Current Research

Beyond Energy Balance: There Is More to Obesity than Kilocalories

GEORGE A. BRAY, MD; CATHERINE M. CHAMPAGNE, PhD, RD, FADA

ABSTRACT

Using an epidemiologic model of the interactions between environmental agents and human hosts to explain obesity, we explored food, medications, physical inactivity, toxins, and viruses as environmental agents that interact with a genetically programmed host to disturb energy balance and cause obesity. Large portion sizes, high fat intakes, easy access to calorically sweetened beverages, and lack of any need to be physically active all play a role in the toxic environment that leads to obesity. The genetic and physiologic responses of a host determine whether or not this toxic environment will produce obesity. Reversing the current trends of obesity requires a new look at the limits of the energy balance concept, and a better understanding of how environmental factors acutely and chronically change the responses of susceptible hosts.

J Am Diet Assoc. 2005;105:S17-S23.

Obesity is a chronic, relapsing, stigmatized, neurochemical disease that is increasing in prevalence (1,2). During the early part of the 20th century the prevalence of obesity rose slowly, but around 1980 it began to rise more rapidly. Children are affected by obesity, with the prevalence rising from 5% in 1960 to 15% in 2000 (2). Associated with this rise in obesity rates was an increase in the prevalence of type 2 diabetes mellitus in children and adolescents (3). This presages a dire future for these children as complications of blindness, heart disease, renal failure, and amputation disable them during the next 20 years or so.

Obesity increases health risk and the cost of health care (4). Diabetes mellitus, gall bladder disease, heart disease, hypertension, osteoarthritis, and several types of cancer are all increased in persons with overweight. These risks can be reversed by modest weight loss. To tackle the hazards of obesity for children, adolescents, and adults, we need to adopt effective strategies for prevention and, where prevention fails, for treatment of obesity. Many children and adults with overweight are traumatized by the stigma of obesity. Children may be teased at school and labeled "fatty." Adults experience prejudice in social and economic situations. Measures of quality of life show that persons with obesity score lower on many scales and that weight loss improves their quality of life.

G. A. Bray is a Boyd professor in the Louisiana State University System and is a professor of medicine at the Pennington Biomedical Research Center and C. M. Champagne is a professor of nutrition at the Pennington Biomedical Research Center, Baton Rouge, LA.

Address correspondence to: George A. Bray, MD, Pennington Center, 6400 Perkins Rd, Baton Rouge, LA 70808. E-mail: brayga@pbrc.edu

0002-8223/05/10505-1003$30.00/0

doi: 10.1016/j.jada.2005.02.018

BEYOND ENERGY BALANCE

There is no doubt that obesity results from energy imbalance, and that we can predict the magnitude of weight change over time if we know the net energy balance. However, it is what the energy balance concept does not tell us that is most important in dealing with obesity. The first law of thermodynamics, which describes the concept of energy balance, does not tell us anything about the regulation of food intake or the way in which genes are involved in this process. It does not help us to understand why men and women distribute fat in different places on their bodies, or to understand how fat distribution changes with age. The first law also doesn't help us understand why some drugs produce weight gain and others weight loss, or why weight loss stops after a period of treatment with diet or medication (5). Understanding these mechanisms will allow us to tackle the epidemic of obesity.

Another problem with the concept of energy balance is that we are never in energy balance. To study energy balance, we housed healthy men in small rooms (respiration calorimeters) where we manipulated food intake and exercise to get as close as possible to zero energy balance; ie, when energy intake equals energy expenditure. In fact, we rarely got closer than 50 kcal/day, or about 2.5% out of an intake of 2,000 kcal/day. The values for energy imbalance in these healthy men ranged from 50 to 150 kcal/day. Had these differences been maintained for 1 year, these men would be expected to gain about 2.5 kg (5.5 lb) at the smaller error and 7.5 kg (16.5 lb) at the larger error. To keep from gaining weight we must correct energy intake or energy expenditure every few days to counterbalance the error that occurred on previous days. These corrective responses around a weight of relative stability make it look like there is weight regulation. For some persons, the oscillations around this balance point can keep weight stable for many years. For others, there is a slow upward drift in this regulatory point and weight is gained gradually. Persons fortunate enough to have robust corrective responses can maintain a stable weight over many years. If their weight is not stable, two other

strategies are available. One is conscious control, exhibited in some persons by a pattern of restrained eating. The second and perhaps best way to maintain weight over a long period is not counting kilocalories, but weighing oneself regularly at the same time of day on an accurate scale, and then decreasing food intake or increasing activity if weight has been gained. This can allow one to correct weight gain before it gets out of hand.

The consequences of energy imbalance are graphically illustrated in the movie by Morgan Spurlock, *Supersize Me* (2004, Hart Sharp Video, Roadside Attractions, and Samuel Goldwyn Films), in which the documentarian gained 25 lb in 1 month by eating all of his meals at McDonald's restaurants, and supersizing the portions if the clerk asked. Because we are never in energy balance, we need to view energy balance as an ideal—not a realistic goal to be obtained by counting kilocalories.

From the perspective of energy balance, the solution to obesity should be simple: Eat less and exercise more. The truth of this advice was shown by Kinsell and colleagues (6) for overweight persons in a metabolic ward who were provided with all of their food. During the course of several months, patients ate diets providing 1,200 kcal/day. After an initial rapid weight loss due to rebalancing body fluids, subsequent weight loss was linear and was not affected by wide variations in macronutrient content of the diet. More recent studies using foods that were tagged with a nonradioactive isotope (carbon-13) showed that the better the adherence to a diet, the greater the weight loss (7). Thus, it is adherence to diets, not diets themselves, that makes the difference (8).

Another limitation to the concept of energy balance as the cause of obesity is the implication that if one is getting fatter, it is one's own fault. One need only to control his or her energy intake and energy expenditure to control the problem. This implies that we should blame our children for their obesity. This seems grossly unfair. If obesity were easily controlled by moderating energy intake, the US military would not discharge up to 5,000 men and women yearly for failing to meet its weight standards. If loss of livelihood is not sufficient motivation to lose weight, then the problem must be more complex.

The cure of obesity in leptin-deficient human beings treated with leptin shows a genetic basis for one type of obesity, and that obesity is more than simply lack of willpower (9). Although simple in theory, applying the ideas of energy balance and counting kilocalories to body weight control has proven unsuccessful. More than 95% of persons using diet, behavior, and lifestyle approaches to lose weight regained it in less than 5 years (10).

ENVIRONMENTAL AGENTS

The current epidemic can be viewed from the perspective of an epidemiologic model, shown in Figure 1. Food, drugs, viruses, toxins, and low physical activity are the environmental agents that facilitate the development of obesity. One or more of these factors acting on a susceptible host can produce obesity. Using this model, we can approach the problem by manipulating either the environment or the host.

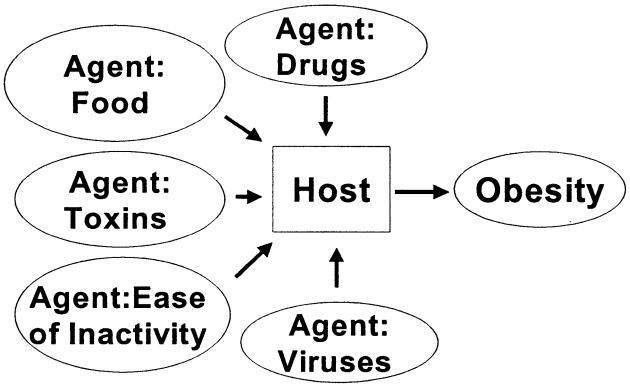


Figure 1. Epidemiologic model of obesity. In this model, the agent that produces obesity is food or food-related products. If food is in limited supply, obesity does not develop. The food that is ingested interacts with the host. In a susceptible host, the toxic effects of food produce the disease of obesity.

Food

As the spokesperson for the Grocery Manufacturers of America said in the movie *Supersize Me*, "The food industry is part of the problem." Several components of our food supply may be important in determining whether or not obesity develops. The first of these is the portion size of packages and servings. There is convincing evidence that when larger portion sizes are provided, more food is eaten (11). Portion sizes have dramatically increased in the past 40 years (12) and now need reduction. Calorically sweetened beverages that contain 10% high-fructose corn syrup (HFCS), available in containers of 12, 20, or 32 oz, provide 150, 250, or 400 kcal if it is all consumed. Many foods list the kilocalories per serving, but the package often contains more than one serving.

Patterns of food consumption have changed during the past 30 years (13). The most striking change from 1970 to 2000 was in the rising consumption of HFCS (14). HFCS is now used as the caloric sweetener in almost all soft drinks as well as in reconstituted juice drinks and many solid foods. The rise in HFCS consumption occurred during the same time interval as the rapid rise in the prevalence of obesity (2,14). On one hand, this relationship may be strictly coincidental. But, on the other hand, it may not (Figure 2). Fructose is sweeter than glucose, or sucrose, a molecule that is a combination of fructose and glucose. In addition, HFCS is a solution of both fructose and glucose as separate molecules, and thus it differs in osmotic properties from a solution with the same concentration of sucrose.

The intake of calorically sweetened beverages can be related to the epidemic of obesity (14-17). Ludwig and colleagues (15) reported that the intake of soft drinks was a predictor of initial body mass index (BMI) in children in the Planet Health Study. They also showed that higher soft drink consumption predicted an increase in BMI during nearly 2 years of follow-up, those with the highest soft drink consumption at baseline having the highest increase in BMI. A Danish study (16) showed that persons consuming calorically sweetened beverages over 10 weeks gained weight, whereas subjects drinking the

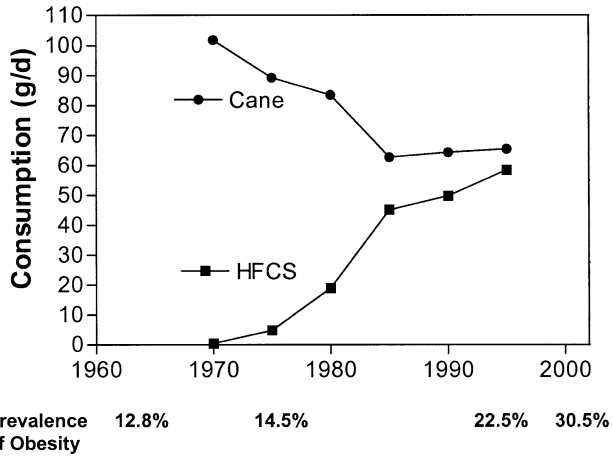


Figure 2. The consumption of sweetened carbonated beverages and the relation of high-fructose corn syrup consumption (HFCS) to the epidemic of obesity.

same amount of artificially sweetened beverages lost weight. In children, a study focusing on reducing intake of carbonated beverages and replacing them with water showed slower weight gain than those not advised to reduce the intake of carbonated beverages (18). These studies strongly suggest that energy-containing soft drinks could play a role in the epidemic of obesity. If so, then their consumption should be curtailed, particularly for very young children in whom neuronal changes may reflect the response of insulin to these beverages, and for school children for whom beverages are a ready source of energy with few other nutrients.

Dietary fat is another component that may be related to the epidemic of obesity (19). Foods combining fat and sugar may be a particular problem because they are often very palatable and usually inexpensive (20). The Leeds Fat Study (21) showed that persons who were high fat consumers had an increased prevalence of obesity. Providing palatable low-fat foods is important.

There are now several studies showing that when breastfeeding is the sole source of nutrition for more than 3 months, risk of obesity is significantly reduced at the time of entry into school and in adolescents when compared with infants who are not breastfed at all or for less than 3 months (22). This may be an example of infant imprinting. The composition of the breast milk may also be important. During the past 50 years, the proportion of n-6 fatty acids in human breast milk has increased, reflecting changes in dietary fat composition. The amount of n-3 fatty acids in breast milk has remained constant. A higher amount of n-6 fatty acids provides prostaglandin derivatives that stimulate fat cell proliferation in infants (23). This is a concept that needs additional evaluation. The rate of weight gain between ages 2 and 12 years also predicts future obesity—those children who gain the most weight have the highest risk of becoming obese (24). Monitoring weight change early can be predictive of future obesity.

Calcium intake is another dietary factor that may be related to the development of obesity in children and adults. The level of calcium intake in population studies is inversely correlated with the risk of being overweight. In other epidemiologic studies and in feeding trials, higher dietary calcium is associated with reduced BMI or reduced incidence of insulin resistance (25).

Low Levels of Physical Activity

Epidemiologic data show that low levels of physical activity and watching more television predict higher body weight (26). Recent studies suggest that persons in US cities where they had to walk more than persons in other cities tended to weigh less. Low levels of physical activity also increase the risk of early mortality. Using normal weight, physically active women as the comparison group, Hu and colleagues (27) found that the relative risk of mortality increased to 1.55 in inactive lean women, to 1.92 in active obese women, and to 2.42 in women who are obese but physically inactive. It is thus better to be thin than fat and to be physically active rather than inactive.

Drugs and Chemicals that Produce Weight Gain

Several drugs can cause weight gain, including a variety of hormones and psychoactive agents (28). The degree of weight gain is generally not sufficient to cause substantial obesity, except occasionally in patients treated with high-dose corticosteroids, some psychoactive drugs, or valproate. These drugs can also increase the risk of future type 2 diabetes mellitus. Cessation of smoking is another environmental agent that will affect body fat stores. Partially mediated by nicotine withdrawal, a weight gain of 1 to 2 kg is seen in the first few weeks and is often followed by an additional 2- to 3-kg weight gain over the next 4 to 6 months, resulting in an average weight gain of 4 to 5 kg or more (29). The concept that increasing energy expenditure through drugs that act like physical activity is being tested in several ways, but as yet no effective agents have been identified.

Viruses

The injection of several viruses into the central nervous system produces obesity in mice. Recent findings of antibodies to one of the adenoviruses (AM-36) in larger amounts in obese human beings raises the possibility that viruses are involved in some cases (30). The adenoviral syndrome can be replicated in nonhuman primates and is characterized by modest obesity and a low circulating cholesterol concentration. Further studies are needed to establish that a syndrome of obesity associated with low concentrations of cholesterol clearly exists in human beings. If so, this would enhance the value of the epidemiologic model.

Toxins

In experimental animals, exposure in the neonatal period to monosodium glutamate, a common flavoring ingredient in food, will produce obesity. A similar effect of reduction in glucose can also produce obesity, suggesting that the brains of growing animals, and possibly those of human beings, may respond with damage to the metabolic sensors that regulate food needs. In human beings, body fat stores many toxic chemicals that are mobilized with

weight loss. The metabolic rate can be reduced by organochlorine molecules (31), and prolonged exposure to many chlorinated chemicals in our environment has conceivably affected metabolic pathways and energy metabolism. Food additives are another class of chemicals that are widely distributed and may be involved in the current epidemic of obesity.

THE HOST

Genetic Factors

Significant insight into the causes of obesity has come from the cloning of genes that produce obesity in animals. Extensive molecular and reverse genetic studies (mouse knockouts) have also helped establish critical pathways regulating body fat and food intake. Leptin, identified in 1994, is an important hormone produced in adipose tissue and secreted into the blood relative to the amount of body fat (32). Leptin-deficient persons are massively obese and when leptin is administered, food intake falls and body fat is mobilized until body weight is nearly normalized, indicating that important metabolic-genetic pathways exist that can control body fat. Similar deficiencies in food intake have been found with genetic changes in the amino acid sequence of a key regulator of food intake called the melanocortin-4 receptor (33). When this receptor is inactive, food intake is nearly as high as when leptin is deficient, but when partially preserved, the food intake is only modestly above control levels (34). These basic biological insights tell us that body fat has important regulation that is largely, if not completely, independent of will power.

Intrauterine Imprinting

Several intrauterine events may lead to obesity later in life, probably due to fetal imprinting as a result of early exposure that affects brain plasticity. The Dutch winter famine of 1945 showed that starvation of infants in utero could affect long-term postnatal weight status. Another example is the infants of mothers who smoked during pregnancy, who have an increased risk of becoming overweight during their first 3 decades of life when compared with infants of mothers who did not smoke during pregnancy (35). Similarly, infants of mothers with diabetes are at higher risk of developing obesity than infants born to mothers who did not have diabetes during pregnancy (36). Infants who are small for their gestational age are at higher risk of developing central adiposity and diabetes than normal-weight infants (24). Finally, experimental studies teach us that exposure to high levels of insulin during the period of brain plasticity can lead to obesity later in life.

Physiologic Control

To maintain a stable body weight over time, the body must correct daily errors in energy balance. A number of physiologic factors are known to disturb this correction. A high rate of carbohydrate oxidation, as measured by a high respiratory quotient predicts future weight gain (37). One explanation is that when carbohydrate oxidation is higher than carbohydrate intake, carbohydrate stores are depleted and we must eat to replace them. Persons with obesity who have lost weight are less effective in increasing fat oxidation in the presence of a high-fat meal than normal-weight persons, and this may be one reason why they are so susceptible to weight regain. Low metabolic rate may also predict future weight gain (38).

Physical activity gradually declines with age, accounting for some increase in body fat. Recent studies suggest moderate exercise is beneficial in reducing risk of cardiovascular disease (39) and type 2 diabetes, and in facilitating the oxidation of fat in the diet (40).

Fat cells in our body serve two major functions. They store and release fatty acids ingested from food or from liver or fat cells and they secrete many important hormones and chemicals. The discovery of leptin catapulted the fat cell into the arena of endocrine cells (41). In addition to leptin, the fat cell secretes a variety of other peptides (lipoprotein lipase, adipsin [complement D], complement C, adiponectin, tumor necrosis factor-α, interleukin-6, plasminogen activator inhibitor-1, angiotensinogen, bradykinin, and resistin). The fat cell also releases other metabolites such as lactate, fatty acids, glycerol, and prostacyclin formed from arachidonic acid. Our understanding of fat cells as important endocrine cells continues to expand.

To maintain a stable body weight over time, the body must correct daily errors in energy balance.

Production of cortisol from inactive cortisone in fat cells by the enzyme 11-β-hydroxysteroid dehydrogenase type 1 may be important in determining the quantity of visceral adipose tissue (42). Changes in this enzyme may contribute to the risk for menopausal women of developing more visceral fat. High levels of this enzyme keep the quantity of cortisol in visceral fat high, providing a fertile environment for developing new fat cells.

Information about hunger and satiety comes from the gastrointestinal tract where several peptides signal the body to stop or start eating. Ghrelin (43) has received recent attention because, in contrast to other gastrointestinal hormones, it stimulates food intake. Levels of ghrelin are low in obesity, except in those with Prader-Willi syndrome, suggesting that it may play a role in the development of hyperphagia seen in these persons.

The brain is a receiver, transducer, and transmitter of information about hunger and satiety. Several neurotransmitter systems are involved in regulation of food intake (44). Receptors for serotonin modulate both the quantity of food eaten and macronutrient selection and their loss through genetic targeting produces obesity. Peptide neurotransmitters also play a very important role in the regulation of feeding. Sleep deprivation is one way to enhance the release of peptides that produce hunger (45). In young men allowed to sleep only 4 hours/night for 2 days, leptin decreased and ghrelin increased relative to the pattern seen with 10 hours of sleep on each of two

nights. Thus, our epidemic of obesity may reflect one response to less sleep.

OBESITY IS A CHRONIC, RELAPSING, NEUROCHEMICAL DISEASE PRODUCED BY THE INTERACTION OF ENVIRONMENT AND HOST

The epidemic of obesity occurs on a genetic background that has not changed significantly in the past 100 years and certainly not since the epidemic began 20 years ago. Nonetheless, it is clear that genetic factors play a critical role in the susceptibility of becoming obese in a "toxic environment" (46). One analogy is that genes load the gun and a permissive or toxic environment pulls the trigger. Modification of environmental factors acting on our ancient genes must be the strategy to prevent the disease. To believe that this can be done by a person alone is to miss the argument of how environmental factors, with major emphasis on the imprinting of the plastic brain of a growing child or adolescent, have acted on these genes to produce the current epidemic.

We argue that the first law of thermodynamics has lulled us into the uncomfortable place of believing that persons, through willpower, increased food choices, or more places to exercise, can overcome the current epidemic of obesity. Cognitive approaches relying on individual commitment and resolve have been unsuccessful in stemming obesity in the past, and nothing suggests that they will be more successful in the future.

At least three preventive strategies are available to deal with the epidemic: education, regulation, and modification of the food supply.

We also argue that it is what the first law of thermodynamics does not tell us that is important. In this context, it is the unconscious host systems on which environmental factors operate to produce obesity. If the vending machines that now provide kickbacks to schools contained beverages with no added sugar or HFCS, available kilocalories would be reduced. We have argued that the exposure of young children to HFCS may produce detrimental imprinting of the brain, making obesity more likely and more difficult to control.

At least three preventive strategies are available to deal with the epidemic: education, regulation, and modification of the food supply. Education in school curricula about good nutrition and healthful weight would be beneficial in helping all children learn how to select appropriate foods and could be included in schools, with school breakfast and lunch programs designed to match these educational messages.

It is unwise to rely on educational strategies alone because they have not prevented the epidemic of obesity. Regulation is a second strategy. Regulating an improved food label is one good idea. Regulations on appropriate serving sizes might be part of the information provided by restaurants when requested.

Modification in some components of the food system is a third and most important strategy. Because the energy we eat comes from food, we need to modify this system to provide smaller portions and less energy density if we are to succeed in combating the epidemic of obesity.

CONCLUSIONS

Where do dietetics professionals fit into this picture? First, educated dietetic professionals need to be keenly aware of the complexity of the obesity problem. A dietetics professional obviously cannot alter a person's genetic makeup, but he or she is able to address the environmental aspects that serve to exacerbate the situation. Simply handing out diet sheets is not enough and should be discouraged. Helping a patient with obesity requires attention to overall diet history, current eating habits, activity patterns, and behavioral obstacles that either cause problems or prevent change. While quick weight loss may be a patient's immediate desire, the need for permanent lifestyle changes should be the primary objective. Tips for addressing this have been outlined previously by Bray and Champagne (47). Finally, dietetics professionals can be instruments of change by appealing to policymakers to modify environmental conditions, such as the school vending machines. We can think of no better professionals to craft this effective message to both lawmakers and school officials alike.

