cytokines (31), which in turn cause OS and IR. IR leads to higher circulating glucose, which itself increases OS (32). Thus a vicious cycle is set up which can result in type 2 diabetes, dyslipidemia, vascular and renal impairment, retinal vascular disease and blindness, peripheral neuropathy, and peripheral vascular disease causing senility, disability, and even amputations. Further evidence that OS is the cause of IR is the increased insulin sensitivity with consumption of potent antioxidants such as chocolate (33) and berries (34) and physical activity and increased muscle mass (35), which decease OS. Finally, Alzheimer disease is strongly associated with chronic insulin resistance (36).

Cancer

Obesity increases the risk of cancers of the colon, rectum, breast, uterus, esophagus, pancreas, kidney, and gallbladder. It has been implicated in several others (e.g., brain [37] and lymphomas) and increases the aggressiveness of prostate cancer, making it more likely to recur (www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet). The American Cancer Society states that "Excess body weight contributes to

as many as one out of five of all cancer-related deaths" (www.cancer.org/cancer/cancercauses/dietandphysicalactivity/bodyweightandcancerrisk/body-weight-and-cancer-risk-effects). Weight loss has been documented to reduce breast cancer risk (38).

Coronary Artery Disease and Hypertension

It has been estimated that for every 10 pounds of weight gain there is a 20% increase in hypertension and that about 70% of "unexplained" hypertension is from obesity (39). Blood pressure can usually be lowered or even normalized by losing weight. Coronary artery disease is the consequence of OS, inflammation, dyslipidemia, and diabetes and is worsened by hypertension. Congestive heart failure, angina, and myocardial infarction are common consequences of obesity, and a significantly elevated BMI increases the risk of a fatal myocardial infarction (40).

Years of Life and Healthy Years Lost

More years are lost from obesity for men than for women, with earlier onset of obesity, and with a higher BMI. At age 20–39 years, obese women will lose ~6 years of life and 15–19 years of healthy life (41).

Osteoarthritis

The joints evolved when humans weighed less and are not designed for supporting an excess load. The incidence of osteoarthritis is more than twice as high in obese U.S. adults compared with normal/underweight individuals (42). In women, loss of as little as 11 pounds reduced the incidence of osteoarthritis by one-half (43).

Other Health Issues

Obesity also increases arrhythmias, sudden cardiac death (44), asthma, sleep apnea, thrombophlebitis, gallstones, urinary incontinence, depression, sexual dysfunction (more for men), low quality of life, and easy fatigability (www.cdc.gov/healthyweight/effects/).

WHAT CAN AN INDIVIDUAL DO TO LIVE AND SURVIVE IN A HEALTH HOSTILE ENVIRONMENT?

The following are 12 things well recognized by specialists working in this field that an individual can do to mitigate the effects of the obesity crisis on him or herself:

1. Record your favorite TV programs and watch one each night as a special treat rather than allowing TV to steal time better spent on maintaining your most precious asset (your body).
2. Get 7–8 hours of sleep each night. Insufficient sleep changes your appetite and satiety hormones to make you crave more food (45, 46).
3. Do a half-hour of moderate exercise daily most days of the week, which is the current recommendation by the Centers for Disease Control and Prevention.

4. Twice per week do 30 minutes of resistance exercises to maintain/build lean muscle that is more metabolically active and will make you more insulin sensitive.
5. Avoid concentrated calories lacking in nutrients such as sweets, fried foods and fatty servings of meat.
6. Eat nutrient-dense foods with greater water content and fewer calories that will better fill you up for the volume consumed (47), such as leafy greens, vegetables, whole fruit, and fish.
7. Eat a well balanced breakfast. Skipping breakfast was shown to be associated with a 4.5-fold risk of obesity (48).
8. Take every opportunity throughout your day to "exercise in real time." Stand rather than sit, take the stairs instead of the elevator, walk to the store from the first parking space you see, or walk to see your colleague down the hall rather than using text or e-mail.
9. Reduce portion sizes by sharing meals or taking half home. Even leaving food uneaten will ultimately save you money by avoiding all of the costs associated with excess weight.
10. Eat slowly to allow yourself to feel full. Stop when feeling almost full, and you will find that 15–20 minutes later you will feel satisfied. Spoiling your appetite with a low-calorie snack a half-hour before a situation that has high risk for overindulgence could save you from yourself.
11. Avoid buffets and "all you can eat" situations or at least look through all of the options and pick just a few that are appealing.
12. Alcohol provides empty calories and should be avoided for anyone trying to control his or her weight. Beer also contains maltose that has a high glycemic index, leading to the well recognized "beer belly."

The most daunting problem causing obesity is that there are ~350 days in every year and 3,500 calories are converted to a pound of fat. Only 10 extra calories per day (e.g., one Life Savers candy) will therefore cause a weight gain of a pound per year and 50 pounds in 50 years, which is sufficient to cause obesity. This is not "rocket science," but it does take will power and proper choices by individuals to behave for their long-term benefit in our extremely health-hostile environment. The good news is that a few good decisions every day can counter some not-so-good decisions and also add up over time to prevent weight gain.

POTENTIAL SOLUTIONS TO THE OBESITY CRISIS

First, governmental agencies, stake-holding organizations, and the public at large must fully understand the magnitude and far-reaching effects of excess body weight and treat it as a true crisis at a level of threat greater than terrorism. Almost ten times as many lives (~300,000) are lost every year in the U.S. because of obesity than all terrorist attacks including and since "9/11," and each of those individuals first suffered 10–20 years of serious health issues and disability. As consumption of finite health resources from this pandemic continues to grow, existing and future treatments will

inevitably have to be rationed, with disproportionate effects on the poorest individuals and nations. Mounting health care costs also divert resources from other pressing needs, even including national security (the epidemic has raised concerns that fewer Americans will be fit enough to serve in our military) [49].

Undoubtedly a major contributor to the crisis is an environment that has increasingly removed most physical activity from everyday life while at the same time providing limitless inexpensive sedentary forms of entertainment. Average TV viewing by American adults is a staggering 4–5 hours per day. Hours of TV viewing correlate with extent of obesity, an effect exaggerated by the effect of low sleep duration on hunger and satiety hormones. To counter those trends is extremely difficult and must involve public education, community planning for and encouragement of exercise opportunities, and efforts by medical insurers such as free gym memberships.

A very large factor in this crisis is the ready availability of inexpensive processed and calorie-dense foods, fast-food outlets, and large portion sizes. Through recognition of the overriding importance of excess weight in childhood in fueling obesity later in life, efforts to alter the food environment in schools have seen limited success, but the gains are easily lost during extended yearly vacations. Unfortunately in society in general, efforts to limit even the most egregious promoters of the crisis, such as taxing or eliminating very large containers of sugary soft drinks, has met major push-back from consumers. Food has become a form of entertainment, often with celebrations centering on unhealthy foods. However, efforts to ban sweets at school parties, for example, have met with vigorous parental opposition.

Perhaps lessons can be drawn from the remarkable progress in decreasing use of tobacco, in part through education of its dangers, such as warnings on cigarette packages, and in part by increasing cost through taxation. Similar measures are possible, such as taxing unhealthy foods such as sugar, processed foods, and fast foods and providing subsidies for vegetables, but any such measures are certain to meet opposition from industry and various groups against government intervention. Also, the harmful effects to others of second-hand smoke is a powerful motivator for regulation, whereas the effects of dietary overindulgence on future rationing of finite health resources is more indirect for the public to consider with the weight it deserves.

Another option, following the model of tobacco, would be to cost the individual more by charging higher health insurance premiums for those who have excess weight and risk factors and do not make the effort to reduce. This has already been occurring through individual employers providing insurance for their workers, but it has resulted in push-back from obesity support groups and conservative media. A further obstacle has been the successful efforts to categorize obesity as a disease, which makes financial disincentives less acceptable. Also, "medicalization" of a condition is usually less cost-effective than prevention. Although we could hope that insurance coverage of obesity would allow physicians to advocate prevention for individual patients, the time requirement involved makes treatment efforts more financially rewarding for the practitioner. In the U.S., a further large obstacle is that government has fewer incentives because health care costs are only partially from government revenue. Countries with a single-payer system for health care have a major advantage in having their incentive for cost control maximized.

Of course, we hope that as biotechnology yields more knowledge regarding the intricacies of energy management by the body and the hormonal control of appetite and satiation, current efforts to find treatments and drugs capable of arresting the epidemic may come to fruition, particularly efforts to alter the gut microbiome. In the interim, we should not ignore any of the measures we have discussed that can be used to effect real progress to stabilize if not reverse the unfortunate trends that have continued to defy efforts by societies and individuals. The single most effective measures may be efforts within motivated communities, including fertility specialists and obstetrician-gynecologists [50], and by each individual to make several responsible choices each and every day to maintain their most precious asset—their body.

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