FUTURE DIRECTIONS

Our lives are constrained by the laws of nature—gravity, momentum, and thermodynamics. The strategies we employ to deal with the influence of these laws on our lives include education, regulation, and product design. Deaths resulting from the effects of the laws of momentum produced by automobile accidents provide a glimpse into the strategies we could use to minimize accidents just as the law of energy balance provides ideas about how we might minimize obesity. Although the laws of momentum or the laws of thermodynamics cannot be changed, their ability to produce automobile accidents and obesity can be mitigated. This can be done through better education about driving and about nutritional needs to prevent obesity. This can be complemented by regulations that, in the case of cars, include requiring seat belts, airbags, and other safety devices. In the case of obesity, it includes limiting access to large portion sizes and high–energy-density foods and having an environment in which physical activity is more difficult to avoid. Finally, product design can make cars safer, and modifying the types of foods that are available can provide strategies to combat the obesity epidemic by redesigning the food environment.

This research was supported in part by the US Department of Agriculture CSREES Special Grant No. 2003-34323-14010 to the Pennington Biomedical Research Center.

References

1. Bray GA. Obesity is a chronic, relapsing neurochemical disease. *Int J Obes Relat Metab Disord*. 2004;28: 34-38.

2. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288:1723-1727.
3. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA*. 2002;288:1728-1732.
4. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH. Clinical implications of obesity with specific focus on cardiovascular disease: A statement for professionals from the American Heart Association Council on Nutrition, Physical Activity and Metabolism endorsed by the American College of Cardiology Foundation. *Circulation*. 2004; 110:2952-2967.
5. Bray GA, Greenway FL. Current and potential drugs for treatment for obesity. *Endocr Rev*. 1999;20:805-875.
6. Kinsell LW, Gunning B, Michaels GD, Richardson J, Cox SE, Lemon C. Calories do count. *Metabolism*. 1964;13:195-204.
7. Lyon XH, Di Vetta V, Milon H, Jequier E, Schutz Y. Compliance to dietary advice directed towards increasing the carbohydrate to fat ratio of the everyday diet. *Int J Obes Relat Metab Disord*. 1995;19:260-269.
8. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. *JAMA*. 2005;293:43-53.
9. Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, O'Kirwan F, Whitby R, Liang L, Cohen P, Bhasin S, Krauss RM, Veldhuis JD, Wagner AJ, DePaoli AM, McCann SM, Wong ML. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. *Proc Natl Acad Sci USA*. 2004;101: 4531-4536.
10. *Weighing the Options: Criteria for Evaluating Weight-Management Programs*. Washington, DC: Institute of Medicine National Academy Press; 1995.
11. Diliberti N, Bordi PL, Conklin MT, Roe LS, Rolls BJ. Increased portion size leads to increased energy intake in a restaurant meal. *Obes Res*. 2004;12:562-568.
12. Nielsen SJ, Popkin BM. Patterns and trends in food portion sizes, 1977-1998. *JAMA*. 2003;289:450-453.
13. Putnam J, Allshouse JE. *Food Consumption, Prices and Expenditures, 1970-97*. Washington, DC: US Dept of Agriculture Economic Research Service; 1999.
14. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr*. 2004;79: 537-543.
15. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: A prospective, observational analysis. *Lancet*. 2001;357:505-508.
16. Raben A, Agerholm-Larsen L, Flint A, Holst JJ, Astrup A. Meals with similar energy densities but rich in protein, fat, carbohydrate, or alcohol have different effects on energy expenditure and substrate metabolism but not on appetite and energy intake. *Am J Clin Nutr*. 2003;77:91-100.
17. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willet WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004; 292:927-934.
18. James J, Thomas P, Cavan D, Kerr D. Preventing childhood obesity by reducing consumption of carbonated drinks: Cluster randomised controlled trial. *BMJ*. 2004;328:1237.
19. Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr*. 1998;68:1157-1173.
20. Drewnowski A, Specter SE. Poverty and obesity: The role of energy density and energy costs. *Am J Clin Nutr*. 2004;79:6-16.
21. Blundell JE, MacDiarmid JI. Fat as a risk factor for overconsumption: Satiation, satiety, and patterns of eating. *J Am Diet Assoc*. 1997;97(suppl):S63-S69.
22. von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H. Breast feeding and obesity: Cross sectional study. *BMJ*. 1999;319: 147-150.
23. Ailhaud G, Guesnet P. Fatty acid composition of fats is an early determinant of childhood obesity: A short review and an opinion. *Obes Rev*. 2004;5:21-26.
24. Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, Biswas SK, Ramji S, Prabhakaran D, Reddy KS. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med*. 2004;350:865-875.
25. Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: The CARDIA Study. *JAMA*. 2002;287:2081-2089.
26. Hancox RJ, Milne BJ, Poulton R. Association between child and adolescent television viewing and adult health: A longitudinal birth cohort study. *Lancet*. 2004;364:257-262.
27. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med*. 2004;351:2694-2703.
28. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: A comprehensive research synthesis. *Am J Psychiatry*. 1999;156:1686-1696.
29. O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the Lung Health Study. *Am J Epidemiol*. 1998;148:821-830.
30. Dhurandhar NV, Israel BA, Kolesar JM, Mayhew GF, Cook ME, Atkinson RL. Increased adiposity in animals due to a human virus. *Int J Obes Relat Metab Disord*. 2000;24:989-996.
31. Tremblay A, Pelletier C, Doucet E, Imbeault P. Thermogenesis and weight loss in obese individuals: A primary association with organochlorine pollution. *Int J Obes Relat Metab Disord*. 2004;28:936-939.
32. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L,

Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372: 425-432.
33. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med*. 2003;348:1085-1095.
34. Farooqi IS, Yeo GS, O'Rahilly S. Binge eating as a phenotype of melanocortin 4 receptor gene mutations. *N Engl J Med*. 2003;349:606-609.
35. Toschke AM, Ehlin AG, von Kries R, Ekbom A, Montgomery SM. Maternal smoking during pregnancy and appetite control in offspring. *J Perinat Med*. 2003;31: 251-256.
36. Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC. Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. *Diabetes Care*. 1999;22: 944-950.
37. Zurlo F, Lillioja S, Esposito-Del Puente A, Nyomba BL, Raz I, Saad MF, Swinburn BA, Knowler WC, Bogardus C, Ravussin E. Low ratio of fat to carbohydrate oxidation as predictor of weight gain: Study of 24-h RQ. *Am J Physiol*. 1990;259:E650-E657.
38. Astrup A, Gotzsche PC, van de Werken K, Ranneries C, Toubro S, Raben A, Buemann B. Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr*. 1999;69:1117-1122.
39. Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical activity recommendations: How much is enough? *Am J Clin Nutr*. 2004;79:913S-920S.
40. Smith SR, de Jonge L, Zachwieja JJ, Roy H, Nguyen T, Rood J, Windhauser M, Volaufova J, Bray GA. Concurrent physical activity increases fat oxidation during the shift to a high-fat diet. *Am J Clin Nutr*. 2000;72:131-138.
41. Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. *Cell*. 2001;104:531-543.
42. Hochberg Z, Friedberg M, Yaniv L, Bader T, Tiosano D. Hypothalamic regulation of adiposity: The role of 11beta-hydroxysteroid dehydrogenase type 1. *Horm Metab Res*. 2004;36:365-369.
43. Cummings DE, Shannon MH. Roles for ghrelin in the regulation of appetite and body weight. *Arch Surg*. 2003;138:389-396.
44. Cowley MA, Cone RD, Enriori P, Louiselle I, Williams SM, Evans AE. Electrophysiological actions of peripheral hormones on melanocortin neurons. *Ann N Y Acad Sci*. 2003;994:175-186.
45. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med*. 2004;141: 846-850.
46. Snyder EE, Walts B, Perusse L, Chagnon YC, Weisnagel SJ, Rankinen T, Bouchard C. The human obesity gene map: The 2003 update. *Obes Res*. 2004;12: 369-439.
47. Bray GA, Champagne CM. Obesity and the metabolic syndrome: Implications for dietetics practitioners. *J Am Diet Assoc*. 2004;104:86-89.

International Journal of Obesity (2010) 34, 84–88
 0307-0565/10 $32.00
www.nature.com/ijo

COMMENTARY

White hat bias: examples of its presence in obesity research and a call for renewed commitment to faithfulness in research reporting

MB Cope[1] and DB Allison[2]

[1]*Department of Pharmacology and Toxicology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA and* [2]*Section of Statistical Genetics, Department of Biostatistics, School of Public Health, and Clinical Nutrition Research Center, University of Alabama at Birmingham, Birmingham, AL, USA*

'White hat bias' (WHB) (bias leading to distortion of information in the service of what may be perceived to be righteous ends) is documented through quantitative data and anecdotal evidence from the research record regarding the postulated predisposing and protective effects of nutritively sweetened beverages and breastfeeding, respectively, on obesity. Evidence of an apparent WHB is found in a degree sufficient to mislead readers. WHB bias may be conjectured to be fuelled by feelings of righteous zeal, indignation toward certain aspects of industry or other factors. Readers should beware of WHB, and our field should seek methods to minimize it.
International Journal of Obesity (2010) **34,** 84–88; doi:10.1038/ijo.2009.239; published online 1 December 2009

Introduction

Scientific dialogue is dependent on fair and open presentation of data and evidence, yet concerns have been raised in recent years about bias in research practice. We present data and examples pertinent to a particular bias, a 'white hat bias' (WHB), which we define to be bias leading to distortion of research-based information in the service of what may be perceived as righteous ends. We evaluate WHB in the context of two illustrative obesity topics, nutritively sweetened beverage (NSB) consumption as a postulated risk factor[1] and breastfeeding as a postulated protective factor.[2]

Example 1—Data on citation bias

If secondary reportings of original research misleadingly cite papers with statements that inaccurately describe available evidence, then inaccurate beliefs may inappropriately influence clinical practice, public policy or future research. Previously,[3] we observed that two papers[4,5] had both statistically and non-statistically significant results on body weight, body mass index (BMI) or overweight/obesity status, which allowed future writers to potentially choose which results to cite, and were also widely cited, permitting a quantitative analysis of citations.

Correspondence: Professor DB Allison, Section of Statistical Genetics, Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Ryals Public Health Building, 1530 3rd Avenue S, RPHB 327, Birmingham, AL 35294-0022, USA. E-mail: Dallison@uab.edu
Published online 1 December 2009

Cited versus citing papers

A Web of Science search (through to October 2008) yielded 195 and 45 papers citing James *et al.*[4] and Ebbeling *et al.*,[5] respectively. We analyzed those in English (165 and 41, respectively).

James *et al.*[4] studied an intervention to decrease NSB consumption and adiposity among children. Dichotomized (overweight or obese versus neither overweight nor obese) and continuous (change in BMI) data were analyzed for statistical significance. The authors wrote:

> 'After 12 months there was no significant change in the difference in body mass index (mean difference 0.13, −0.08–0.34) or z score (0.04, −0.04–0.12). At 12 months the mean percentage of overweight and obese children increased in the control clusters by 7.5%, compared with a decrease in the intervention group of 0.2% (mean difference 7.7%, 2.2–13.1%).'

Ebbeling *et al.*[5] described a randomized controlled trial of a 25-week NSB reduction program in adolescents and wrote:

> 'The net difference (in BMI), $0.14 \pm 0.21\,kg/m^2$, was not significant overall.'

They then report a subgroup finding:

Table 1 Categorization of 165 papers citing James *et al.*[2]

Score	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*
No. of references in each category	14	74	2	21	2	1	1	50
Proportion (exact CIs)[a]	0.127 (0.071–0.199)	0.644 (0.548–0.729)	0.017 (0.003–0.068)	0.183 (0.119–0.268)	0.017 (0.003–0.068)	0.009 (0.001–0.055)	0.009 (0.001–0.055)	

Abbreviations: BMI, body mass index; CI, confidence interval. [a]Proportions and CIs are calculated with only categories A through to G in the denominator. Scoring key: (A) Accurate—described the non-significant result on continuous outcome (change in BMI) and described the significant result on the dichotomous outcome (overweight versus non-overweight). (B) Mildly misleading (positively)—Described the result of the intervention study as showing efficacy, benefit or statistical significance for the dichotomous outcome of overweight status, without mentioning the non-significant result on the continuous outcome. (C) Moderately misleading (positively)—Described the result of the intervention study as showing efficacy, benefit or statistical significance on some weight-related outcome without explicitly stating that it was on the proportion overweight *per se*. (D) Explicitly misleading (positively)—Described, with a factually incorrect statement, that the result of the intervention for a continuous weight-related outcome was significant or showed effectiveness. (E) Mildly misleading (negatively)—Described the result of the intervention study as not showing efficacy, benefit or statistical significance on the continuous measure of BMI, without mentioning the significant result on the dichotomous outcome. (F) Moderately misleading (negatively)—Described the result of the intervention study as not showing efficacy, benefit or statistical significance on some weight-related outcome without explicitly stating that it was on the continuous measure of BMI. (G) Explicitly misleading (negatively)—Described, with a factually incorrect statement, that the result for the dichotomous outcome was not significant or that a lack of effectiveness was shown for the dichotomous outcome. (H) Unscorable—Did not make explicit statements about the effects of the study, made statements that were too ambiguous to code or made statements that were self-contradictory.

> 'Among the subjects in the upper baseline-BMI tertile, BMI change differed significantly between the intervention…and control…groups, a net effect of $0.75 \pm 0.34\ kg/m^2$.'

Ebbeling *et al*. (p. 676) label the analysis in the total sample as the 'primary analysis.'

Data coding and analysis

Each paper citing either James *et al.*[4] or Ebbeling *et al.*[5] was categorized (see Tables 1 and 2) on the basis of how authors cited results related to body weight, BMI or overweight/obesity outcomes from these two papers in their report. Papers citing James *et al*. were independently coded by the authors of this paper (DBA or MBC). Any discrepancies were resolved by discussion. Papers citing Ebbeling *et al*. were scored by DBA and cross-checked by MBC. Proportions (with confidence intervals) were calculated (Tables 1 and 2). Exact binomial calculation tested the null hypothesis that the proportion citing papers in a misleading manner that exaggerated the strength of evidence was equal to the proportion citing papers in a misleading manner that diminished the strength of evidence; as such an equal proportion would suggest a lack of bias in the overall literature, even if not in any one paper.

Citation analysis results

Results were quite consistent across papers citing either James *et al.*[4] or Ebbeling *et al*.[5] The majority, 84.3% for James *et al*.[4] and 66.7% for Ebbeling *et al.*,[5] described results in a misleadingly positive manner to varying degrees (that is, exaggerating the strength of the evidence that NSB reduction showed beneficial effects on obesity outcomes). Some were blatantly factually incorrect in their misleading statements, describing the result as showing an effect for a continuous obesity outcome, when no statistically significant effect for continuous obesity outcomes was observed. In contrast, only four papers (3.5%) were negatively misleading (that is, underplayed the strength of evidence) for James *et al*.[4] and none were negatively misleading for Ebbeling *et al*.[5] Only 12.7 and 33% of papers accurately described complete overall findings related to obesity outcomes from James *et al*.[4] and Ebbeling *et al.*,[5] respectively.

To test whether the proportion of misleading reporting in the positive direction was equal to the proportion in the negative direction, we calculated the confidence interval on the proportion of misleading reportings in either direction that was positively misleading. This yields a proportion of 0.96 (95% CI: 0.903–0.985) for those citing James *et al*.[4] and 1.00 (95% CI: .832–1.000) for those citing Ebbeling *et al*.[5] and is significantly different from $\frac{1}{2}$ for each ($P<0.0001$), indicating a clear bias and potential for readers of the secondary literature to be deceived.

Example 2—Data on publication bias

NSB consumption

A meta-analysis on NSB consumption and obesity[6] found that estimated adverse associations were significantly smaller (that is, less adverse) among industry-funded than among non-industry-funded studies. One troubling conceivable explanation for this is that industry does something to bias results to make NSBs seem less harmful, but this is not the only conceivable explanation.

To examine this further, we requested, and Dr Vartanian[6] graciously provided, his meta-analysis data file. Focusing on cross-sectional studies, because a large number had adiposity indicators as outcomes, we conducted publication bias (PB) detection analyses.[7] PB causes the sample of studies published to not constitute a representative sample of the relevant studies that hypothetically could have been

Table 2 Categorization of 41 papers citing Ebbeling *et al.*[3]

Score	*A*	*B*	*C*	*D*	E	*F*	*G*
No. of references in each category	10	9	11	0	0	7	4
Proportion (exact CIs)[a]	0.333 (0.173–0.528)	0.300 (0.147–0.494)	0.367 (0.199–0.561)	0.000 (0.000–0.116)	0.000 (0.000–0.116)		

Abbreviation: CI, confidence interval. [a]Proportions and CIs are calculated with only categories A through to E in the denominator. Scoring key: (A) Accurate—Described both the non-significant result in the total sample and the significant result in the heaviest subgroup. (B) Patently misleading over-positive—Described as positive on weight without mentioning anything about the result only being in heaviest children. (C) Mildly misleading over-positive—Described as positive among the heaviest children without explicitly mentioning that there was no significant result in the total sample. (D) Mildly misleading over-negative—Described the null result in the total sample without explicitly mentioning the significant result in the heaviest subgroup. (E) Patently misleading over-negative—Described as negative in a way that explicitly indicated that there were no significant effects even in sub-groups. (F) Not directly relevant—Did not make clear and explicit statements about the effects of the study. (G) Ambiguous as to whether category A or E applies.

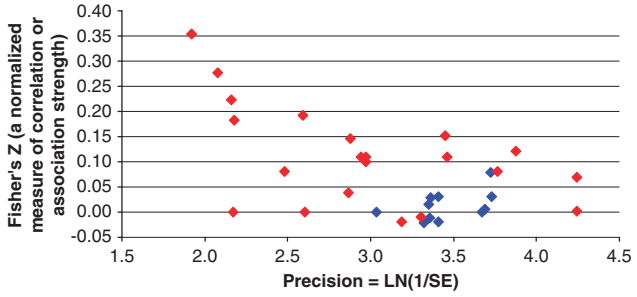


Figure 1 Plot of sample effect sizes from cross-sectional studies of the association between sugar-sweetened beverage consumption and obesity indexes indicating publication bias among non-industry-funded studies (Blue diamonds = industry funded; Red diamonds = non-industry funded).

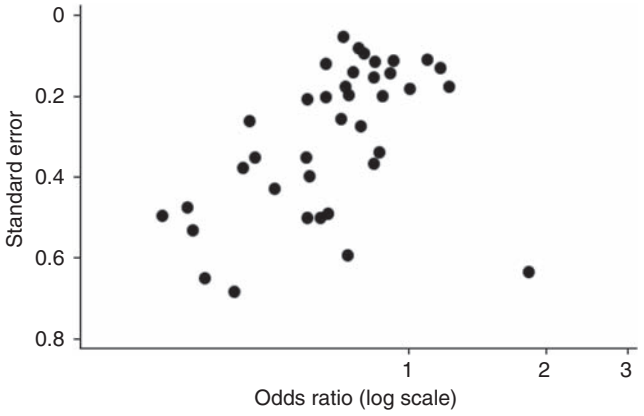


Figure 2 Plot of the relationship between association magnitude and study precision indicating publication bias in studies of breastfeeding and obesity (from Horta *et al.*[8]).

published. With PB, the probability of a study being published depends on its outcome. Typically, PB involves statistically significant studies having a higher likelihood of being published than non-statistically significant ones. Our analysis (Figure 1) shows a clear inverse association between study precision and association magnitude. This PB hallmark suggests that studies with statistically significant NSB findings are more likely to be published than are non-statistically significant ones. Interestingly, this bias seems to be present only for non-industry-funded research, suggesting that non-industry-funded scientists tend not to publish their non-significant associations in this area. Contrarily, all industry-funded studies seem to exceed a minimal level of precision. Thus, much of the reason for the smaller associations detected by Vartanian *et al.*[6] for industry-funded research seems to be because of PB in non-industry-funded research. However, even after accounting for precision, the mean difference between the association magnitudes of industry and non-industry-funded studies is reduced by 33%, but not eliminated, suggesting that there may be competing biases operating in industry-funded research.

Breastfeeding

The World Health Organization (WHO;[8]) published a meta-analysis on whether breastfeeding protects against obesity and also found evidence of PB. Figure 2 indicates this strikingly. We retrieved all papers from which data were obtained for Figure 2 to evaluate the impact of industry funding on this PB. None of the papers reported any industry funding or were obviously authored by authors employed by the infant formula industry. Thus, as with the NSB literature, there seems to be a strong PB that is not apparently fueled by industry interests.

Example 3—Anecdotal examples of miscommunications in press releases

Evidence suggests that 'Press releases from academic medical centers often promote research that has uncertain relevance to human health and do not provide key facts or acknowledge important limitations'.[9] This is also occurring in the obesity field. For example, the paper by Ebbeling *et al.*[5] states, 'change in body mass index (BMI) was the primary end point. The net difference, $0.14 \pm 0.21\,kg/m^2$, was not significant overall,' and then reports the subgroup finding, 'Among the subjects in the upper baseline-BMI tertile, BMI

change differed significantly between the intervention…and control…groups.' Contrast this modest finding in a sample subset and the circumspect presentation in the original paper with the presentation in the press release issued by the authors' institution (http://www.childrenshospital.org/newsroom/Site1339/mainpageS1339P1sublevel192.html (accessed on 31 October 2008)), which states 'In randomized trial, a simple beverage-focused intervention led to weight loss' and never states that the primary analysis was not statistically significant.

When the paper by James *et al.*[4] was released, the press release issued on the *BMJ* website (http://www.bmj.com/content/vol328/issue7446/press_release.shtml (accessed on 20 September 2009)) stated 'Discouraging children from drinking fizzy drinks can prevent excessive weight gain, according to new research available on bmj.com,' despite the facts that no analysis of weight change *per se* was reported and that there was no significant effect on BMI change. Neither of these facts was mentioned in the press release.

Finally, in 2009, describing an observational epidemiological study, UCLA issued a press release (http://www.healthpolicy.ucla.edu/NewsReleaseDetails.aspx?id=35 (accessed on 20 September 2009)) stating '…research released today provides the first scientific evidence of the potent role soda and other sugar-sweetened beverages play in fueling California's expanding girth' One of the study authors was quoted in a subsequent news story stating 'For the first time, we have strong scientific evidence that soda is one of the—if not the largest—contributors to the obesity epidemic' (http://www.drcutler.com/poor-diet/study-soda-making-californians-fat-19373657/ (accessed on 25 September 2009)). These statements are inaccurate and also unfair to all authors of observational studies who published such research years before. The press release further stated 'The science is clear and *conclusive* [emphasis added],' despite the fact that this was a correlational research, and offered no statement to the reader to interpret the results as indicative of correlation and not necessarily causation.

Example 4—Inappropriate or questionable inclusion of information

Research may also be misleadingly presented by inclusion of incorrect or questionable material in reviews. In our critical review of the WHO report on breastfeeding, we noted several examples (see, Cope and Allison[2], p 597) in which an inspection of the original papers reviewed revealed that the authors of the WHO report selectively included some values from certain primary papers that led to stronger associations of breastfeeding with reduced obesity risk and excluded less impressive values from the same papers without explanation.

Similarly, Mattes *et al.*[3] noted that several reviews of NSB consumption and obesity inappropriately included a study[10] that was actually neither a test of nutritive sweetener-containing solid food versus beverage nor of NSB consumption versus non-NSB consumption. Sweeteners were presented in both solid and beverage food forms. The original authors[10] wrote, '…subjects who were given supplemental *drinks and foods* [emphasis added] containing sucrose for 10 wk experienced increases in …body weight', and thus the study should never have been considered as evaluative of NSB effects. Mattes *et al.*[3] provide other examples of papers being inappropriately included in past reviews of NSB consumption and obesity.

Conclusion

Finding effective methods to reduce obesity is an important goal, and appropriate evaluations of the strength of the evidence supporting the procedures under consideration are vital. Sound evaluations critically depend on evidence being presented in non-misleading ways. Alarms have been sounded about dramatic rises in obesity levels, not without justification. And yet, these alarms may also have aroused passions. Certain postulated causes have come to be demonized (for example, fast food, NSBs, formula feeding of infants) and certain postulated palliatives (for example, consumption of fruits and vegetables, building of sidewalks and walking trails) seem to have been sanctified. Such demonization and sanctification may come at a cost. Such casting may ignite feelings of righteous zeal.

Some authors compare NSBs, fast foods and other food and restaurant industry offerings to the tobacco industry (for example, see Brownell and Warner[11]), suggesting, for example, comparisons between 'Joe Camel' and 'Ronald McDonald' (http://www.time.com/time/magazine/article/0,9171,1187241,00.html). To the extent that such comparisons inform us about important causes of obesity and how to reduce them, this is all to the good. But to the extent that such comparisons and other appeals to passions inflame rather than inform, they may cloud judgment and decrease inhibitions against breaching ordinary rules of conduct. Historians indicate that during times of war, propagandists demonize (that is, dehumanize) the enemy to inflame spirits and this facilitates some breaches of codes of conduct such as massacres.[12] Although inflaming the passions of scientists interested in public health is unlikely to provoke bloodshed, we scientists have, as a discipline, our own code of conduct. Central to it is a commitment to faithful reporting, to acknowledging our study limitations, to evaluating bodies of evidence without selectively excluding information on the basis of its desirability—in short, a commitment to truthfulness. The demonization of some aspects and sanctification of others, although perhaps helpful in spurring social action, may be more harmful to us in the long run by giving unconscious permission to breach that code, thereby eroding the foundation of scientific discipline.

Evidence presented herein suggests that at least one aspect has been demonized (NSB consumption) and another sanctified (breastfeeding), leading to bias in the presentation of research literature to other scientists and to the public at large, a bias sufficient to misguide readers. Interestingly, although many papers point out what seem to be biases resulting from industry funding, we have identified here, perhaps for the first time, clear evidence that WHBs can also exist in opposition to industry interests.

Whether WHB is intentional or unintentional, and whether it stems from a bias toward anti-industry results, significant findings, feelings of righteous indignation, results that may justify public health actions, or yet other factors, is unclear. Future research should study approaches to minimize such distortions in the research record. We suggest that authors be more attentive to reporting primary results from earlier studies rather than selectively including only a part of the results, to avoiding PB, as well as to ensuring that their institutional press releases are commensurate with the studies described. Journal editors and peer reviewers should also be vigilant and seek to minimize WHB. Clinicians, media, public health policy makers and the public should also be cognizant of such biases and view the literature on NSBs, breastfeeding and other obesity-related topics more critically.

Conflict of interest

Drs Allison and Cope have received grants, honoraria, donations and consulting fees from numerous food, beverage, dietary supplement, pharmaceutical companies, litigators and other commercial, government and nonprofit entities with interests in obesity and nutrition, including interests in breastfeeding and NSBs. Dr Cope has recently accepted a position with The Solae Company (St Louis, MO, USA).

Acknowledgements

We gratefully acknowledge Dr Alfred A Bartolucci for his comments on our data analysis and Dr Lenny Vartanian for sharing his data file. Supported in part by the NIH grant P30DK056336. The opinions expressed are those of the authors and not necessarily those of the NIH or any other organization with which the authors are affiliated.

References

1 Allison DB, Mattes RD. Nutritively sweetened beverage consumption and obesity: the need for solid evidence on a fluid issue. *JAMA* 2009; **301**: 318–320.
2 Cope MB, Allison DB. Critical review of the World Health Organization's (WHO) 2007 report on 'evidence of the long-term effects of breastfeeding: systematic reviews and meta-analysis' with respect to obesity. *Obes Rev* 2008; **9**: 594–605.
3 Mattes RD, Shikany JM, Allison BD. What is the demonstrated value of moderating nutritively sweetened beverage consumption in reducing weight gain or promoting weight loss? An evidence-based review and meta-analysis of randomized studies. (Submitted for publication).
4 James J, Thomas JT, Cavan D, Kerr D. Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial. *BMJ* 2004; **328**: 123743.
5 Ebbeling CB, Feldman HA, Osganian SK, Chomitz VR, Ellenbogen SJ, Ludwig DS. Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study. *Pediatrics* 2006; **117**: 673–680.
6 Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health* 2007; **97**: 667–675.
7 Sterne JAC, Egger M. Regression methods to detect publication and other bias in meta-analysis. In: Rothstein HR, Sutton AJ, Borenstein M (eds). *Publication Bias in Meta-Analysis*. John Wiley & Sons Ltd: West Sussex, UK, 2005.
8 Horta B, Bahl R, Martines J, Victora C. *Evidence of the Long-Term Effects of Breastfeeding: Systematic Reviews and Meta- Analysis*. World Health Organization Publication: Geneva, Switzerland, 2007.
9 Woloshin S, Schwartz LM, Casella SL, Kennedy AT, Larson RJ. Press releases by academic medical centers: not so academic? *Ann Intern Med* 2009; **150**: 613–618.
10 Raben A, Vasilaras TH, Møller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on *ad libitum* food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr* 2002; **76**: 721–729.
11 Brownell KD, Warner KE. The perils of ignoring history: big tobacco played dirty and millions died. How similar is Big Food? *Milbank Q* 2009; **87**: 259–294.
12 Levene M, Roberts P (eds). *The Massacre in History (Studies on War and Genocide)*. Berghahn Books: Oxford, UK, 1999.

Annual Medical Spending Attributable To Obesity: Payer-And Service-Specific Estimates

Amid calls for health reform, real cost savings are more likely to be achieved through reducing obesity and related risk factors.

by Eric A. Finkelstein, Justin G. Trogdon, Joel W. Cohen, and William Dietz

ABSTRACT: In 1998 the medical costs of obesity were estimated to be as high as $78.5 billion, with roughly half financed by Medicare and Medicaid. This analysis presents updated estimates of the costs of obesity for the United States across payers (Medicare, Medicaid, and private insurers), in separate categories for inpatient, non-inpatient, and prescription drug spending. We found that the increased prevalence of obesity is responsible for almost $40 billion of increased medical spending through 2006, including $7 billion in Medicare prescription drug costs. We estimate that the medical costs of obesity could have risen to $147 billion per year by 2008. [*Health Affairs* 28, no. 5 (2009): w822–w831 (published online 27 July 2009; 10.1377/hlthaff.28.5.w822)]

There is an undeniable link between rising rates of obesity and rising medical spending. In a previous paper, Eric Finkelstein and colleagues[1] demonstrated the extent to which excess weight increased annual medical spending for public and private payers alike. That study showed that the costs of overweight and obesity could have been as high as $78.5 billion in 1998 and that roughly half of this total was financed by Medicare and Medicaid. This analysis updates those previous findings. Our overall estimates show that the annual medical burden of obesity has risen to almost 10 percent of all medical spending and could amount to $147 billion per year in 2008. Other studies have also quantified the extent to which obesity influences aggregate health spending. For example, Kenneth Thorpe and colleagues[2] found that obesity was responsible for 27 percent of the rise in inflation-adjusted health spending between 1987 and 2001.

Eric Finkelstein (finkelse@rti.org) is director of the Public Health Economics Program at RTI International in Research Triangle Park, North Carolina. Justin Trogdon is a research economist in that program. Joel Cohen is director of the Division of Social and Economic Research, Center for Financing, Access, and Cost Trends, Agency for Healthcare Research and Quality, in Rockville, Maryland. William Dietz is director of the Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, at the Centers for Disease Control and Prevention in Atlanta, Georgia.

DOI 10.1377/hlthaff.28.5.w822

Although national, state, and local governments and many private employers and payers have increased their efforts to address obesity since 1998, data from the Centers for Disease Control and Prevention's (CDC's) Behavioral Risk Factor Surveillance System (BRFSS)[3] reveal that obesity rates increased by 37 percent between 1998 and 2006 (from 18.3 percent to 25.1 percent of the population), which suggests that the increased prevalence of obesity is driving increases in total medical spending.

We present nationally representative estimates of per capita and aggregate costs of obesity for all payers and separately for Medicare, Medicaid, and private insurers. We present these costs in total and separately for inpatient, non-inpatient, and prescription drug spending—which was not possible at the time the previous papers were written.[4] This additional detail helps specify the drivers of the costs of obesity. This is especially important for Medicare because of the prescription drug benefit that was added in 2006. Our research shows that obese beneficiaries, on average, cost Medicare over $600 per beneficiary per year more compared to normal-weight beneficiaries.[5] Finally, we estimate the extent to which rising prevalence of obesity is responsible for the increase in obesity costs that occurred between 1998 and 2006.

Study Data And Methods

■ **Data.** This analysis relies on data from the 1998 and 2006 Medical Expenditure Panel Surveys (MEPS). MEPS is a nationally representative survey of the civilian noninstitutionalized population that quantifies a person's total annual medical spending by type of service and source of payment (including Medicare, Medicaid, private, and other sources). The data also include information about each person's health insurance status and sociodemographic characteristics, including age; race/ethnicity; sex; and, most importantly for this analysis, body mass index (BMI) based on self-reported height and weight.[6] As in our prior work,[1] the analysis data set includes all adults age eighteen or older with data on BMI, excluding pregnant women. This includes 10,597 and 21,877 adults in 1998 and 2006, respectively, with weighting variables that allow for the generation of nationally representative estimates.

■ **Methods.** Although our estimation strategy largely tracks the approach used in our earlier work,[1] we have made several modifications to allow for more detailed stratifications. First, that study used a four-equation regression approach to predict total medical spending separately for those who did or did not require an inpatient visit. However, for the 2006 data, in addition to a two-part model on total spending, for this study we ran separate two-part models for inpatient, non-inpatient (outpatient, emergency room, office-based, dental, vision, home health, and other), and prescription drug spending, to quantify the costs of obesity separately for each type of service.[7] The two-part model separately estimated the probability of having a specific type of expenditure (for example, inpatient) in the first part and then esti-

mated total spending conditional on having positive spending in the second part. The predictions from each part were then combined to generate total predicted spending for each type of service.

As is typical with medical spending data, the samples included many people with zero spending for some points of service, especially inpatient services, and some with extremely high spending. We used a two-part model that includes a logit model in the first part and a generalized linear model (GLM) with a log link and gamma distribution in the second part. Application of the specification tests outlined by Willard Manning and John Mullahy[8] supported our choice of models. Therefore, we used that approach to generate the spending estimates for both the 1998 and 2006 data for all regressions.[9]

Separating payers. The specification from our earlier work[1] used total annual medical payments as the dependent variable and dummy variables for BMI category, insurance status, and BMI category/insurance status interaction terms to generate overweight- and obesity-attributable fractions for each payer. However, this approach assumed that, for example, the total increase in costs for people with Medicare coverage is paid for by Medicare. In the current analysis, we ran separate models for each payer and used payer-specific spending as the dependent variable. By running separate models by payer, we did not restrict the coefficients on the sociodemographic variables to be the same across payers, as was done in our prior study. In addition, by running separate models, we could subset the total payment variable in each regression to include only payments made by that payer.

Body mass index. The inclusion of variables depicting each person's BMI category (underweight: BMI <18.5, normal: BMI 18.5–<25 [omitted reference group], overweight: BMI 25–<30, or obese: BMI >30) in the regressions allows for predicting the impact of these variables on annual medical spending. Although our earlier work focused on quantifying costs separately for overweight and obesity, because the overweight expenditure variable was not statistically different from normal-weight spending in that work, for this effort we present results only for those with a BMI greater than 30 kg/m^2.

Respondents' characteristics. All regressions controlled for sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other), age, region (Northeast, Midwest, South, West), household income (less than 100 percent of poverty, 100–199 percent, 200–399 percent, 400 percent or more), education (less than high school, high school, some college, college degree), marital status (married, widowed, divorced/separated, single), and smoking status (current smoker, former/never smoker). The total expenditure regression also included dichotomous variables for each person's insurance category (uninsured, privately insured, Medicaid, Medicare, or other payers) and allowed for multiple insurers throughout the year.

Impact on spending by type of service. The regression results allowed for assessing the impact of obesity on annual medical spending for each type of service. The average

"Across all payers, obese people had medical spending that was $1,429 greater than spending for normal-weight people in 2006."

increase in medical spending attributable to obesity for each type of service, compared to normal weight, was calculated by subtracting average predicted spending for obese people with the dichotomous obesity variable set to 1, from average predicted spending for these people with the obesity variable set to 0 (that is, predicted spending for obese people had they been of normal weight). The corresponding percentage increase was generated by dividing this figure by the average predicted spending for obese people had they been of normal weight. The fraction that medical spending would be reduced by if all obese people were suddenly returned to normal weight (termed "attributable fraction") was calculated by dividing total predicted spending attributable to obesity by total predicted spending for the entire sample. The regressions were estimated using Stata. Standard errors were computed via the bootstrap method. Note that these standard errors accounted only for sampling variability and not for any potential household reporting or model specification errors.

Bringing in data from the NHEA. We present obesity-attributable spending estimates at the national level based on aggregate spending in MEPS and based on the higher personal health care spending estimates presented in the National Health Expenditure Accounts (NHEA), generally considered the gold standard for data on aggregate health spending.[10] The NHEA estimates are much higher than the MEPS estimates primarily because NHEA includes spending for people residing in institutions and MEPS does not. The largest difference occurs for Medicaid, which finances the majority of institutionalized costs. The NHEA also includes expenses for services that are not included in MEPS (for example, over-the-counter medications). In addition, household surveys are subject to potential underreporting by respondents. The latest effort to reconcile NHEA and MEPS suggests that MEPS may underestimate spending by roughly 14 percent.[11]

To compute the NHEA estimates, as in our earlier work,[1] we multiplied the attributable fractions generated from MEPS by total spending for the corresponding insurance category reported in the 1998 and 2006 NHEA. Although this requires the strong assumption that the percentage of costs attributable to obesity is the same in institutionalized and noninstitutionalized populations, this assumption was necessary to provide an estimate of the costs of obesity from all types of health care spending. All results are presented in 2008 dollars using the gross domestic product (GDP) general price index as recommended by the Agency for Healthcare Research and Quality (AHRQ), the agency that conducts MEPS.[12]

Obesity prevalence. Because the regression results reveal that the per capita spending attributable to obesity was not statistically different in 2006 versus 1998, we estimate the extent to which increased prevalence of obesity is responsible for the

increase in the medical cost of obesity between 1998 and 2006. To compute this estimate, we predicted spending for 2006 using the 2006 two-part model and 2006 sample but with each person's BMI dummy variables set to the average levels in 1998 (0.03 for underweight, 0.35 for overweight, and 0.19 for obese). We then predicted spending in the same way but with each person's BMI dummy variables set to the average levels in 1998 if all obese people were of normal weight (0.03 for underweight, 0.35 for overweight, and 0 for obese). The difference in these predicted expenditures represents hypothetical obesity-attributable costs in 2006 if the prevalence of obesity had remained at 1998 levels.

Results

Exhibit 1 uses the regression results (available upon request) to present estimates of the increase in per capita medical spending attributable to obesity in 1998 and in 2006, using the updated regression specification. For comparison, this figure also presents 1998 estimates as reported in our earlier work.[1]

Across all payers, obese people had per capita medical spending that was $1,429 (42 percent) greater than spending for normal-weight people in 2006. In 1998 the per capita spending increase attributable to obesity was several hundred dollars less than, although not statistically different from, the 2006 estimate. It is important to note that the specification changes between this and our earlier work had almost no impact on the 1998 estimates. In both cases, it was estimated that obesity increased costs by 37 percent.

Exhibit 2 presents estimates separately by payer. With the exception of the percentage increase for private payers, the estimated spending increase attributable to obesity is larger for 2006 than for 1998, although the differences are not statistically significant. For 2006, the per capita percentage increase in annual costs attributable to obesity was estimated to be 36 percent for Medicare, 47 percent for Medicaid, and 58 percent for private payers. Both the 2006 dollar and percentage increases are statistically different from zero for all payers, although none are sta-

EXHIBIT 1
Adult Per Capita Medical Spending Attributable To Obesity (Compared To Normal Weight), 1998 And 2006 (In 2008 Dollars)

Year	Spending difference compared to normal weight ($)	Percent difference compared to normal weight
2006	1,429 (156)	41.5 (4.9)
1998 (updated)	1,145 (270)	36.5 (8.9)
1998 (original)	930[a] (438)	37.4[a] (17.4)

SOURCE: Authors' calculations based on data from the 1998 and 2006 Medical Expenditure Panel Survey.
NOTES: Bootstrapped standard errors are shown in parentheses. Obese is body mass index (BMI) ≥30 kg/m^2. Dollar values were updated to 2008 using the gross domestic product (GDP) price index provided by the Bureau of Economic Analysis, U.S. Department of Commerce. For all data, the increased spending estimate is significantly greater than zero ($p < 0.05$).
[a] Relative standard error is greater than 0.3, indicating that the estimate is unstable.

EXHIBIT 2
Increase In Adult Per Capita Medical Spending Attributable To Obesity, By Insurance Status, 1998 And 2006 (In 2008 Dollars)

Insurance category	Year	Spending increase ($)	Percent increase
Medicare	2006	1,723[a] (345)	36.4[a] (8.5)
	1998	1,006[b] (540)	30.2[b] (18.1)
Medicaid	2006	1,021[a] (303)	46.7[a,b] (15.4)
	1998	284[b] (495)	10.3[b] (15.9)
Private	2006	1,140[a] (143)	58.1[a] (8.4)
	1998	957[a] (193)	67.2[a] (16.0)

SOURCE: Authors' calculations based on data from the 1998 and 2006 Medical Expenditure Panel Survey.
NOTES: Bootstrapped standard errors are shown in parentheses. Obese is body mass index (BMI) ≥30 kg/m^2. Dollar values were updated to 2008 using the gross domestic product price index provided by the Bureau of Economic Analysis, U.S. Department of Commerce.
[a] Increased spending estimate is significantly greater than zero ($p < 0.05$).
[b] Relative standard error is greater than 0.3, indicating that the estimate is unstable.

tistically different from the 1998 estimates. Using the updated regression approach, neither the 1998 Medicare spending increase nor the Medicaid spending or percentage increases are statistically different from zero.

Exhibit 3 presents the 2006 payer-specific estimates by type of service—inpatient, non-inpatient, or prescription drug spending—to identify the cost drivers

EXHIBIT 3
Increase In Adult Per Capita Medical Spending Attributable To Obesity, By Insurance Status And Type Of Service, 2006 (In 2008 Dollars)

Insurance category	Type of service	Spending increase ($)	Percent increase
Medicare	Inpatient	95[b] (296)	4.4[b] (13.0)
	Non-inpatient	693[a] (128)	40.1[a] (8.4)
	Rx drug	608[a] (65)	72.7[a] (10.3)
Medicaid	Inpatient	213[b] (153)	39.2[b] (34.2)
	Non-inpatient	175[b] (172)	14.8[b] (12.8)
	Rx drug	230[a,b] (80)	60.6[a,b] (24.2)
Private	Inpatient	443[a] (85)	90.3[a] (23.9)
	Non-inpatient	398[a] (60)	37.9[a] (6.6)
	Rx drug	284[a] (41)	81.8[a] (12.4)
All payers	Inpatient	420[a] (93)	45.5[a] (12.0)
	Non-inpatient	444[a] (76)	26.9[a] (4.7)
	Rx drug	568[a] (59)	80.4[a] (8.3)

SOURCE: Authors' calculations based on data from the 2006 Medical Expenditure Panel Survey.
NOTES: Bootstrapped standard errors are shown in parentheses. Obese is body mass index (BMI) ≥30 kg/m^2. Dollar values were updated to 2008 using the gross domestic product price index provided by the Bureau of Economic Analysis, U.S. Department of Commerce.
[a] Increased spending estimate is significantly greater than zero ($p < 0.05$).
[b] Relative standard error is greater than 0.3, indicating that the estimate is unstable.

attributable to obesity. For Medicare, non-inpatient services and pharmaceuticals (as a result of the introduction of prescription drug coverage) were major drivers of spending. Our results suggest that spending within these categories for each obese beneficiary was more than $600 per year higher than for a normal-weight beneficiary in 2006. For Medicaid, only prescription drug spending was statistically significant, accounting for a $230 (61 percent) increase in annual spending from 1998 to 2006. However, in part because of the smaller sample size, all Medicaid type-of-service estimates, in addition to the Medicare estimate for inpatient services, are associated with large standard errors and therefore should be interpreted with caution. The spending increase from 1998 to 2006 for private payers was statistically significant for each type of service and ranged from $284 for prescription drugs to $443 for inpatient services. In percentage terms, these increases represent 82 percent and 90 percent increases in costs, respectively, compared with people of normal weight. Estimates for all payers combined range between $420 (inpatient) and $568 (prescription drugs). In percentage terms, the increases for all payers combined range from 27 percent (non-inpatient) to 80 percent (prescription drugs) from 1998 to 2006.

Exhibit 4 combines the per capita cost and obesity prevalence data to present the attributable fractions and aggregate estimates of the costs of obesity separately by payer and by type of service. Focusing on total payments, the attributable fractions indicate that 8.5 percent of Medicare spending, 11.8 percent of Medicaid spending, and 12.9 percent of private payer spending is attributable to obesity. Across all payers, our results indicate that obesity is associated with a 9.1 percent increase in annual medical spending, compared with 6.5 percent in 1998: $86 billion based on the MEPS estimates or as much as $147 billion per year based on the NHEA data. For 1998 these estimates were $42 billion and $74 billion, respectively, when we used the updated regression specification. By point of service, prescription drug spending is the largest cost driver.

Across all payers, we estimate that had obesity prevalence remained at 1998 levels, spending attributable to obesity would have been $47 billion in 2006 rather than $86 billion (based on MEPS spending data). This implies that the rise in obesity prevalence accounted for 89 percent of the increase in obesity spending that occurred during this period.[13]

Discussion

These results reveal that obesity continues to impose an economic burden on both public and private payers. Across all payers, per capita medical spending for the obese is $1,429 higher per year, or roughly 42 percent higher, than for someone of normal weight. In aggregate, the annual medical burden of obesity has increased from 6.5 percent to 9.1 percent of annual medical spending and could be as high as $147 billion per year (in 2008 dollars) based on the NHEA estimate. Moreover, unlike Thorpe and colleagues,[2] who found that the per capita costs of obesity

EXHIBIT 4
Aggregate Medical Spending Attributable To Obesity, By Insurance Status And Type Of Service, In Two Different Data Sets, 2008 Dollars

Insurance category	Type of service	Attributable fraction (%)	MEPS ($ millions)	NHEA ($ millions)
Medicare	Inpatient	1.1[b] (3.5)	1,085	1,888[a]
	Non-inpatient	9.1[a] (1.6)	7,920[a]	13,787[a]
	Rx drug	15.2[a] (1.6)	6,951[a]	12,100[a]
	Total	8.5[a] (1.7)	19,683[a]	34,263[a]
Medicaid	Inpatient	8.8[b] (6.1)	2,054	7,031
	Non-inpatient	3.9[b] (3.8)	1,260	4,314
	Rx drug	11.9[a,b] (4.3)	1,479[a]	5,061[a]
	Total	11.8[a] (3.4)	8,054[a]	27,566[a]
Private	Inpatient	18.1[a] (3.3)	20,942[a]	31,544[a]
	Non-inpatient	8.5[a] (1.3)	16,594[a]	24,828[a]
	Rx drug	17.1[a] (2.1)	11,665[a]	18,250[a]
	Total	12.9[a] (1.6)	49,386[a]	74,615[a]
All payers	Inpatient	10.3[a] (2.3)	27,361[a]	44,654[a]
	Non-inpatient	5.9[a] (1.0)	26,380[a]	45,157[a]
	Rx drug	15.2[a] (1.4)	32,726[a]	59,333[a]
	2006 total	9.1[a] (1.0)	85,739[a]	146,624[a]
All payers	1998 (updated) total	6.5[a] (1.5)	41,840[a]	74,157[a]
	1998 (original) total	5.3[a,b] (2.6)	34,036[a]	60,325[a]

SOURCE: Authors' calculations based on data from the 2006 Medical Expenditure Panel Survey (MEPS) and the 2006 National Health Expenditure Accounts (NHEA).

NOTES: Bootstrapped standard errors are shown in parentheses. Obese is body mass index (BMI) ≥30 kg/m^2. Dollar values were updated to 2008 using the gross domestic product price index provided by the Bureau of Economic Analysis, U.S. Department of Commerce.

[a] Increased spending estimate is significantly greater than zero ($p < 0.05$).

[b] Relative standard error is greater than 0.3, indicating that the estimate is unstable.

increased between 1987 and 2001, our estimates reveal that the 37 percent increase in obesity prevalence, and not per capita cost increases, was the main driver of the increase in obesity-attributable costs between 1998 and 2006. These results also provide new evidence of the important role of prescription drug spending in driving the costs of obesity. For example, as a result of the Part D prescription drug benefit, the obesity-attributable prescription drug costs to Medicare are $7 billion for the noninstitutionalized population (see Exhibit 4).

■ **Effects of obesity treatment.** Although pharmaceutical, medical, and surgical interventions to treat obesity are available, these treatments remain rare. As a result, the costs attributable to obesity are almost entirely a result of costs generated from treating the diseases that obesity promotes. For example, Charles Roehrig and colleagues[14] show that annual medical costs for people with diabetes total $190.5 billion. Although not all of these costs are attributable to obesity, excess weight is the single greatest predictor of developing diabetes. If not for obesity, these costs would be much lower, as would costs for other conditions caused by excess weight.

Although our results indicate that private payers bear the majority of the costs resulting from obesity, public-sector spending remains substantial; Medicare and Medicaid spending would be 8.5 percent and 11.8 percent lower, respectively, in

"The connection between rising rates of obesity and rising medical spending is undeniable."

the absence of obesity. Given the current budget crisis in most jurisdictions, the high public-sector spending for obesity is a major cause for concern. However, if the motivation to prevent or treat obesity were solely based on cost, then only cost-saving obesity interventions would be implemented once all costs and benefits are taken into account.

From a payer's perspective, although there is increasing evidence suggesting that bariatric surgery may be cost saving,[15] not all obesity treatments will meet this threshold (nor do most treatments for other conditions). This is not to say that these treatments should or should not be offered, but the extent to which greater use of obesity treatments would reduce spending in either the short or the long run remains unknown. The same is true for prevention. Many successful obesity prevention efforts are likely to be cost-effective (that is, have a low cost-effectiveness ratio) but not cost saving. From a public health perspective that focuses on identifying cost-effective strategies for improving the health of the population, these interventions may still be worth pursuing, even at significant cost.

■ **Study limitations.** This analysis has several limitations. One is the reliance on self-reported height and weight. Unfortunately, no nationally representative data set includes both measured height/weight and annual medical spending. In addition, the lack of statistical significance in some regressions may be attributable to the relatively small sample size. For example, the 1998 data set is only half as large as the 2006 data set; in 2006 only 329 (unweighted) Medicaid enrollees had an inpatient visit, compared with 767 (unweighted) individuals in the private-payer regression.

As noted in the methods section, the application of the attributable fractions generated from the MEPS data (on only the noninstitutionalized) to spending estimates from NHEA (including people in institutions) requires the strong assumption that the prevalence and per capita costs of obesity can be equally applied to both populations. This was necessary to present comprehensive estimates of the costs of obesity considering all payment sources. However, if obese people account for a lower percentage of the institutionalized population or the cost profile is smaller relative to those in institutions who are not obese, then the NHEA-adjusted estimates are upwardly biased.

Finally, the regression-based approach allows for quantifying the spending attributable to obesity by payer and point of service, but it does not directly allow for apportioning spending across specific diseases or the underlying behavior that causes excess weight (that is, poor diet and inactivity). This should be an area of future research.

ALTHOUGH THESE LIMITATIONS REPRESENT important considerations, the connection between rising rates of obesity and rising medical spending is undeniable. The take-home message is that without a strong and sustained reduction in obesity prevalence, obesity will continue to impose major costs on the health system for the foreseeable future. And although health reform may be necessary to address health inequities and rein in rising health spending, real savings are more likely to be achieved through reforms that reduce the prevalence of obesity and related risk factors, including poor diet and inactivity. These reforms will require policy and environmental changes that extend far beyond what can be achieved through changes in health care financing and delivery.

Eric Finkelstein and Justin Trogdon received external support for this work through a contract with the CDC Foundation. The authors thank Charles Feagan for his research assistance.

NOTES

1. Finkelstein EA, Fiebelkorn IC, Wang G. National medical spending attributable to overweight and obesity: how much, and who's paying? Health Aff (Millwood). 2003;22:w3-219–26.
2. Thorpe KE, Florence CS, Howard DH, Joski P. The impact of obesity on rising medical spending. Health Aff (Millwood). 2004;23:w4-480–6.
3. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System [Internet]. Atlanta (GA): CDC; 2009 Apr 30 [cited 2009 Jul 14]. Available from: http://www.cdc.gov/brfss
4. Data used to calculate body mass index (BMI) in the 1998 analysis came from the Sample Adult File of the National Health Interview Survey, the sampling frame for the Medical Expenditure Panel Survey (MEPS). Because only a subset of MEPS participants took this NHIS module, the analysis file for 1998 is much smaller than in 2006 (N = 10,597 and 21,877, respectively), where data used to calculate BMI are directly captured in MEPS.
5. U.S. Department of Health and Human Services. Medicare. Washington (DC): DHHS; [cited 2009 Jul 14]. Available from: http://www.medicare.gov/MedicareReform/drugbenefit.asp
6. In the 1998 data, MEPS does not include BMI; however, this information was available for a subset of MEPS participants. See Note 4.
7. The smaller sample size for 1998 does not allow for this level of analysis.
8. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ 2001;20(4):461–94.
9. Full regression results are available online at http://content.healthaffairs.org/cgi/content/full/hlthaff.28.5.w822/DC2.
10. Centers for Medicare and Medicaid Services. National health expenditure data overview. Baltimore (MD): CMS; [updated 2009 Mar 7]. Available from: http://www.cms.hhs.gov/nationalhealthexpenddata
11. Sing M, Banthin JS, Selden TM, Cowan CA, Keehan SP. Reconciling medical expenditure estimates from the MEPS and NHEA, 2002. Health Care Financ Rev 2006;28(1):25–40.
12. AHRQ recommends that a general price index be used because it provides an overall sense of what a dollar can buy across different time periods. For a detailed discussion, see Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey [Internet]. Rockville (MD): AHRQ; [cited 2009 Jul 14] Available from: http://www.meps.ahrq.gov/mepsweb/about_meps/Price_Index.shtml
13. From Exhibit 4: ($85,739 – $47,000)/($85,739 – $41,840) = 89 percent.
14. Roehrig C, Miller G, Lake C, Bryant J. National health spending by medical condition, 1996–2005. Health Aff (Millwood). 2009;28(2):w358–67.
15. Cremieux PY, Buchwald H, Shikora SA, Ghosh A, Yang HE, Buessing M. A study on the economic impact of bariatric surgery. Am J Manag Care 2008 Sep;14(9):589–96.

Prevalence and Trends in Obesity Among US Adults, 1999-2008

Katherine M. Flegal, PhD
Margaret D. Carroll, MSPH
Cynthia L. Ogden, PhD
Lester R. Curtin, PhD

Context The prevalence of obesity increased in the United States between 1976-1980 and 1988-1994 and again between 1988-1994 and 1999-2000.

Objective To examine trends in obesity from 1999 through 2008 and the current prevalence of obesity and overweight for 2007-2008.

Design, Setting, and Participants Analysis of height and weight measurements from 5555 adult men and women aged 20 years or older obtained in 2007-2008 as part of the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the US population. Data from the NHANES obtained in 2007-2008 were compared with results obtained from 1999 through 2006.

Main Outcome Measure Estimates of the prevalence of overweight and obesity in adults. Overweight was defined as a body mass index (BMI) of 25.0 to 29.9. Obesity was defined as a BMI of 30.0 or higher.

Results In 2007-2008, the age-adjusted prevalence of obesity was 33.8% (95% confidence interval [CI], 31.6%-36.0%) overall, 32.2% (95% CI, 29.5%-35.0%) among men, and 35.5% (95% CI, 33.2%-37.7%) among women. The corresponding prevalence estimates for overweight and obesity combined (BMI ≥25) were 68.0% (95% CI, 66.3%-69.8%), 72.3% (95% CI, 70.4%-74.1%), and 64.1% (95% CI, 61.3%-66.9%). Obesity prevalence varied by age group and by racial and ethnic group for both men and women. Over the 10-year period, obesity showed no significant trend among women (adjusted odds ratio [AOR] for 2007-2008 vs 1999-2000, 1.12 [95% CI, 0.89-1.32]). For men, there was a significant linear trend (AOR for 2007-2008 vs 1999-2000, 1.32 [95% CI, 1.12-1.58]); however, the 3 most recent data points did not differ significantly from each other.

Conclusions In 2007-2008, the prevalence of obesity was 32.2% among adult men and 35.5% among adult women. The increases in the prevalence of obesity previously observed do not appear to be continuing at the same rate over the past 10 years, particularly for women and possibly for men.

JAMA. 2010;303(3):235-241 www.jama.com

THE NATIONAL HEALTH AND NUTRITION Examination Survey (NHANES) provides the opportunity to track trends in the prevalence of obesity in the United States by collecting data on height and weight measurements. Data from 1988-1994 showed that the prevalence of obesity in adults had increased by approximately 8 percentage points in the United States since 1976-1980, after being relatively stable over the period 1960-1980.[1,2] Analyses of data from 1999-2000 showed further increases in obesity for both men and women and in all age groups.[3]

The increases in obesity from 1976-1980 to 1988-1994 were statistically significant in all sex and age groups. The increases in obesity from 1988-1994 to 1999-2000 were statistically significant in all sex and age groups except men aged 40 to 59 years. Analyses of data from 2001-2002 and 2003-2004 suggested increasing trends since 1999-2000 among men but not among women.[4,5] Comparisons between 2003-2004 and 2005-2006 showed no significant changes but had limited statistical power.[6]

Herein we report the results from the latest NHANES data from 2007-2008 regarding population trends in obesity and compare the results over the 10-year period from 1999 through 2008.

See also pp 242 and 275.

CME available online at www.jamaarchivescme.com and questions on p 283.

METHODS

The NHANES program of the National Center for Health Statistics, Centers for Disease Control and Prevention, includes a series of cross-sectional, nationally representative health examination surveys beginning in 1960. To obtain a nationally representative sample of the US civilian noninstitutionalized population, each survey period used a complex, stratified, multistage probability cluster sampling design. Beginning in 1999, NHANES became a continuous survey (without a break between cycles) and data are released in 2-year cycles, including 1999-2000, 2001-2002, 2003-2004, 2005-2006, and 2007-2008.

In 2007-2008, the sample consisted of 8082 men and women aged 20 years or older; of whom 73.4% (n=5935) were interviewed and 70.6% (n=5707) were both interviewed and examined. Participants missing weight or height measurements (n=95) and pregnant women (n=57) were excluded from the analyses. This report uses data for 2750 adult men and 2805 nonpregnant adult women with measured weights and

Author Affiliations: National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland.
Corresponding Author: Katherine M. Flegal, PhD, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Rd, Room 4315, Hyattsville, MD 20782 (kmf2@cdc.gov).

heights from the most recent 2 years of the continuous NHANES 2007-2008, in addition to data from NHANES 1999-2006. NHANES 1999-2008 received approval from the National Center for Health Statistics research ethics review board. Written informed consent was obtained.

Weight and height were measured in a mobile examination center using standardized techniques and equipment. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, rounded to the nearest tenth. For adults aged 20 years or older, overweight was defined as a BMI of 25.0 to 29.9 and obesity was defined as a BMI of 30.0 or higher.[7] Obesity may be divided into grade 1 (BMI, 30-<35), grade 2 (BMI, 35-<40), and grade 3 (BMI ≥40).[8]

Individuals were grouped by age at the interview: 20-39 years, 40-59 years, and 60 years or older. Race and ethnicity were self-reported; for the purposes of this report, race and ethnicity are classified as non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, and other. Data for 2007-2008 are presented overall, including all racial and ethnic groups, and separately for non-Hispanic white, non-Hispanic black, all Hispanics (including both Mexican Americans and other Hispanics) and

Table 1. Sample Size for US Adults Aged 20 Years or Older[a]

Categories by Age	All (N = 5555)[b]	Non-Hispanic White (n = 2618)	Non-Hispanic Black (n = 1144)	All Hispanics (n = 1566)[c]	Mexican American (n = 945)
Men, age, y					
≥20	2750	1335	554	739	460
20-39	896	383	187	275	195
40-59	883	391	173	276	164
≥60	971	561	194	188	101
Women, age, y					
≥20	2805	1283	590	827	485
20-39	877	344	191	307	189
40-59	910	402	198	270	158
≥60	1018	537	201	250	138

[a] Based on data from the National Health and Nutrition Examination Survey (NHANES) 2007-2008.
[b] Includes racial and ethnic groups not shown separately.
[c] Includes Mexican Americans.

Table 2. Prevalence of Obesity and Overweight for Adults Aged 20 Years or Older[a]

Categories by Age	% of Adults (95% Confidence Interval)				
	All[b]	Non-Hispanic White	Non-Hispanic Black	All Hispanics[c]	Mexican American
BMI ≥30					
All, age, y					
≥20	33.9 (31.7-36.1)	32.8 (29.4-36.1)	44.1 (39.9-48.3)	37.9 (32.3-43.4)	39.3 (32.0-46.6)
≥20[d]	33.8 (31.6-36.0)	32.4 (28.9-35.9)	44.1 (40.0-48.2)	38.7 (33.5-43.9)	40.4 (34.2-46.6)
Men, age, y					
≥20[d]	32.2 (29.5-35.0)	31.9 (28.1-35.7)	37.3 (32.3-42.4)	34.3 (28.2-40.3)	35.9 (26.3-44.4)
20-39	27.5 (23.8-31.2)	26.3 (20.9-31.7)	34.7 (28.5-40.9)	32.3 (23.9-40.7)	33.8 (22.7-44.9)
40-59	34.3 (29.8-38.8)	34.0 (28.1-39.8)	39.7 (30.0-49.5)	37.4 (29.0-45.8)	38.2 (26.3-50.1)
≥60	37.1 (33.1-41.0)	38.4 (34.1-42.6)	38.0 (31.3-44.7)	32.6 (23.5-41.7)	35.8 (21.9-49.8)
Women, age, y					
≥20[d]	35.5 (33.2-37.7)	33.0 (29.3-36.6)	49.6 (45.5-53.7)	43.0 (37.9-48.2)	45.1 (38.9-51.2)
20-39	34.0 (29.0-39.1)	31.3 (23.3-39.3)	47.2 (41.3-53.1)	37.6 (32.3-42.8)	39.6 (33.7-45.5)
40-59	38.2 (33.8-42.6)	35.7 (29.7-41.7)	51.7 (47.2-56.1)	46.6 (37.3-55.9)	48.9 (38.0-59.8)
≥60	33.6 (30.2-36.9)	31.4 (27.3-35.5)	50.5 (40.5-60.5)	46.7 (41.0-52.3)	48.1 (43.0-53.3)
BMI ≥25					
All, age, y					
≥20	68.3 (66.6-70.0)	67.5 (65.0-70.1)	73.7 (71.2-76.2)	76.9 (72.9-80.8)	77.5 (73.4-81.6)
≥20[d]	68.0 (66.3-69.8)	66.7 (64.1-69.3)	73.8 (71.3-76.3)	77.9 (74.5-81.4)	78.8 (75.2-82.4)
Men, age, y					
≥20[d]	72.3 (70.4-74.1)	72.6 (69.9-75.3)	68.5 (65.2-71.8)	79.3 (74.7-83.9)	80.0 (75.5-84.5)
20-39	63.5 (60.8-66.2)	62.6 (58.0-67.2)	61.5 (54.6-68.5)	74.2 (66.8-81.5)	75.0 (67.4-82.7)
40-59	77.8 (74.0-81.7)	77.7 (72.8-82.6)	73.5 (65.9-81.2)	87.2 (81.4-93.0)	88.0 (80.8-95.1)
≥60	78.4 (74.8-81.9)	81.4 (77.9-84.9)	72.5 (65.2-79.8)	75.4 (70.2-80.7)	75.8 (68.4-83.1)
Women, age, y					
≥20[d]	64.1 (61.3-66.9)	61.2 (56.7-65.7)	78.2 (74.5-81.9)	76.1 (72.0-80.1)	76.9 (71.8-81.9)
20-39	59.5 (54.5-64.5)	54.9 (46.3-63.6)	78.0 (71.8-84.2)	68.5 (61.4-75.7)	70.3 (62.7-77.9)
40-59	66.3 (63.3-69.3)	63.8 (59.8-67.8)	78.4 (74.1-82.6)	81.2 (77.3-85.1)	80.3 (73.6-87.0)
≥60	68.6 (64.4-72.7)	67.6 (62.2-73.1)	78.2 (70.7-85.8)	80.7 (77.3-84.1)	82.6 (77.2-88.0)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Based on data from the National Health and Nutrition Examination Survey (NHANES) 2007-2008.
[b] Includes racial and ethnic groups not shown separately.
[c] Includes Mexican Americans.
[d] Age adjusted by the direct method to the year 2000 Census population using the age groups 20-39 years, 40-59 years, and 60 years or older.

Mexican Americans. In 2007-2008, non-Hispanic blacks and Hispanics were oversampled to provide adequate sample sizes for analyses of these groups. In surveys from 1999 through 2006, Mexican Americans but not all other Hispanics were oversampled, so trends are examined for Mexican Americans rather than for all Hispanics.

Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina) and SUDAAN software version 10.0 (RTI, Research Triangle Park, North Carolina). Calculation of sampling weights took into account unequal probabilities of selection resulting from the sample design, nonresponse, and noncoverage. All analyses took into account differential probabilities of selection and the complex sample design. Standard errors were estimated with SUDAAN software using Taylor series linearization. Statistical tests were 2-sided and a *P* value of less than .05 was considered statistically significant.

Linear trends over the five 2-year survey cycles and variations in the prevalence of obesity by age and racial and ethnic groups over the 10-year period were tested using sex-specific logistic regression models with adjustment for age group, racial and ethnic group, and survey period; survey was treated as a continuous (ordered categorical) variable.

Approximate power calculations were performed using POWER software version 3 (National Cancer Institute, Bethesda, Maryland), assuming a survey design effect of 2. These calculations indicated that the sex-specific sample sizes were adequate to detect an odds ratio (OR) equivalent to an increase of 5 percentage points between 1999-2000 and 2007-2008 with 80% power and an OR equivalent to an increase of 6 percentage points with greater than 90% power.

In addition, sex-specific logistic regression models were fitted that included survey as a categorical variable, with adjustment for age group and racial and ethnic group. Logistic models with survey as a continuous variable were fitted within sex, age, and racial and ethnic subgroups. For graphical presentation only, the frequency distributions of BMI were smoothed using a 4253 H nonparametric smoothing algorithm, based on sequential calculations of running medians for groups of adjacent points.[9]

RESULTS

Sample sizes for analyses from 2007-2008 are presented in TABLE 1. Detailed infor-

Table 3. Prevalence of Grade 2 and Grade 3 Obesity for Adults Aged 20 Years or Older[a]

Categories by Age	% of Adults (95% Confidence Interval)				
	All[b]	Non-Hispanic White	Non-Hispanic Black	All Hispanics[c]	Mexican American
BMI ≥35					
All, age, y					
≥20	14.3 (12.8-15.8)	13.6 (11.3-15.9)	21.9 (18.2-25.6)	15.5 (13.5-17.5)	16.0 (13.2-18.8)
≥20[d]	14.3 (12.7-15.8)	13.6 (11.2-16.0)	21.7 (18.1-25.4)	15.4 (13.3-17.5)	15.9 (13.3-18.6)
Men, age, y					
≥20[d]	10.7 (9.1-12.3)	10.5 (8.5-12.5)	14.4 (10.4-18.4)	12.0 (8.9-15.2)	12.4 (7.9-16.8)
20-39	9.4 (6.7-12.0)	8.5 (4.6-12.4)	14.2 (8.5-20.0)	12.5 (8.0-17.1)	12.5 (6.1-18.8)
40-59	11.6 (9.3-13.9)	11.6 (8.8-14.3)	13.8 (8.9-18.7)	13.2 (9.0-17.3)	13.8 (8.6-19.0)
≥60	11.6 (9.3-13.8)	12.0 (9.5-14.6)	15.5 (11.1-19.9)	9.3 (5.4-13.2)	9.8 (3.8-15.8)[e]
Women, age, y					
≥20[d]	17.8 (15.8-19.8)	16.6 (13.4-19.9)	27.9 (23.3-32.5)	18.9 (16.3-21.5)	19.9 (17.3-22.5)
20-39	18.9 (15.0-22.7)	17.2 (11.6-22.9)	30.2 (23.8-36.6)	19.1 (14.8-23.4)	20.9 (13.9-27.9)
40-59	19.5 (16.5-22.6)	18.7 (14.6-22.9)	29.1 (23.2-35.0)	19.1 (12.7-25.4)	19.0 (11.4-26.6)
≥60	13.3 (11.0-15.5)	12.3 (9.1-15.4)	22.0 (15.9-28.2)	18.3 (13.3-23.2)	19.6 (13.3-26.0)
BMI ≥40					
All, age, y					
≥20	5.7 (4.9-6.5)	5.2 (3.8-6.5)	11.1 (8.3-13.8)	5.7 (4.4-7.1)	6.0 (4.3-7.6)
≥20[d]	5.7 (4.9-6.6)	5.2 (3.8-6.6)	10.8 (8.2-13.5)	5.5 (4.3-6.8)	5.6 (4.3-6.9)
Men, age, y					
≥20[d]	4.2 (3.3-5.1)	4.0 (2.9-5.1)	7.0 (4.5-9.4)	3.8 (2.1-5.6)	4.4 (2.1-6.6)
20-39	4.2 (2.7-5.6)	3.4 (1.4-5.4)	7.5 (3.5-11.4)	6.1 (3.0-9.2)	7.0 (3.0-10.9)
40-59	4.2 (2.8-5.6)	4.4 (2.4-6.4)	5.6 (1.9-9.3)[e]	3.5 (1.4-5.7)[e]	3.7 (1.0-6.4)[e]
≥60	4.2 (2.9-5.6)	4.4 (3.0-5.9)	8.2 (3.7-12.7)	NA	NA
Women, age, y					
≥20[d]	7.2 (6.1-8.4)	6.4 (4.2-8.5)	14.2 (10.5-17.8)	7.0 (5.7-8.4)	6.7 (5.2-8.2)
20-39	7.6 (5.6-9.7)	6.8 (3.4-10.3)	15.0 (9.4-20.6)	6.2 (4.6-7.8)	6.8 (3.6-10.1)
40-59	8.4 (6.6-10.2)	7.3 (4.4-10.1)	17.7 (12.2-23.1)	8.0 (4.8-11.2)	5.9 (2.9-8.9)
≥60	4.7 (2.9-6.5)	4.1 (1.8-6.5)	7.2 (3.9-10.5)	7.0 (4.4-9.6)	7.6 (4.5-10.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, data not shown because the estimate does not meet the standard of statistical reliability and precision (relative standard error >40%).
[a] Based on data from the National Health and Nutrition Examination Survey (NHANES) 2007-2008.
[b] Includes racial and ethnic groups not shown separately.
[c] Includes Mexican Americans.
[d] Age adjusted by the direct method to the year 2000 Census population using the age groups 20-39 years, 40-59 years, and 60 years or older.
[e] Relative standard error of 30% or greater but less than 40%.

mation on the prevalence of obesity (BMI ≥30) and of overweight and obesity combined (BMI ≥25) overall and by age, sex, and racial and ethnic group from NHANES 2007-2008 is presented in TABLE 2.

The prevalence of obesity in the United States is high, exceeding 30% in most age and sex groups except for men aged 20 to 39 years. Among men, age-adjusted obesity prevalence was 32.2% overall (95% confidence interval [CI], 29.5%-35.0%) and within racial and ethnic groups ranged from 31.9% (95% CI, 28.1%-35.7%) among non-Hispanic white men to 37.3% (95% CI, 32.3%-42.4%) among non-Hispanic black men. For women, the age-adjusted prevalence was 35.5% (95% CI, 33.2%-37.7%), ranging from 33.0% (95% CI, 29.3%-36.6%) among non-Hispanic white women to 49.6% (95% CI, 45.5%-53.7%) among non-Hispanic black women. The age-adjusted prevalence of overweight and obesity combined was 68.0% (95% CI, 66.3%-69.8%) overall, 72.3% (95% CI, 70.4%-74.1%) among men, and 64.1% (95% CI, 61.3%-66.9%) among women.

Additional information on the age-adjusted prevalence of grades 2 and 3 obesity (BMI ≥35) and of grade 3 obesity (BMI ≥40) by age, sex, and racial and ethnic group from NHANES 2007-2008 is presented in TABLE 3. The age-adjusted values for grades 2 and 3 obesity combined (BMI ≥35) ranged from 10.5% (95% CI, 8.5%-12.5%) among non-Hispanic white men to 14.4% (95% CI, 10.4%-18.4%) for non-Hispanic black men; corresponding values for women were 16.6% (95% CI, 13.4%-19.9%) and 27.9% (95% CI, 23.3%-32.5%). The overall age-adjusted prevalence of grade 3 obesity (BMI ≥40) was 5.7% (95% CI, 4.9%-6.5%) overall, 4.2% (95% CI, 3.3%-5.1%) for men, and 7.2% (95% CI, 6.1%-8.4%) for women, with particularly high values 14.2% (95% CI, 10.5%-17.8%) among non-Hispanic black women.

The age-adjusted prevalence of obesity by 2-year survey cycles is presented overall and by age and racial and ethnic group in TABLE 4 for men and in TABLE 5 for women. Logistic regression analyses for men, adjusted for age group and racial and ethnic group, showed a significant linear trend across survey cycles as a continuous variable for 2007-2008 vs 1999-2000 (OR, 1.32 [95% CI, 1.12-1.58]; $P = .002$) and significant differences among survey cycles as a categorical variable for 2007-2008 vs 1999-2000 (OR, 1.24 [95% CI, 1.03-1.52], $P = .02$). However, in analyses adjusted for age and racial and ethnic group with survey cycle as a categorical variable, there were no significant differences between the last 3 survey cycles (2003-2004, 2005-2006, and 2007-2008) for men.

To examine these findings for men further, additional linear trend tests by survey cycle were fitted within race and ethnicity and age subgroups. Within age groups, linear trends adjusted for racial

Table 4. Trends in the Age-Adjusted and Age-Specific Prevalence of Obesity (BMI ≥30) in US Men Aged 20 Years or Older for 1999-2008

	No. (%) of Men [95% Confidence Interval]			
	Age ≥20 y[a]	Ages 20-39 y	Ages 40-59 y	Age ≥60 y
All[b]				
1999-2000	2043 (27.5) [24.4-30.6]	666 (23.7) [20.5-27.0]	595 (28.8) [23.0-34.7]	782 (31.8) [27.3-36.3]
2001-2002	2219 (27.8) [25.8-29.7]	750 (22.3) [19.4-25.1]	773 (32.2) [28.8-35.5]	696 (30.2) [26.5-33.9]
2003-2004	2237 (31.1) [28.5-33.7]	756 (28.0) [23.7-32.4]	649 (34.8) [29.9-39.7]	832 (30.4) [26.6-34.2]
2005-2006	2237 (33.3) [29.3-37.4]	793 (28.1) [22.3-33.8]	709 (39.7) [33.9-45.4]	735 (32.2) [28.1-36.3]
2007-2008	2750 (32.2) [29.5-35.0][c]	896 (27.5) [23.8-31.2][c]	883 (34.3) [29.8-38.8][c]	971 (37.1) [33.1-41.0][c]
Non-Hispanic white				
1999-2000	946 (27.3) [23.8-30.8]	276 (22.0) [17.3-26.7]	262 (28.5) [21.8-35.2]	408 (34.3) [28.8-39.9]
2001-2002	1157 (29.1) [26.5-31.7]	322 (23.9) [19.5-28.2]	407 (33.2) [29.5-36.9]	428 (31.5) [27.7-35.3]
2003-2004	1183 (31.1) [28.1-34.2]	336 (27.2) [21.4-33.0]	340 (35.6) [29.3-41.9]	507 (30.6) [26.3-35.0]
2005-2006	1145 (33.1) [28.7-37.5]	328 (25.8) [18.6-33.1]	368 (41.0) [35.0-47.0]	449 (32.9) [28.6-37.3]
2007-2008	1335 (31.9) [28.1-35.7][c]	383 (26.3) [20.9-31.7]	391 (34.0) [28.1-39.8]	561 (38.4) [34.1-42.6]
Non-Hispanic black				
1999-2000	374 (28.1) [24.8-31.5]	125 (27.4) [22.0-32.8]	127 (29.9) [23.3-36.4]	122 (26.4) [18.5-34.4]
2001-2002	435 (27.9) [24.0-31.8]	148 (22.2) [16.4-28.0]	161 (30.0) [23.9-36.1]	126 (34.2) [25.3-43.0]
2003-2004	432 (34.0) [27.1-40.9]	175 (32.3) [24.1-40.5]	146 (37.6) [31.6-43.6]	111 (31.1) [17.8-44.3]
2005-2006	507 (37.2) [32.5-41.8]	185 (39.7) [33.3-46.0]	170 (34.8) [26.2-43.3]	152 (36.8) [31.3-42.2]
2007-2008	554 (37.3) [32.3-42.4][c]	187 (34.7) [28.5-40.9][c]	173 (39.7) [30.0-49.5]	194 (38.0) [31.3-44.7][c]
Mexican American				
1999-2000	538 (28.9) [25.2-32.7]	184 (30.4) [24.2-36.5]	157 (27.0) [19.6-34.3]	197 (29.7) [22.0-37.4]
2001-2002	480 (25.9) [21.8-29.9]	215 (17.4) [11.1-23.8]	152 (34.8) [27.5-42.1]	113 (25.9) [19.5-32.2]
2003-2004	458 (31.6) [26.6-36.6]	165 (32.7) [23.0-42.3]	118 (31.8) [21.3-42.4]	175 (29.5) [22.0-36.9]
2005-2006	443 (27.0) [23.2-30.7]	210 (24.7) [19.5-29.9]	128 (27.6) [20.9-34.3]	105 (30.0) [20.7-39.2]
2007-2008	460 (35.9) [28.9-43.0]	195 (33.8) [22.7-44.9]	164 (38.2) [26.3-50.1]	101 (35.8) [21.9-49.8]

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Age adjusted by the direct method to the year 2000 Census population using the age groups 20-39 years, 40-59 years, and 60 years or older.
[b] Includes racial and ethnic groups not shown separately.
[c] Indicates significant linear trend over survey cycle ($P < .05$).

Table 5. Trends in the Age-Adjusted and Age-Specific Prevalence of Obesity (BMI ≥30) in US Women Aged 20 Years or Older for 1999-2008

	No. (%) of Women (95% Confidence Interval)			
	Age ≥20 y[a]	Ages 20-39 y	Ages 40-59 y	Age ≥60 y
All[b]				
1999-2000	2072 (33.4) [30.0-36.8]	640 (28.4) [24.4-32.4]	653 (37.8) [31.2-44.4]	779 (35.0) [30.7-39.3]
2001-2002	2171 (33.3) [30.2-36.3]	712 (29.8) [25.6-34.1]	721 (35.7) [31.6-39.9]	738 (35.2) [31.2-39.2]
2003-2004	2194 (33.2) [29.7-36.6]	661 (28.9) [24.3-33.6]	662 (38.8) [33.4-44.1]	871 (31.5) [28.0-34.9]
2005-2006	2119 (35.3) [32.5-38.1]	707 (30.5) [25.9-35.0]	718 (41.1) [36.5-45.6]	694 (34.4) [29.7-39.1]
2007-2008	2805 (35.5) [33.2-37.7]	877 (34.0) [29.0-39.1]	910 (38.2) [33.8-42.6]	1018 (33.6) [30.2-36.9]
Non-Hispanic white				
1999-2000	885 (30.1) [25.9-34.3]	249 (24.4) [19.2-29.6]	249 (34.2) [25.1-43.3]	387 (33.3) [28.9-37.7]
2001-2002	1130 (31.3) [28.0-34.6]	313 (25.2) [20.5-29.8]	376 (35.4) [31.3-39.6]	441 (35.2) [29.6-40.8]
2003-2004	1174 (30.2) [25.9-34.4]	327 (23.8) [17.6-29.9]	333 (37.8) [31.1-44.5]	514 (28.9) [25.9-31.8]
2005-2006	1048 (32.9) [29.4-36.5]	288 (27.4) [20.5-34.2]	340 (39.3) [34.4-44.1]	420 (32.3) [27.2-37.4]
2007-2008	1283 (33.0) [29.3-36.6]	344 (31.3) [23.3-39.3]	402 (35.7) [29.7-41.7]	537 (31.4) [27.3-35.5]
Non-Hispanic black				
1999-2000	420 (49.7) [43.7-55.8]	140 (46.2) [38.3-54.1]	141 (53.2) [46.8-59.6]	139 (50.2) [36.1-64.4]
2001-2002	434 (48.3) [42.9-53.6]	157 (47.2) [39.6-54.9]	148 (47.8) [41.6-54.0]	129 (50.8) [37.8-63.8]
2003-2004	444 (53.9) [47.9-59.8]	153 (50.3) [41.1-59.6]	160 (57.5) [48.8-66.2]	131 (54.0) [43.9-64.2]
2005-2006	512 (52.9) [48.7-57.0]	175 (47.7) [40.3-55.1]	195 (53.3) [46.8-59.8]	142 (61.0) [54.3-67.7]
2007-2008	590 (49.6) [45.5-53.7]	191 (47.2) [41.3-53.1]	198 (51.7) [47.2-56.1]	201 (50.5) [40.5-60.5]
Mexican American				
1999-2000	567 (39.7) [32.1-47.2]	180 (30.6) [19.3-41.9]	193 (48.5) [38.9-58.1]	194 (41.0) [32.6-49.3]
2001-2002	445 (37.0) [30.6-43.4]	178 (31.5) [20.8-42.2]	139 (47.1) [38.8-55.4]	128 (30.2) [22.0-38.4]
2003-2004	415 (42.3) [36.8-47.7]	130 (35.7) [28.6-42.9]	110 (48.3) [38.5-58.1]	175 (43.8) [37.7-49.9]
2005-2006	400 (42.1) [36.4-47.7]	170 (36.5) [29.5-43.4]	124 (51.1) [42.2-60.0]	106 (37.1) [25.6-48.6]
2007-2008	485 (45.1) [38.9-51.2]	189 (39.6) [33.7-45.5]	158 (48.9) [38.0-59.8]	138 (48.1) [43.0-53.3]

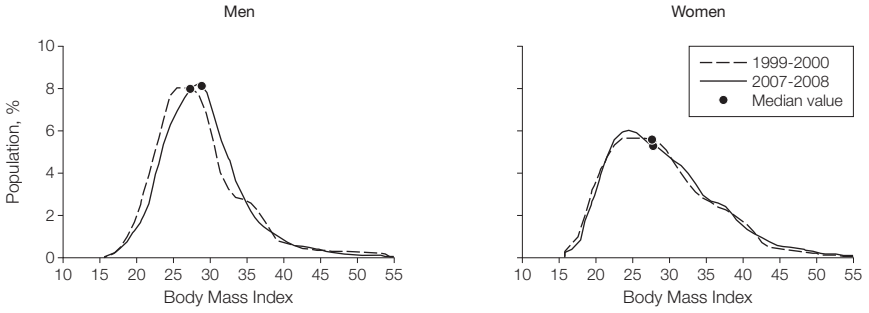
Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Age adjusted by the direct method to the year 2000 Census population using the age groups 20-39 years, 40-59 years, and 60 years or older.
[b] Includes racial and ethnic groups not shown separately.

and ethnic group were significant for men aged 20 to 39 years ($P=.03$), aged 40 to 59 years ($P=.03$), and aged 60 years or older ($P=.04$). Within racial and ethnic groups, linear trends adjusted for age were significant for non-Hispanic whites ($P=.02$) and non-Hispanic blacks ($P<.001$), but not for Mexican American men ($P=.15$). Within racial and ethnic and age groups, linear trend tests across survey cycles were significant only for non-Hispanic black men aged 20 to 39 years ($P=.001$) and aged 60 years or older ($P=.02$). There may be limited power to detect statistically significant trends within subgroups.

For women overall, there were no significant differences by survey cycle either as a continuous variable (adjusted OR for 2007-2008 vs 1999-2000, 1.12 [95% CI, 0.89-1.32]; $P=.21$) or a categorical variable ($P=.68$). There were not any significant trends by survey cycle within any subgroup of women.

In analyses over the 10-year period adjusted for survey cycle for both men and women, the likelihood of being obese was significantly higher in the age group of 40-59 years (OR for men, 1.46 [95% CI, 1.29-1.66]; OR for women, 1.50 [95% CI, 1.31-1.72]) and in the age group of 60 years or older (OR for men, 1.35 [95% CI, 1.19-1.54]; OR for women, 1.26 [95% CI, 1.11-1.44]) than among those in the age group of 20-39 years. Relative to non-Hispanic whites, the likelihood of being obese was significantly greater among non-Hispanic blacks (OR for men, 1.13 [95% CI, 1.01-1.27]; OR for women, 2.26 [95% CI, 2.02-2.51]) and for Mexican American women (OR, 1.53; 95% CI, 1.31-1.78), but not for Mexican American men (OR, 1.01; 95% CI, 0.85-1.19).

Figure. Smoothed Frequency Distributions of Body Mass Index for Men and Women Aged 40 to 59 Years in 1999-2000 and 2007-2008



Smoothed distributions of BMI in 1999-2000 and 2007-2008 are shown by age group in the FIGURE for men and women aged 40 to 59 years. (Distributions for men and women aged 20-39 years and aged ≥60 years are available online in eFigure 1 and eFigure 2 at http://www.jama.com.) For both men and women,

the estimated median BMI (50th percentile) tended to be slightly higher in 2007-2008 than in 1999-2000 within all age groups; however, some of the differences were extremely small. In 1999-2000, the median BMI for men aged 20 to 39 years was 26.0 (95% CI, 25.6-26.7) vs 26.6 (95% CI, 26.1-27.2) in 2007-2008; for men aged 40 to 59 years, 27.4 (95% CI, 26.8-27.9) vs 28.3 (95% CI, 27.7-29.0); and for men aged 60 years or older, 27.5 (95% CI, 27.2-28.0) vs 28.3 (95% CI, 27.9-28.7). In 1999-2000, the median BMI for women aged 20 to 39 years was 25.6 (95% CI, 24.8-26.3) vs 26.5 (95% CI, 25.7-27.5) in 2007-2008; for women aged 40 to 59 years, 27.6 (95% CI, 26.2-28.8) vs 27.7 (95% CI, 27.0-28.5); and for women aged 60 years or older, 27.4 (95% CI, 26.8-28.1) vs 27.6 (95% CI, 26.9-28.3).

COMMENT

The prevalence of obesity in the United States continues to be high, exceeding 30% in most sex and age groups. Comparisons between Canada and the United States show that obesity prevalence was higher in the United States in 1999-2002 than in Canada in 2004, with the difference largely due to higher obesity prevalence among women.[10] Comparisons of obesity prevalence between Canada and the United States that are limited to white adults show no significant differences for men.[10] A review of prevalence estimates in European countries found that the prevalence of obesity based on measured weights and heights varies widely from country to country, with higher prevalences in Central, Eastern, and Southern Europe.[11] In most cases, the prevalence of obesity appeared lower in European countries than in the United States. However, estimates from other countries are not precisely comparable with US estimates because of differences in study methods, years of measurement and the age ranges, and methods of age adjustment or age categorization.

The prevalence of obesity shows significant variation by racial and ethnic groups. Racial and ethnic differences in the prevalence of obesity as defined by BMI should be interpreted cautiously because they do not necessarily correspond to differences in fat mass or percentage of body fat. Body mass index is a valuable tool to provide a standardized definition of obesity for the purposes of national surveillance and international comparisons.[12] In the NHANES surveys, BMI is highly correlated with percentage of body fat, slightly more so for women than for men.[13] However, BMI does not distinguish fat and lean tissue or represent adiposity directly.

The degree of adiposity associated with a given level of BMI varies by age, sex, and racial and ethnic group.[14] Relative to white men and women at the same BMI level, black men and women tend to have higher lean mass and lower fat mass.[13,15-17] The relative, although not absolute, health risks associated with a given BMI level may be lower for blacks than for whites.[18-20] Asian populations tend to have higher body fat percentages at a given BMI level and possible higher risks; however, this theory has been disputed.[21] Considerable discussion[22-24] has addressed the public health and policy issues of using different BMI cutoff points for different ethnic groups that have different relationships with BMI, body fat, and health risks.

For women, the prevalence of obesity showed no statistically significant changes over the 10-year period from 1999 through 2008. For men, there was a significant linear trend over the same period, but estimates for the period 2003-2004, 2005-2006, and 2007-2008 did not differ significantly from each other. These data suggest that the increases in the prevalence of obesity previously observed between 1976-1980 and 1988-1994[1,3] and between 1988-1994 and 1999-2000[3] may not be continuing at a similar level over the period 1999-2008, particularly for women but possibly for men.

The prevalence of obesity for adults aged 20 to 74 years increased by 7.9 percentage points for men and by 8.9 percentage points for women between 1976-1980 and 1988-1994, and subsequently by 7.1 percentage points for men and by 8.1 percentage points for women between 1988-1994 and 1999-2000.[1] If the trends between 1988-1994 and 1999-2000 continued at approximately the same annual level, an increase of 6 to 7 percentage points between 1999-2000 and 2008-2009 would be expected for both men and women. The sample size was sufficient to detect a linear increase of this magnitude with 90% power. Between 1999-2000 and 2007-2008, there was an increase of 4.7 percentage points (95% CI, 0.5 to 9.0) for men and a nonsignificant increase of 2.1 percentage points (95% CI, –2.1 to 6.3) for women.

In the United States, a study of data from military recruits, veterans, and national surveys suggests mean BMI has increased over a long period since the Civil War up to recent times, with increases in the last several decades perhaps less steep than those observed earlier.[25] Over the period 1960-1980 (covered by the earliest NHANES surveys and the National Health Examination Survey), obesity prevalence was relatively stable, but then it showed striking increases in the 1980s and 1990s. The data presented in our current study using 2007-2008 data suggest that the prevalence may have entered another period of relative stability, perhaps with small increases in obesity, although future large changes cannot be ruled out. Because relatively little is known about the causes of the trends previously observed, it is difficult to predict the future trends in obesity.

This study has several limitations. These data were obtained from a sample survey and like other survey data, they may be subject to sampling error or nonsampling error. In addition, the power of this study is limited to detect small changes in prevalence, particularly among subgroups defined by sex, age, and racial and ethnic group.

Obesity is a risk factor for a variety of chronic conditions including diabetes, hypertension, high cholesterol, stroke, heart disease, certain cancers, and arthritis.[26] Higher grades of obesity are associated with excess mortality, primarily from cardiovascular disease, diabetes, and certain cancers.[26-28] Trends in obesity-related health outcomes do not always parallel trends in the prevalence of obesity. Despite the increases in obesity prevalence, mortality rates and mortality from coronary heart disease and stroke have declined

over several decades,[29] possibly due to improvements in public health and medical care and in other cardiovascular risk factors[30]; however, hypertension appears to be increasing.[31] Of these obesity-related conditions, diabetes may be most closely linked to obesity, and the increasing incidence of diabetes worldwide is of considerable concern.[32] In the United States, the prevalence of diagnosed diabetes increased significantly from 1988-1994 through 2005-2006, although the total prevalence of diabetes increased significantly only among non-Hispanic blacks.[33]

The prevention and treatment of overweight and obesity on a populationwide basis are challenging. Population-based strategies that improve social and physical environmental contexts for healthful eating and physical activity are complementary to clinical preventive strategies and to treatment programs for those who are already obese.[34] For example, innovative public policy approaches include a variety of policy and environmental initiatives designed to increase fruit and vegetable consumption in underserved areas.[35,36] Preventive population-level interventions having to do with the built environment and the food environment may lead to health benefits for the entire population, not only for the obese population; and some interventions may reduce excess body fat among the obese population even without large concomitant changes in weight.[37] Enhanced efforts to provide environmental interventions may lead to improved health and to future decreases in the prevalence of obesity.

Published online: January 13, 2010 (doi:10.1001/jama.2009.2014).
Author Contributions: Dr Flegal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Flegal.
Analysis and interpretation of data: Flegal, Carroll, Ogden, Curtin.
Drafting of the manuscript: Flegal.
Critical revision of the manuscript for important intellectual content: Flegal, Carroll, Ogden, Curtin.
Statistical analysis: Flegal, Carroll, Ogden, Curtin.
Financial Disclosures: None reported.
Role of the Sponsor: All data used in this study were collected by the National Center for Health Statistics, Centers for Disease Control and Prevention. The Centers for Disease Control and Prevention reviewed and approved this report before submission for publication.
Disclaimer: The findings and conclusions in this report are those of the authors and not necessarily those of the Centers for Disease Control and Prevention.
Online-Only Material: eFigure 1 and eFigure 2 are available at http://www.jama.com.

REFERENCES

1. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int J Obes Relat Metab Disord*. 1998;22(1):39-47.
2. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA*. 1994;272(3):205-211.
3. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288(14):1723-1727.
4. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA*. 2004;291(23):2847-2850.
5. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006; 295(13):1549-1555.
6. Ogden CL, Carroll MD, McDowell MA, Flegal KM. Obesity among adults in the United States: no statistically significant change since 2003-2004. http://www.cdc.gov/nchs/data/databriefs/db01.pdf. Accessed December 5, 2009.
7. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary: Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr*. 1998;68(4):899-917.
8. WHO Expert Committee on Physical Status. *Physical Status: The Use and Interpretation of Anthropometry*. Geneva, Switzerland: World Health Organization; 1995.
9. Velleman PF, Hoaglin DC. *Applications, Basics and Computing of Exploratory Data Analysis*. Boston, MA: Duxbury Press; 1981.
10. Tjepkema M. Adult obesity. *Health Rep*. 2006; 17(3):9-25.
11. Berghöfer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. Obesity prevalence from a European perspective: a systematic review. *BMC Public Health*. 2008;8:200.
12. Bouchard C. How much progress have we made over the last few decades? *Int J Obes (Lond)*. 2008; 32(suppl 7):S2-S7.
13. Flegal KM, Shepherd JA, Looker AC, et al. Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. *Am J Clin Nutr*. 2009;89(2):500-508.
14. Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol*. 1996;143(3):228-239.
15. Aloia JF, Vaswani A, Mikhail M, Flaster ER. Body composition by dual-energy X-ray absorptiometry in black compared with white women. *Osteoporos Int*. 1999;10(2):114-119.
16. Fernández JR, Heo M, Heymsfield SB, et al. Is percentage body fat differentially related to body mass index in Hispanic Americans, African Americans, and European Americans? *Am J Clin Nutr*. 2003;77 (1):71-75.
17. Rahman M, Temple JR, Breitkopf CR, Berenson AB. Racial differences in body fat distribution among reproductive-aged women. *Metabolism*. 2009; 58(9):1329-1337.
18. Abell JE, Egan BM, Wilson PW, Lipsitz S, Woolson RF, Lackland DT. Differences in cardiovascular disease mortality associated with body mass between black and white persons. *Am J Public Health*. 2008; 98(1):63-66.
19. Sanchez AM, Reed DR, Price RA. Reduced mortality associated with body mass index (BMI) in African Americans relative to Caucasians. *Ethn Dis*. 2000; 10(1):24-30.
20. Stevens J, Plankey MW, Williamson DF, et al. The body mass index-mortality relationship in white and African American women. *Obes Res*. 1998;6(4): 268-277.
21. Gu D, He J, Duan X, et al. Body weight and mortality among men and women in China. *JAMA*. 2006; 295(7):776-783.
22. Misra A. Revisions of cutoffs of body mass index to define overweight and obesity are needed for the Asian-ethnic groups. *Int J Obes Relat Metab Disord*. 2003;27(11):1294-1296.
23. Stevens J. Ethnic-specific cutpoints for obesity vs country-specific guidelines for action. *Int J Obes Relat Metab Disord*. 2003;27(3):287-288.
24. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004; 363(9403):157-163.
25. Costa DL, Steckel RH. Long-term trends in health, welfare, and economic growth in the United States. In: Steckel RH, Floud R, eds. *Health and Welfare During Industrialization*. Chicago, IL: The University of Chicago Press; 1997:47-89.
26. Malnick SD, Knobler H. The medical complications of obesity. *QJM*. 2006;99(9):565-579.
27. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2007; 298(17):2028-2037.
28. Orpana HM, Berthelot JM, Kaplan MS, Feeny DH, McFarland B, Ross NA. BMI and mortality: results from a national longitudinal study of Canadian adults [published ahead of print June 18, 2009]. *Obesity (Silver Spring)*. doi:10.1038/oby.2009.191.
29. National Center for Health Statistics. Health, United States, 2008 with chartbook. http://www.cdc.gov/nchs/data/hus/hus08.pdf. Accessed December 3, 2009.
30. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA*. 2005; 293(15):1868-1874.
31. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension*. 2008;52(5):818-827.
32. McKinlay J, Marceau L. US public health and the 21st century: diabetes mellitus. *Lancet*. 2000;356 (9231):757-761.
33. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the US population in 1988-1994 and 2005-2006. *Diabetes Care*. 2009;32(2):287-294.
34. Kumanyika SK, Obarzanek E, Stettler N, et al; American Heart Association Council on Epidemiology and Prevention, Interdisciplinary Committee for Prevention. Population-based prevention of obesity: the need for comprehensive promotion of healthful eating, physical activity, and energy balance: a scientific statement from American Heart Association Council on Epidemiology and Prevention, Interdisciplinary Committee for Prevention (formerly the Expert Panel on Population and Prevention Science). *Circulation*. 2008;118(4):428-464.
35. Giang T, Karpyn A, Laurison HB, Hillier A, Perry RD. Closing the grocery gap in underserved communities: the creation of the Pennsylvania Fresh Food Financing Initiative. *J Public Health Manag Pract*. 2008;14(3):272-279.
36. Glanz K, Yaroch AL. Strategies for increasing fruit and vegetable intake in grocery stores and communities: policy, pricing, and environmental change. *Prev Med*. 2004;39(suppl 2):S75-S80.
37. Ross R, Bradshaw AJ. The future of obesity reduction: beyond weight loss. *Nat Rev Endocrinol*. 2009; 5(6):319-325.

Association of Maternal Weight Gain in Pregnancy With Offspring Obesity and Metabolic and Vascular Traits in Childhood

Abigail Fraser, PhD; Kate Tilling, PhD; Corrie Macdonald-Wallis, MSc; Naveed Sattar, PhD, FRCPath; Marie-Jo Brion, PhD; Li Benfield, PhD; Andy Ness, PhD, FFPH; John Deanfield, BA, BCh, FRCP; Aroon Hingorani, PhD, FRCP; Scott M. Nelson, PhD, FRCOG; George Davey Smith, MD, DSc; Debbie A. Lawlor, PhD, FFPH

Background—We sought to examine the association of gestational weight gain (GWG) and prepregnancy weight with offspring adiposity and cardiovascular risk factors.

Methods and Results—Data from 5154 (for adiposity and blood pressure) and 3457 (for blood assays) mother-offspring pairs from a UK prospective pregnancy cohort were used. Random-effects multilevel models were used to assess incremental GWG (median and range of repeat weight measures per woman: 10 [1, 17]). Women who exceeded the 2009 Institute of Medicine–recommended GWG were more likely to have offspring with greater body mass index, waist, fat mass, leptin, systolic blood pressure, C-reactive protein, and interleukin-6 levels and lower high-density lipoprotein cholesterol and apolipoprotein A1 levels. Children of women who gained less than the recommended amounts had lower levels of adiposity, but other cardiovascular risk factors tended to be similar in this group to those of offspring of women gaining recommended amounts. When examined in more detail, greater prepregnancy weight was associated with greater offspring adiposity and more adverse cardiovascular risk factors at age 9 years. GWG in early pregnancy (0 to 14 weeks) was positively associated with offspring adiposity across the entire distribution but strengthened in women gaining >500 g/wk. By contrast, between 14 and 36 weeks, GWG was only associated with offspring adiposity in women gaining >500 g/wk. GWG between 14 and 36 weeks was positively and linearly associated with adverse lipid and inflammatory profiles, with these associations largely mediated by the associations with offspring adiposity.

Conclusions—Greater maternal prepregnancy weight and GWG up to 36 weeks of gestation are associated with greater offspring adiposity and adverse cardiovascular risk factors. Before any GWG recommendations are implemented, the balance of risks and benefits of attempts to control GWG for short- and long-term outcomes in mother and child should be ascertained. **(*Circulation*. 2010;121:2557-2564.)**

Key Words: blood pressure ■ epidemiology ■ gestational weight gain ■ lipids ■ obesity

A recent systematic review found evidence of associations of maternal prepregnancy weight and greater gestational weight gain (GWG) with a wide range of adverse perinatal health outcomes.[1] Fewer studies have examined the long-term effects of these on offspring health, and this systematic review and the recently revised 2009 US Institute of Medicine (IOM) guidance on GWG identified a need for further high-quality research with long-term offspring outcomes.[1,2]

Clinical Perspective on p 2564

Several studies have examined associations of GWG with offspring adiposity and have consistently (all but 1 study[3]) reported positive associations with offspring body mass index (BMI) in childhood,[4–6] adolescence,[7] and adulthood.[8] Other studies have examined the association with offspring blood pressure (BP), with conflicting results.[4,8–12] The 2 most recent and largest studies suggest positive associations of GWG with offspring BP in childhood[4] and adulthood[8] that may be mediated by the association of GWG with offspring adiposity.[8]

No studies have examined associations of maternal prepregnancy weight or GWG with offspring cardiovascular risk factors other than BMI and BP. Most previous studies have been unable to examine patterns of GWG with offspring

Received August 31, 2009; accepted April 13, 2010.

From the Medical Research Council Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, University of Bristol, Bristol, UK (A.F., K.T., C.M.-W., M.B., L.B., G.D.S., D.A.L.); Faculty of Medicine, University of Glasgow, Glasgow, Scotland (N.S., S.M.N.); Department of Oral and Dental Science, University of Bristol, Bristol, UK (A.N.); Vascular Physiology Unit, University College London, London, UK (J.D.); and Centre for Clinical Pharmacology, University College London, London, UK (A.H.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.109.906081/DC1.

Correspondence to Professor D.A. Lawlor, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Rd, Bristol, UK BS8 2PR. E-mail d.a.lawlor@bristol.ac.uk

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.109.906081**

Table 1. IOM-Recommended Levels of GWG According to Prepregnancy BMI Categories[2]

Prepregnancy BMI	Range of Recommended Absolute Weight Gain, kg
Underweight (<18.5 kg/m^2)	12.5–18
Normal weight (18.5–24.9 kg/m^2)	11.5–16
Overweight (25–29.9 kg/m^2)	7–11.5
Obese (≥30 kg/m^2)	5–9

outcomes. No studies have examined associations of the newly defined IOM GWG categories with offspring outcomes.[2] Our aim was to examine associations of GWG and prepregnancy weight with a range of offspring cardiovascular risk factors (BMI, fat mass, waist circumference, BP, lipids, apolipoproteins, adiponectin, leptin, interleukin-6 [IL-6], and C-reactive protein [CRP]) with the use of detailed repeat measures of gestational weight.

Methods

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective, population-based birth cohort study that recruited 14 541 pregnant women resident in Avon, UK, with expected dates of delivery April 1, 1991, to December 31, 1992 (http://www.alspac.bris.ac.uk.).[13] There were 13 678 mother-offspring pairs from singleton live births who survived to at least 1 year of age; only singleton pregnancies are considered in this article. We further restricted analyses in this article to women with term deliveries (between 37 and 44 weeks of gestation; n=12 447). Of these women, 11 702 (94%) gave consent for abstraction of data from their obstetric records, and 6668 offspring (57%) of these 11 702 women attended the 9-year follow-up clinic. Of the 6668 mother-offspring eligible pairs, complete data on GWG, offspring anthropometry, BP, and potential confounders were available for 5154 (77% of attendees; 41% of 12 47 total). In addition, 3457 (52% of attendees; 28% of total) had complete data on offspring blood assays.

Six trained research midwives abstracted data from obstetric medical records. There was no between-midwife variation in mean values of abstracted data, and repeat data entry checks demonstrated error rates consistently <1%. Obstetric data abstractions included every measurement of weight entered into the medical records and the corresponding gestational age and date. To allocate women to IOM categories (Table 1), we used weight measurements from the obstetric notes and subtracted the first from the last weight measurement in pregnancy to derive absolute weight gain. Prepregnancy BMI was based on the predicted prepregnancy weight with the use of multilevel models (see below) and maternal report of height.

Maternal age, parity, mode of delivery (cesarean section/vaginal delivery), and the child's sex were obtained from the obstetric records. On the basis of questionnaire responses, the highest parental occupation was used to allocate the children to family social class groups (classes I [professional/managerial] to V [unskilled manual workers]). Information on maternal smoking in pregnancy, categorized as (1) never smoked, (2) smoked before pregnancy or in the first trimester and then stopped, and (3) smoked throughout pregnancy, was obtained from questionnaire responses.

Offspring weight and height were measured in light clothing, without shoes. Weight was measured to the nearest 0.1 kg with the use of Tanita scales. Height was measured to the nearest 0.1 cm with the use of a Harpenden stadiometer. Waist circumference was measured to the nearest 1 mm at the midpoint between the lower ribs and the pelvic bone with a flexible tape and with the child breathing normally. Fat mass was assessed with the use of dual-energy x-ray densitometry. We examined BMI, waist circumference, and fat mass as continuously measured variables. We also examined binary outcomes of overweight/obese (BMI) and abdominally obese (waist circumference) subjects using age- and sex-specific thresholds for both child BMI (International Obesity Task Force)[14] and waist circumference (≥90th percentile[15] based on waist circumference percentile curves derived for British children[16]).

BP was measured with the use of a Dinamap 9301 Vital Signs Monitor with the child rested and seated and with the arm supported at chest level on a table. Two readings of systolic and diastolic BP (SBP and DBP, respectively) were recorded, and the mean of each was used. Nonfasting blood samples were taken with the use of standard procedures with samples immediately spun and frozen at −80°C. The measurements were assayed in plasma in 2008 after a median of 7.5 years in storage with no previous freeze-thaw cycles during this period. Analysis of lipids (total cholesterol, triglycerides, and high-density lipoprotein cholesterol [HDL-C]) was performed by modification of the standard Lipid Research Clinics protocol with the use of enzymatic reagents for lipid determinations. Apolipoprotein A1 (apoA1) and apolipoprotein B (apoB) were measured by immunoturbidimetric assays (Hitachi/Roche). Leptin was measured by an in-house enzyme-linked immunosorbent assay validated against commercial methods. Adiponectin and high-sensitivity IL-6 were measured by enzyme-linked immunosorbent assay (R&D Systems), and CRP was measured by automated particle-enhanced immunoturbidimetric assay (Roche UK, Welwyn Garden City, UK). All assay coefficients of variation were <5%. Non–HDL-C was calculated as total cholesterol minus HDL-C.

All pregnancy weight measurements (median number of repeat measurements per woman, 10; range, 1, 17) were used to develop a linear spline multilevel model (with 2 levels: woman and measurement occasion) relating weight (outcome) to gestational age (exposure). Full details of this statistical modeling are provided in the online-only Data Supplement. High levels of agreement were found between estimated and observed weights (Table I and Figure II in the online-only Data Supplement). We scaled maternal prepregnancy weight and gestational weight change to be clinically meaningful, examining the variation in offspring outcomes per additional 1 kg of maternal weight at conception and per 400-g gain per week of gestation for GWG.[2] Sensitivity analyses were conducted in which we repeated analyses including only those women who had at least 9 measurements of gestational weight.

Associations of offspring outcomes with the IOM categories and with the estimates of maternal prepregnancy weight and early-, mid-, and late-pregnancy GWG were undertaken with the use of linear regression. We explored the linearity of the relationships between all outcomes and the exposures using fractional polynomials. When there was evidence of nonlinearity, we used spline models to approximate the relationship. In the basic model, we adjusted for offspring gender and age at the time of outcome measurement and for all models with fat mass for height and height squared. We considered the following potential confounders: prepregnancy weight and GWG in the previous period (for the multilevel model exposures only), gestational age (for IOM categories only because this is taken into account in the multilevel models), maternal age, parity, smoking during pregnancy, social class, and mode of delivery. To examine whether effects were mediated by birth weight, we adjusted for it, and for nonadiposity outcomes, we also examined potential mediation by adiposity. Triglycerides, leptin, CRP, and IL-6 were log transformed to normalize their distributions. The resultant regression coefficients were exponentiated to give a ratio of geometric means per change in exposure. Results are presented jointly for mothers of female and male offspring because associations were very similar in both genders.

Ethical Approval

Ethical approval for all aspects of data collection was obtained from the ALSPAC Law and Ethics Committee (IRB 00003312) and the local Research Ethics Committee.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Table II in the online-only Data Supplement shows the characteristics of mothers and offspring. Table 2 shows the association of IOM categories with adiposity and cardiovascular risk factors. Offspring of women who gained more than IOM-recommended GWG were more likely to have greater BMI, waist circumference, fat mass, leptin, SBP, CRP, and IL-6 levels. They were also more likely to have lower HDL-C and apoA1 levels. Children of women who gained less than recommended amounts had lower levels of adiposity, but other cardiovascular risk factors tended to be similar in this group to those of offspring of women gaining recommended amounts. IOM categories were not associated with DBP, non–HDL-C, apoB, or triglyceride levels. Associations remained with adjustment for confounders. IOM categories were associated with binary outcomes of offspring overweight/obesity. In confounder-adjusted models, offspring of women who gained less than recommended levels compared with those gaining recommended levels had odds ratios of overweight/obesity (based on BMI) of 0.80 (0.67, 0.96) and of central obesity (based on waist) of 0.79 (0.69, 0.90), and offspring of mothers who gained more than recommended levels compared with those gaining recommended levels had odd ratios of overweight/obesity and central obesity of 1.73 (1.45, 2.05) and 1.36 (1.19, 1.57), respectively.

When we used multilevel models including repeat measures of gestational weight to estimate GWG in more detail, 3 distinct periods of GWG were identified: early pregnancy, 0 to 14 weeks; mid pregnancy, >14 to 36 weeks; and late pregnancy, >36 weeks (Figure). In early pregnancy, 20.0% of women either lost weight or remained stable. The majority of women in both mid (99.9%) and late pregnancy (95.7%) gained weight. Table III in the online-only Data Supplement shows the correlations between estimated prepregnancy weight, estimated GWG in early, mid, and late pregnancy, total absolute GWG over the whole pregnancy, and birth weight. Most correlations were modest or weak. There was a strong inverse association of estimated GWG in early and late pregnancy and a strong positive association of estimated GWG in mid and late pregnancy.

Table 3 shows the associations of estimated prepregnancy weight (per 1-kg change) and estimated GWG (per 400 kg/wk) with offspring adiposity (BMI, waist circumference, fat mass, leptin) and BP. Estimated prepregnancy weight was positively linearly associated with all 4 measurements of offspring adiposity and SBP and DBP, with these associations remaining after adjustment for confounders.

For associations of estimated GWG with adiposity and BP, there was evidence of nonlinearity with knots (changes in the direction and/or magnitude of association) at 0 and 500 g/wk for GWG in early pregnancy and at 250 and 500 g/wk in both mid and late pregnancy. Estimated GWG in all 3 periods generally had U-shaped associations with offspring adiposity, with null or inverse associations in women gaining low levels of weight, then null associations in the middle range of estimated GWG, and then positive associations (model 1, Table 3). However, with adjustment for confounding factors (model 2), the inverse associations at low levels of estimated GWG attenuated. In the confounder-adjusted model, women who lost weight or did not gain weight in early pregnancy (ie, low estimated GWG women) had no association between their average gestational weight change per week and offspring adiposity. However, for those women (ie, medium or high estimated GWG women) gaining weight during this period, there was a positive association of estimated GWG with measures of offspring adiposity, which strengthened in women gaining on average >500 g/wk.

For mid pregnancy, estimated GWG up to 500 g/wk (ie, low or medium estimated GWG) was not associated with offspring adiposity, but offspring adiposity increased linearly with estimated GWG in mid pregnancy after this level (ie, in women with high GWG). There was no clear association of estimated GWG in late pregnancy (beyond 36 weeks) with offspring adiposity or of estimated GWG in any periods with SBP or DBP. Associations of prepregnancy weight and estimated GWG with binary outcomes of adiposity (Table IV in the online-only Data Supplement) were consistent with those seen for the continuously measured variables shown in Table 3.

Table 4 shows the associations of estimated prepregnancy weight and estimated GWG with lipids, apolipoproteins, and inflammatory markers. For these outcomes, there was no strong evidence of nonlinear associations. Estimated prepregnancy weight and GWG in mid pregnancy were positively associated with triglyceride levels and IL-6 and inversely associated with HDL-C and apoA1, although for triglycerides and apoA1, confidence intervals were wide and included the null value. Estimated prepregnancy weight was also positively associated with non–HDL-C, apoB, and CRP but not with adiponectin. GWG in early and late pregnancy was not associated with lipids, apolipoproteins, or inflammatory markers, with point estimates all close to the null value.

Further adjustment for birth weight did not substantively alter any of the confounder-adjusted models (Table Va to Vc in the online-only Data Supplement). All associations of maternal exposures that were present in confounder-adjusted models were attenuated to the null with further adjustment for offspring fat mass (Table VIa and VIb in the online-only Data Supplement). When these additional analyses were repeated with offspring BMI, waist circumference or leptin results instead of fat mass results were very similar to those presented.

We found no evidence that associations of estimated GWG with any of our outcomes were modified by prepregnancy BMI or weight, irrespective of whether this was estimated or observed (all P for interaction >0.2). When the analyses with estimated GWG were repeated with only those women who had at least 2, 4, and 3 measures in each time period, respectively (ie, total of at least 9 per woman across pregnancy), there was no substantial change in the results. Associations with estimated GWG in late pregnancy did not differ substantively from those presented when we used absolute weight gain. Associations did not differ substantively with the removal of women whose first antenatal measurement was after 15 weeks or whose last measurement was before 35 weeks.

Table 2. Mean Difference (95% Confidence Interval) in Offspring Adiposity, BP, Lipids, Apolipoproteins, and Inflammatory Markers by IOM Categories of Maternal GWG (n=5154 or 3457 as Indicated)

Outcome	IOM Category	Model 1*	Model 2*
BMI, kg/m^2 (n=5154)	<Recommended	−0.293 (−0.471, −0.116)	−0.326 (−0.504, −0.148)
	=Recommended	Reference	Reference
	>Recommended	0.780 (0.588, 0.971)	0.744 (0.552, 0.937)
Waist, cm (n=5154)	<Recommended	−0.830 (−1.310, −0.350)	−0.897 (−1.379, −0.415)
	=Recommended	Reference	Reference
	>Recommended	1.974 (1.457, 2.492)	1.931 (1.410, 2.452)
Fat mass, g (n=5154)	<Recommended	−217 (−497, 63)	−260 (−540, 21)
	=Recommended	Reference	Reference
	>Recommended	1162 (860, 1464)	1075 (773, 1378)
SBP, mm Hg (n=5154)	<Recommended	−0.280 (−0.875, 0.315)	−0.372 (−0.969, 0.226)
	=Recommended	Reference	Reference
	>Recommended	1.339 (0.697, 1.981)	1.250 (0.604, 1.896)
DBP, mm Hg (n=5154)	<Recommended	−0.248 (−0.657, 0.162)	−0.232 (−0.642, 0.179)
	=Recommended	Reference	Reference
	>Recommended	0.299 (0.142, 0.741)	0.229 (−0.216, 0.672)
HDL-C, mmol/L (n=3457)	<Recommended	0.007 (−0.017, 0.031)	0.007 (−0.017, 0.031)
	=Recommended	Reference	Reference
	>Recommended	−0.031 (−0.057, −0.005)	−0.030 (−0.055, −0.005)
Non–HDL-C, mmol/L (n=3457)	<Recommended	−0.042 (−0.091, 0.007)	−0.043 (−0.092, 0.006)
	=Recommended	Reference	Reference
	>Recommended	−0.003 (−0.055, 0.050)	−0.009 (−0.062, 0.044)
ApoA1, mg/dL (n=3457)	<Recommended	−0.109 (−1.658,1.441)	−0.167 (−1.726, 1.391)
	=Recommended	Reference	Reference
	>Recommended	−1.625 (−3.292, −0.042)	−1.649 (−3.327, −0.029)
ApoB, mg/dL (n=3457)	<Recommended	−0.391 (−1.400, 0.619)	−0.449 (−1.461, 0.563)
	=Recommended	Reference	Reference
	>Recommended	0.203 (−0.882, 1.289)	0.027 (−1.063, 1.118)
Adiponectin, ng/mL (n=3457)	<Recommended	−278 (−711, 154)	−287 (−722, 147)
	=Recommended	Reference	Reference
	>Recommended	−206 (−672, 259)	−171 (−640, 297)
Leptin, ratio GM† (n=3457)	<Recommended	0.949 (0.895, 1.007)	0.948 (0.893, 1.005)
	=Recommended	Reference	Reference
	>Recommended	1.179 (1.106, 1.256)	1.178 (1.105, 1.256)
Triglycerides, ratio GM† (n=3457)	<Recommended	0.975 (0.942, 1.008)	0.977 (0.944, 1.011)
	=Recommended	Reference	Reference
	>Recommended	1.021 (0.984, 1.059)	1.020 (0.983, 1.058)
CRP, ratio GM† (n=3457)	<Recommended	1.003 (0.913, 1.101)	1.012 (0.921, 1.111)
	=Recommended	Reference	Reference
	>Recommended	1.155 (1.045, 1.277)	1.150 (1.040, 1.273)
IL-6, ratio GM† (n=3457)	<Recommended	1.000 (0.935, 1.070)	1.005 (0.939, 1.076)
	=Recommended	Reference	Reference
	>Recommended	1.139 (1.059, 1.225)	1.129 (1.050, 1.215)

*Model 1: adjusted for age and gender and for fat mass for height and height squared. Model 2: as model 1 plus additional adjustment for prepregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth, and mode of delivery.

†Results in bold are ratio of geometric means (GM) by IOM categories. The null value for these ratios is 1; for all other values, the results are mean differences, and the null value is 0.

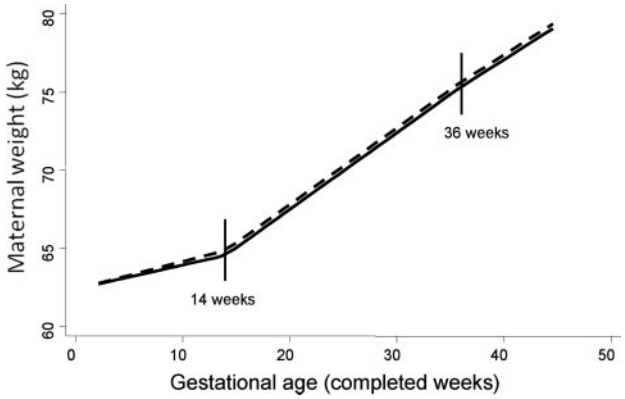


Figure. Weight (kilograms) by gestational age (weeks) for mothers of boys (dashed line) and girls (solid line).

Discussion

To our knowledge, this is the most detailed study of the association of GWG and prepregnancy weight with offspring adiposity and associated cardiovascular risk factors. Women who gained more weight than recommended by the 2009 IOM criteria had offspring who were more adipose and had higher levels of SBP, CRP, and IL-6 and lower levels of HDL-C and apoA1. When we examined these associations in more detail, we found that any weight gain in the first 14 weeks of gestation was incrementally associated with increased offspring adiposity, but for between 14 and 36 weeks of gestation, only GWG >500 g/wk was associated with increased offspring adiposity. By contrast, the cardiovascular risk factors that were associated with GWG (triglycerides, HDL-C, apoA1, and IL-6) were associated with GWG linearly across all levels of GWG in mid pregnancy (>14 to 36 weeks). Prepregnancy weight was positively associated with offspring adiposity and adverse cardiovascular risk factors, but we found no interaction between prepregnancy weight/BMI and GWG in their associations with offspring outcomes. The associations of greater than recommended IOM weight gain, prepregnancy weight, and GWG in mid pregnancy with adverse lipid profiles and inflammatory markers appeared to be largely mediated by offspring adiposity.

Table 3. Mean Difference (95% Confidence Interval) in Offspring Measurements of Adiposity and BP per 1-kg Change in Maternal Estimated Prepregnancy Weight and 400-g/wk Estimated GWG (n=5154)

		Model 1*			Model 2*		
Outcome	Exposure	Low GWG†: ≤0 g 0–14 wk, ≤250 g/wk Other GWG Periods	Medium GWG†: 0–500 g 0–14 wk, 250 to 500 g Other GWG Periods	High GWG†: >500 g for All GWG Periods	Low GWG†: ≤0 g 0–14 wk, ≤250 g/wk Other GWG Periods	Medium GWG†: 0–500 g 0–14 wk, 250 to 500 g Other GWG Periods	High GWG†: >500 g for All GWG Periods
BMI, kg/m^2	Prepregnancy		0.070 (0.064, 0.076)			0.069 (0.063, 0.075)	
	GWG 0–14 wk	−0.787 (−1.154, −0.420)	0.012 (−0.212, 0.236)	0.615 (0.214, 1.016)	0.165 (−0.196, 0.525)	0.329 (0.111, 0.547)	0.624 (0.241, 1.007)
	GWG >14–36 wk	−3.547 (−5.113, −1.980)	−0.042 (−0.516, 0.431)	1.120 (0.742, 1.498)	−0.536 (−2.059, 0.986)	0.386 (−0.069, 0.841)	0.623 (0.257, 0.989)
	GWG >36 wk	−0.232 (−0.630, 0.167)	0.394 (0.001, 0.788)	0.631 (0.396, 0.865)	0.091 (−0.345, 0.526)	−0.031 (−0.483, 0.422)	0.168 (−0.129,0.464)
Waist circumference, cm	Prepregnancy weight		0.184 (0.168, 0.201)			0.183 (0.166, 0.199)	
	GWG 0–14 wk	−2.374 (−3.363, −1.384)	−0.084 (−0.688, 0.520)	1.400 (0.318, 2.481)	0.093 (−0.885,1.071)	0.910 (0.320, 1.500)	1.446 (0.409, 2.484)
	GWG >14–36 wk	−8.752 (−12.974, −4.529)	0.030 (−1.246, 1.305)	3.139 (2.119, 4.159)	−1.170 (−5.295, 2.955)	1.105 (−0.129, 2.338)	1.892 (0.900, 2.884)
	GWG >36 wk	−0.646 (−1.715, 0.430)	1.126 (0.066, 2.185)	1.967 (1.337, 2.597)	0.166 (−1.014, 1.345)	−0.028 (−1.255,1.198)	0.722 (−0.081,1.525)
Fat mass, g	Prepregnancy weight		88 (77, 98)			84 (74, 94)	
	GWG 0–14 wk	−1300 (−1900, −699)	110 (−253, 474)	1163 (512, 1814)	−70 (−646, 505)	314 (−33, 662)	1137 (527, 1748)
	GWG >14–36 wk	−4800 (−7400, −2300)	−599 (−1400, 171)	1599 (983, 2214)	−717 (−3100, 1713)	6 (−722, 733)	962 (378, 1547)
	GWG >36 wk	−151 (−799, 497)	74 (−567, 715)	987 (606, 1368)	447 (−248, 1142)	−172 (−895, 551)	349 (−124, 822)
SBP, mm Hg	Prepregnancy weight		0.112 (0.091, 0.133)			0.108 (0.087, 0.130)	
	GWG 0–14 wk	−1.190 (−2.328, 0.110)	−0.128 (−0.872, 0.617)	−0.254 (−1.586, 1.077)	0.396 (−0.850, 1.642)	0.459 (−0.293, 1.211)	−0.220 (−1.542, 1.101)
	GWG >14–36 wk	−8.043 (−13.249, −2.836)	0.998 (−0.575, 2.571)	1.787 (0.529, 3.044)	−3.819 (−9.083, 1.445)	1.704 (0.130, 3.279)	0.861 (−0.405, 2.128)
	GWG >36 wk	0.379 (−0.945, 1.703)	0.679 (−0.629, 1.987)	1.103 (0.324, 1.881)	0.476 (−1.029, 1.982)	−0.475 (−2.041, 1.090)	0.368 (−0.658, 1.393)
DBP, mm Hg	Prepregnancy weight		0.030 (0.015, 0.044)			0.028 (0.013, 0.043)	
	GWG 0–14 wk	−0.768 (−1.606, 0.069)	0.178 (−0.333, 0.690)	0.309 (−0.606, 1.224)	−0.268 (−1.131, 0.594)	0.393 (−0.128, 0.913)	0.348 (−0.567, 1.264)
	GWG >14–36 wk	−5.293 (−8.873, −1.713)	0.847 (−0.234, 1.929)	0.605 (−0.260, 1.470)	−4.481 (−8.127, −0.834)	1.004 (−0.087, 2.094)	0.196 (−0.681, 1.073)
	GWG >36 wk	−0.037 (−0.948, 0.874)	0.437 (−0.464, 1.337)	0.321 (−0.214, 0.856)	0.486 (−0.557, 1.529)	0.179 (−0.905, 1.264)	0.073 (−0.638, 0.783)
Leptin, geometric mean (null value=1) (n=3457)	Prepregnancy weight		1.012 (1.010, 1.014)			1.012 (1.010, 1.015)	
	GWG 0–14 wk	0.833 (0.734, 0.946)	0.998 (0.926, 1.075)	1.197 (1.042, 1.375)	0.969 (0.857, 1.096)	1.032 (0.961, 1.109)	1.216 (1.067, 1.386)
	GWG >14–36 wk	0.437 (0.266, 0.719)	1.053 (0.899, 1.233)	1.322 (1.166, 1.499)	0.718 (0.444, 1.160)	1.079 (0.928, 1.253)	1.246 (1.105, 1.405)
	GWG >36 wk	0.927 (0.814, 1.056)	1.124 (0.986, 1.282)	1.149 (1.062, 1.243)	0.974 (0.848, 1.119)	1.006 (0.867, 1.167)	1.026 (0.932, 1.129)

*Model 1: adjusted for age and gender and for fat mass for height and height squared. Model 2: as model 1 plus additional adjustment for prepregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth, and mode of delivery.

†The exposures, prepregnancy weight, and GWG are estimated for each woman from the multilevel models with the use of all repeat measurements of gestational weight in each woman. Because of strong evidence for nonlinear associations with these outcomes for estimated GWG, results are presented for subgroups of women in whom magnitudes of associations differ.

Table 4. Mean Difference (95% Confidence Interval) in Offspring Lipids, Apolipoproteins, and Inflammatory Markers per 1-kg Change in Maternal Estimated Prepregnancy Weight and 400-g/wk Estimated GWG for Blood Assay Results (n=3457)

Outcome	Exposure Period*	Model 1†	Model 2†
HDL-C, mmol/L	Prepregnancy weight	−0.002 (−0.003, −0.001)	−0.002 (−0.003, −0.001)
	GWG 0–14 wk	−0.007 (−0.025, 0.010)	−0.007 (−0.025, 0.010)
	GWG 14–36 wk	−0.028 (−0.055,−0.002)	−0.028 (−0.055, −0.002)
	GWG after 36 wk	−0.020 (−0.035, −0.005)	−0.007 (−0.035, 0.021)
Non–HDL-C, mmol/L	Prepregnancy weight	0.002 (0.000, 0.003)	0.001 (0.000, 0.003)
	GWG 0–14 wk	−0.030 (−0.113, 0.053)	−0.033 (−0.118, 0.052)
	GWG 14–36 wk	0.010 (−0.125, 0.145)	0.013 (−0.123, 0.150)
	GWG after 36 wk	0.005 (−0.071, 0.081)	0.005 (−0.073, 0.082)
ApoA1, mg/dL	Prepregnancy weight	−0.087 (−0.144, −0.031)	−0.087 (−0.144, −0.031)
	GWG 0–14 wk	−0.231 (−1.294, 0.833)	−0.872 (−2.004, 0.260)
	GWG 14–36 wk	−1.350 (−3.066, 0.367)	−1.409 (−3.145, 0.326)
	GWG after 36 wk	−0.707 (−1.674, 0.260)	−0.387 (−2.214, 1.440)
ApoB, mg/dL	Prepregnancy weight	0.046 (0.009, 0.083)	0.041 (0.004, 0.077)
	GWG 0–14 wk	0.198 (−0.500, 0.897)	0.257 (−0.480, 0.993)
	GWG 14–36 wk	−0.150 (−1.278, 0.977)	−0.106 (−1.235, 1.024)
	GWG after 36 wk	−0.192 (−0.828, 0.443)	−0.667 (−1.855, 0.522)
Adiponectin, ng/mL	Prepregnancy weight	−16 (−31, 0)	−15 (−31, 0)
	GWG 0–14 wk	200 (−96, 496)	97 (−220, 414)
	GWG 14–36 wk	151 (−327, 629)	151 (−334, 637)
	GWG after 36 wk	−54 (−323, 215)	88 (−421, 600)
Triglycerides, ratio GM‡	Prepregnancy weight	1.002 (1.000, 1.003)	1.002 (1.000, 1.003)
	GWG 0–14 wk	0.986 (0.964, 1.010)	0.997 (0.972, 1.022)
	GWG 14–36 wk	1.037 (0.999, 1.077)	1.035 (0.996, 1.075)
	GWG after 36 wk	1.028 (1.006, 1.050)	1.009 (0.969, 1.050)
CRP, ratio GM‡	Prepregnancy weight	1.009 (1.005, 1.012)	1.009 (1.005, 1.012)
	GWG 0–14 wk	0.986 (0.924, 1.052)	1.040 (0.972, 1.113)
	GWG 14–36 wk	1.073 (0.966, 1.192)	1.057 (0.952, 1.174)
	GWG after 36 wk	1.082 (1.020, 1.148)	1.074 (0.962, 1.199)
IL-6, ratio GM‡	Prepregnancy weight	1.004 (1.001, 1.006)	1.003 (1.001, 1.006)
	GWG 0–14 wk	0.996 (0.950, 1.043)	1.023 (0.974, 1.075)
	GWG 14–36 wk	1.096 (1.016, 1.181)	1.082 (1.003, 1.168)
	GWG after 36 wk	1.047 (1.004, 1.093)	1.005 (0.928, 1.089)

*The exposures, prepregnancy weight, and GWG are estimated for each woman from the multilevel models with the use of all repeat measurements of gestational weight in each woman.

†Model 1: adjusted for age and gender and for fat mass for height and height squared. Model 2: as model 1 plus additional adjustment for prepregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth, and mode of delivery.

‡Results in bold are ratio of geometric means (GM) per 1 kg prepregnancy weight or per 400 g GWG in each period. The null value for these ratios is 1; for all other values, the results are mean differences, and the null value is 0.

A number of mechanisms may explain our findings. First, our results could reflect tracking in size across the life course. However, consistent with previous studies,[4,5,8] we found only weak associations of prepregnancy weight and GWG with birth weight, and adjustment for birth weight did not substantively alter associations. Furthermore, GWG in early pregnancy (up to 14 weeks) was associated across the entire distribution with offspring adiposity (compared with GWG >14 to 36 weeks, which was only associated if women gained >500 g/wk), but at this stage most GWG will be related to maternal fat deposition and not to fetal growth. Second, offspring could inherit their mother's genetic potential to gain weight. We are unable to assess this possibility in our study. Third, mothers with greater GWG may engage in lifestyles (high-energy diet and low levels of physical activity) during and after their pregnancy that promote weight gain, and they may pass them on to their offspring. Fourth, greater maternal prepregnancy adiposity and GWG might program greater adiposity and cardiovascular risk in offspring resulting from the persistent and adverse influences on the fetus that arise from the greater delivery of glucose,

amino acids, and free fatty acids to the developing fetus in utero.[17] The continuous association, across the whole distribution, of GWG up to 14 weeks with offspring adiposity provides some support for this because most weight gain in this period will be an increase in maternal fat stores, with concomitant increases in circulating glucose, amino acids, and free fatty acids. The fact that GWG in this period was not statistically strongly associated with cardiovascular risk factors might be a consequence of limited statistical power, and, ideally, replication of our findings in larger cohorts with detailed repeat measurements of weight in pregnancy would be useful, although we are unaware of other larger cohorts with such detailed measurements. Finally, our results may be due to chance. We examined a large number of maternal exposure–offspring outcomes in this study. However, we believe that this is a strength of our study. Our work builds importantly on previous publications examining only offspring adiposity and BP and using very limited information on GWG. We acknowledge that replication of these associations in larger studies, but with similarly detailed exposure and outcome measurements, would be beneficial.

The levels of attrition in ALSPAC are similar to those found in previous studies. Offspring of women from higher socioeconomic positions, of more educated women, and of older women are more likely to attend follow-up clinics in ALSPAC.[13] However, we found no evidence of differences in distributions of GWG between women whose offspring had outcome measurements and those whose offspring did not (all $P>0.4$). The consistency of associations between adiposity measurements and circulating leptin levels suggests that exclusion of those participants who did not complete a blood test did not bias these associations. Offspring blood tests were completed on nonfasting blood samples, but the majority of measures are not appreciably altered by this approach.[18–20] We used maternal self-report of height to calculate prepregnancy BMI, which may be inaccurate. With respect to associations examined (outcomes assessed in offspring 9 years later), any measurement error would be nondifferential, and therefore the expectation would be that it might bias results toward the null.

The fact that GWG in mid pregnancy was only associated with offspring adiposity in women gaining >500 g/wk suggests that from 14 to 36 weeks, women could "safely" (with respect to offspring adiposity) gain 11 kg, which is close to the range of recommended levels of weight gain across the whole of pregnancy for normal and overweight women according to IOM categories, but we found no evidence that this (or other) associations differed by maternal prepregnancy BMI categories. It should be acknowledged that in this cohort, just 7% of women were obese before pregnancy, and obesity prevalence is greater for contemporary women. The lack of association with GWG beyond 36 weeks may reflect the fact that the length of this period varies for different maternal-offspring pairs. Very large sample sizes would be required to determine whether different patterns in this late stage were important.

Maternal prepregnancy weight was more consistently associated with offspring adiposity and a wider range of cardiovascular risk factors in offspring than were any measurements of GWG, and this finding supports initiatives aimed at maintaining healthy weight in women of reproductive age. Long-term follow-up of ongoing randomized controlled trials aimed at controlling GWG[21] and mendelian randomization studies (using genetic variants that are robustly associated with maternal adiposity and fat gain in pregnancy as instrumental variables)[22] are necessary to establish whether the associations we have found are causal. The extent to which antenatal care guidelines should be modified to monitor GWG and promote adherence to IOM levels requires additional research that establishes clear benefits and lack of important risk in the short and long term for both mother and child.

Acknowledgments

We are grateful to all of the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Sources of Funding

This work was funded by a grant from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK077659). The UK Medical Research Council, Wellcome Trust, and University of Bristol provide core funding support for ALSPAC. The blood assays were funded by a British Heart Foundation grant (PG07/002). The Medical Research Council and University of Bristol provide core funding for Medical Research Council Centre for Causal Analyses in Translational Epidemiology. Dr Fraser is funded by a Medical Research Council research fellowship, and Dr Brion is funded by a Wellcome Trust Henry Wellcome research fellowship. Dr Hingorani is funded by a British Heart Foundation senior research fellowship (FS05/125).

Disclosures

None.

References

1. Viswanthan M, Siega-Riz AM, Moos M-K, Deierlein A, Mumford S, Knaack J, Thieda P, Lux LJ, Lohr KN. *Outcomes of Maternal Weight Gain, Evidence Report/Technology Assessment No. 168*. Rockville, Md: Agency for Healthcare Research and Quality; 2008. AHRQ publication 08-E009.
2. Rasmussen KM, Yaktine AL, eds. Weight gain during pregnancy: reexamining the guidelines. Committee to Reexamine IOM Pregnancy Weight Guidelines; Institute of Medicine; National Research Council. 2009. Prepublication uncorrected proofs available at http://www.nap.edu/catalog/12584.html. Accessed June 10, 2009.
3. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics*. 2004;114:e29–e36.
4. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol*. 2007;196:322.
5. Moreira P, Padez C, Mourao-Carvalhal I, Rosado V. Maternal weight gain during pregnancy and overweight in Portuguese children. *Int J Obes.* 2007;31:608–614.
6. Wrotniak BH, Shults J, Butts S, Stettler N. Gestational weight gain and risk of overweight in the offspring at age 7 y in a multicenter, multiethnic cohort study. *Am J Clin Nutr*. 2008;87:1818–1824.
7. Oken E, Rifas-Shiman SL, Field AE, Frazier AL, Gillman MW. Maternal gestational weight gain and offspring weight in adolescence. *Obstet Gynecol*. 2008;112:999–1006.
8. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. *Circulation*. 2009;119:1720–1727.

9. Clark PM, Atton C, Law CM, Shiell A, Godfrey K, Barker DJ. Weight gain in pregnancy, triceps skinfold thickness, and blood pressure in offspring. *Obstet Gynecol*. 1998;91:103–107.
10. Godfrey KM, Forrester T, Barker DJ, Jackson AA, Landman JP, Hall JS, Cox V, Osmond C. Maternal nutritional status in pregnancy and blood pressure in childhood. *Br J Obstet Gynaecol*. 1994;101:398–403.
11. Margetts BM, Rowland MG, Foord FA, Cruddas AM, Cole TJ, Barker DJ. The relation of maternal weight to the blood pressures of Gambian children. *Int J Epidemiol*. 1991;20:938–943.
12. Laor A, Stevenson DK, Shemer J, Gale R, Seidman DS. Size at birth, maternal nutritional status in pregnancy, and blood pressure at age 17: population based analysis. *BMJ*. 1997;315:449–453.
13. Golding J, Pembrey M, Jones R. ALSPAC: the Avon Longitudinal Study of Parents and Children, I: study methodology. *Paediatr Perinat Epidemiol*. 2001;15:74–87.
14. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320:1240–1243.
15. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S. The metabolic syndrome in children and adolescents. *Lancet*. 2007;369:2059–2061.
16. McCarthy HD, Jarrett KV, Crawley HF. The development of waist circumference percentiles in British children aged 5.0–16.9 y. *Eur J Clin Nutr*. 2001;55:902–907.
17. Taylor PD, Poston L. Developmental programming of obesity in mammals. *Exp Physiol*. 2007;92:287–298.
18. Rifai N, Merrill JR, Holly RG. Postprandial effect of a high fat meal on plasma lipid, lipoprotein cholesterol and apolipoprotein measurements. *Ann Clin Biochem*. 1990;27:489–493.
19. Poppitt SD, Keogh GF, Lithander FE, Wang Y, Mulvey TB, Chan YK, McArdle BH, Cooper GJ. Postprandial response of adiponectin, interleukin-6, tumor necrosis factor-alpha, and C-reactive protein to a high-fat dietary load. *Nutrition*. 2008;24:322–329.
20. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309–316.
21. Dodd JM, Crowther CA, Robinson JS. Dietary and lifestyle interventions to limit weight gain during pregnancy for obese of overweight women: a systematic review. *Acta Obstet Gynecol*. 2008;87:702–706.
22. Lawlor DA, Harbord RM, Sterne JAC, Timpson NJ, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27:1133–1163.

CLINICAL PERSPECTIVE

Variation in gestational weight gain (GWG) is associated with perinatal outcomes, but whether it is importantly associated with longer-term outcomes is unclear. In a prospective cohort of 5154 (for adiposity and blood pressure) and 3457 (for blood assays) mother-offspring pairs, we examined the association of GWG and prepregnancy weight with offspring cardiovascular risk factors at age 9 years. Women who gained more than 2009 Institute of Medicine–recommended amounts of weight during gestation were more likely to have offspring with greater body mass index, waist, fat mass, leptin, systolic blood pressure, C-reactive protein, and interleukin-6 levels and lower high-density lipoprotein cholesterol and apolipoprotein A levels. Detailed examination demonstrated that greater prepregnancy weight was also independently associated with greater offspring adiposity and adverse cardiovascular risk factors. Furthermore, women who gained weight before 14 weeks of gestation or who gained >500 g/wk from 14 to 36 weeks had offspring with greater adiposity. Greater GWG across the whole distribution between 14 and 36 weeks of gestation was associated with adverse lipid and inflammatory profiles in offspring, largely because of the association of GWG with offspring adiposity. Collectively, our findings support initiatives to maintain healthy weight in women of reproductive age and potentially to prevent excessive GWG, broadly in agreement with current Institute of Medicine recommendations. However, before guidelines on GWG are implemented, long-term follow-up of randomized controlled trials targeting GWG is needed to determine the effects of controlling GWG on a wide range of short- and long-term outcomes for both mother and infant.

SUPPLEMENTAL MATERIAL

Supplemental methods

Details of random effects statistical modelling to determine gestational weight gain parameters

The sample was limited to mothers of offspring born at term (at least 37 weeks gestation) and alive. We divided the gestational period into 2-week stages, from 4 weeks onwards. Where an individual woman had more than one measurement in one of these two-week periods, one was chosen randomly for inclusion in the sample. Thus, each woman could contribute a maximum of 20 weight measures to the model. Deletion of obvious errors in weights and dates, and elimination of repeat measures within the two week period, gave a sample for model development of 11,336 women with a total of 104, 671 weight measures.

There was little evidence that patterns of gestational weight gain (GWG) differed markedly between mothers of female and male offspring; GWG between 14 and 36 weeks was slightly greater for mothers of male compared to female offspring (0.18kg/week versus 0.16kg/week, $p = 0.08$) but otherwise there were no differences. One model was constructed for mothers of both female and male offspring, and interactions between sex of offspring and gestational weight gain included.

Multilevel models (with two levels: antenatal visit, within mother) were used to relate weight at each visit to gestational age of the child at that visit. Fractional polynomials were used to derive the best-fitting function to describe the pattern of weight gain with gestational age. However, although fractional polynomials provide a flexible way to examine such relationships, they do not provide parameters that are clinically

relevant or easily interpreted. For example, here the best-fitting polynomial had powers of 2 and 3, indicating that weight was related to gestational age squared and gestational age cubed. We therefore used the best-fitting fractional polynomial to derive a piecewise linear spline model. Here, the best approximation to the fractional polynomial was provided by a spline model with three linear portions: from 0 to 14 weeks gestation; from 14 to 36 weeks gestation; and, from 36 weeks gestation to birth.

The positioning of the knots was chosen by varying the positions of the knots (in whole gestational weeks) around the approximate times and selecting the model with the smallest residuals throughout the range of gestational age. This linear spline multilevel model enabled estimation of the individual pre-pregnancy weight and weight gain during each period, for each woman. In addition, the model allowed variation in measurement between occasions and within subjects, thereby capturing the change in the variance of measurements with age. The model was estimated using maximum likelihood estimation within MLWiN.[1] The final multilevel spline model is shown below.

Multilevel spline model:

$weight_{ij}=\beta_{0i}+\beta_{1i}age0to14_{ij}+\beta_{2i}age14to36_{ij}+\beta_{3i}age36plus_{ij}+e_{ij}$

where, for mother i (i=1 to 11,336) at measurement occasion j (j=1 to 17):

$\beta 0_i$=individual estimate of weight at gestational age=0 for the i^{th} mother

$\beta_{1i=}$ individual estimate of rate of weight gain during the first 14 weeks for the i^{th} mother

β_{2i}=individual estimate of rate of weight gain during weeks 14-36 for the i^{th} mother

β_{3i}=individual estimate of rate of weight gain after week 36 for the i^{th} mother

$age0to14_{ij}$= the value of the first linear spline at the gestational age of the j^{th} observation for the i^{th} mother

$age14to36_{ij}$= the value of the second linear spline at the gestational age of the j^{th} observation for the i^{th} mother

$age36tomax_{ij}$= the value of the third linear spline at the gestational age of the j^{th} observation for the i^{th} mother

e_{ij} = measurement error

Table 1 shows the fit of this model when compared to the measured weights at each time point. It shows high level of agreement between predicted and actual weight, demonstrating the goodness of fit of the model.

With analyses restricted to births occurring between 37-44 weeks there were between 1 and 17 measures of weight per woman, with an average of 9.2 (median 10, sd 2.6, IQR 8, 11). In the first period (0-14 weeks) there were between 0 and 5 measures per woman, with an average of 1.2 (median 1, sd 0.82, IQR 1, 2). In the second period (14-36 weeks) there were between 0 and 11 measures per woman, with an average of 6.1 (median 6, sd 1.9, IQR 5, 7). In the third period (36+ weeks) there were between 0 and 4 measures per woman, with an average of 1.9 (median 2, sd 0.9, IQR 1,3). All mother-offspring pairs are included in the analyses provided the mother has at least one measure of gestational weight. This approach to modelling repeat measurements provides estimated coefficients in each gestational age period even if the woman has no measurements in that particular period. This is because the overall model uses all

data and will use the woman's values in other periods to give a predicted coefficient for the period where she has no data based on the overall model using data from all women. If women with few weight measurements differed from those with more measurements (in particular those who had measurements in all periods) in such a way that associations with outcomes differed between the two groups then our results would be biased. In order to explore this possibility we conducted sensitivity analyses in which predicted GWG derived from multilevel models were repeated with only those women who had at least 2, 4 and 3 measures in each time period respectively (i.e. total of at least 9 per woman across pregnancy).

Supplemental results

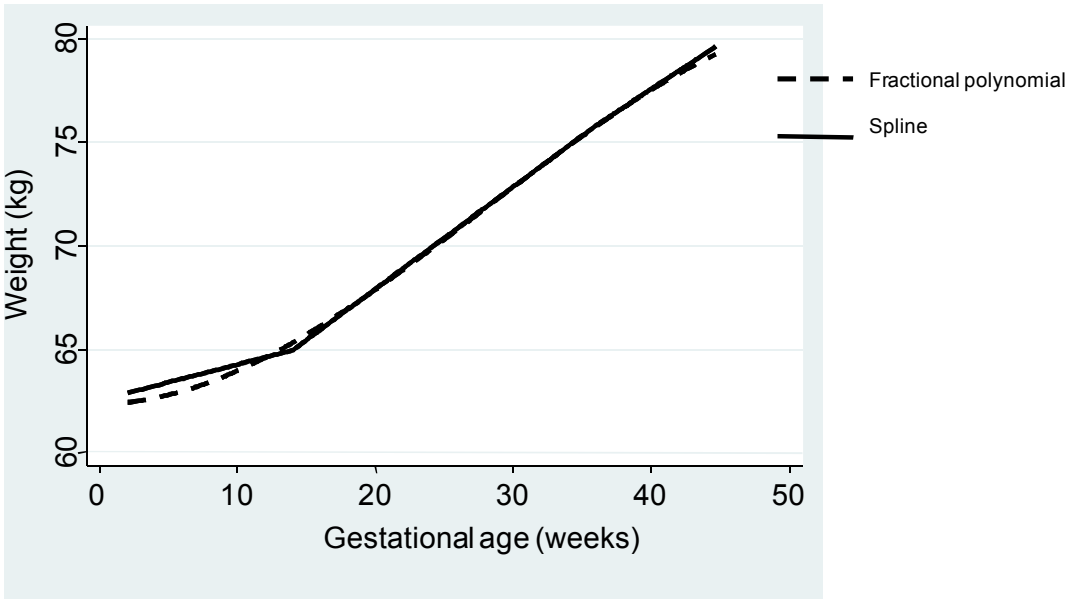
Web-Table 1: Fit of the model (predicted weight) to actual weight at each time period.

Gestational age (weeks)	Number of measurements[a]	Weight (mean (sd)) kg	Predicted weight (mean(sd)) kg	Difference ( ) (actual-predicted) (mean(sd)) kg[b]	90% limits of agreement (kg)[c]
<=4	18	69.2 (14.6)	69.1 (14.5)	0.09 (0.34)	-0.44, 0.97
5-6	155	64.7 (13.1)	64.7 (13.0)	-0.04 (0.56)	-0.95, 0.66
7-8	1100	64.6 (12.1)	64.6 (12.1)	0.03 (0.55)	-0.74, 0.76
9-10	2831	64.2 (11.9)	64.3 (11.8)	-0.03 (0.55)	-0.89, 0.78
11-12	4367	64.3 (11.9)	64.3 (11.8)	-0.01 (0.72)	-1.19, 1.10
13-14	4912	64.7 (11.7)	64.6 (11.6)	0.07 (0.86)	-1.34, 1.44
15-16	4250	65.6 (12.0)	65.4 (12.0)	0.03 (0.82)	-1.31, 1.33
17-18	6015	66.1 (11.8)	66.1 (11.7)	-0.07 (0.83)	-1.37, 1.31
19-20	4335	67.2 (12.0)	67.3 (12.0)	-0.12 (0.88)	-1.48, 1.27
21-22	5278	68.1 (11.9)	68.2 (11.9)	-0.07 (0.92)	-1.54, 1.38
23-24	4580	69.3 (12.0)	69.2 (11.9)	0.01 (0.99)	-1.59, 1.55
25-26	5258	70.1 (11.9)	70.0 (11.9)	0.11 (1.00)	-1.53, 1.71
27-28	5525	71.5 (12.0)	71.4 (11.9)	0.11 (1.00)	-1.48, 1.66
29-30	7598	72.2 (12.0)	72.2 (11.9)	0.06 (0.94)	-1.44, 1.53
31-32	8154	73.1 (12.1)	73.1 (12.0)	-0.01 (0.88)	-1.38, 1.37
33-34	8913	73.9 (12.0)	74.0 (11.9)	-0.07 (0.82)	-1.34, 1.23
35-36	9368	74.9 (12.2)	75.0 (12.2)	-0.03 (0.80)	-1.28, 1.27
37-38	9946	75.9 (12.2)	75.9 (12.2)	0.02 (0.82)	-1.27, 1.33
39-40	8331	76.9 (12.3)	76.9 (12.2)	0.03 (0.68)	-1.03, 1.14
41-42	3607	78.1 (12.4)	78.1 (12.4)	-0.04 (0.56)	-0.94, 0.87
>42	130	80.1 (12.6)	80.2 (12.5)	-0.07 (0.70)	-1.15, 1.32

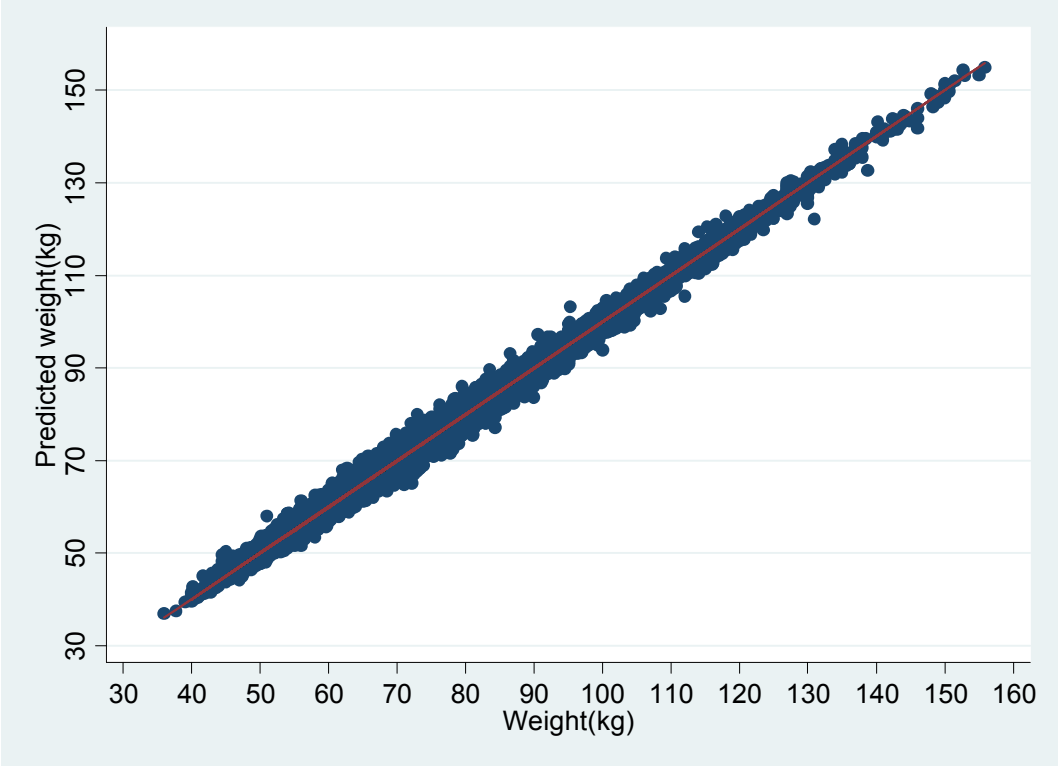
[a] Total number of measurements in each strata of gestational age (i.e. number of women*number of measurements that woman had)
[b] Because the difference between the observed and predicted weights are small these are given to two decimal places (whereas the observed and predicted weights are given to one decimal place)
[c] These indicate the range within which 90% of the differences lie in this sample

Web-Figure 1 shows the pattern predicted by the multilevel fractional polynomial model. This shows that the final spline model used in the analyses fits closed to the fractional polynomial fitted to the data in the multilevel model.

Web-Figure 1: Graph showing the pattern predicted by the fractional polynomial for the multilevel model and the spline that was fitted to the data



Web-Figure 2 Graph showing the weight values predicted by the multilevel spline models against the actual weights for each mother at each occasion



Web-Table 2: Characteristics of mothers and offspring at 9 years. Maximum eligible N = 5154 based on women with gestational weight gain data.

Characteristic		N	Mean (SD) or Median (IQR)	N (%)
Maternal				
Pre-pregnancy BMI (mean)		5154	23.1 (4.3)	
Pre-pregnancy BMI	Underweight			406 (7.9)
	Normal			3540 (68.7)
	Overweight			856 (16.6)
	Obese			352 (6.8)
N of weight measurements (median, IQR)		5154	10 (8, 11)	
Gestational week at 1st measure (median, IQR)		5154	10 (8, 12)	
Gestational week at last measure (median, IQR)		5154	39 (38, 40)	
Pre-pregnancy weight (kg)*	Boy offspring	2532	63.4 (12.0)	
	Girl offspring	2622	62.1 (11.9)	
Gestational weight gain early pregnancy (kg/week)*	Boy offspring	2532	0.16 (0.25)	
	Girl offspring	2622	0.19 (0.25)	
Gestational weight gain mid-pregnancy (kg/week)*	Boy offspring	2532	0.49 (0.15)	
	Girl offspring	2622	0.49 (0.15)	
Gestational weight gain late-pregnancy (kg/week)*	Boy offspring	2532	0.43 (0.28)	
	Girl offspring	2622	0.43 (0.27)	
Absolute weight gain in pregnancy (kg)		5154	12.1 (5.1)	
IOM recommended weight gain in pregnancy	Under	5154		1894 (36.8)
	Adequate			1857 (36.0)
	Over			1403 (27.2)
Age at delivery (years)		5154	29.2 (4.5)	
C-section		5154		515 (9.9)
Length of gestation (weeks)		5154	39.8 (1.3)	
No previous pregnancies		5154		2416 (46.9)
Smoked throughout pregnancy		5154		634 (12.3)
Manual social class		5154		727 (14.1)
Offspring				
Male		5154		2689 (49.5)
Birth weight (g)		5102	3488 (468)	
BMI (kg/m^2)		5154	17.7 (2.8)	
Overweight or obese based on BMI		5154		944 (18.3)
Waist circ. (cm)		5154	62.8 (7.7)	
Centrally obese based on waist circ.		5154		2026 (39.3)
Fat mass (g)		5154	8529 (5041)	
SBP (mmHg)		5154	102.6 (9.4)	
DBP (mmHg)		5154	57.5 (6.4)	
HDL-c (mmol/l)		3457	1.40 (0.31)	
Non-HDL-c (mmol/l)		3457	2.87 (0.63)	

Web-Table 2: continued

Triglycerides (mmol/l)[$]	3457	1.01 (0.76, 1.39)	
Apo A1 (mg/dl)	3457	135.7 (20.0)	
Apo B(mg/dl)	3457	59.2 (13.1)	
Adiponectin (pg/ml)	3457	13185 (5543)	
Leptin (ng/ml) [$]	3457	5.4 (3.2, 10.3)	
CRP (mg/l) [$]	3457	0.22 (0.12, 0.54)	
IL-6 (pg/ml) [$]	3457	0.78 (0.49, 1.37)	

* Derived from random effects multi-level models: Early pregnancy: 0-14; Mid-pregnancy >14-36 weeks; late-pregnancy >36 weeks. [$] Median (IQR)

Web-Table 3: Correlation coefficients between maternal estimated pre-pregnancy weight, estimated gestational weight gain (GWG) and birthweight (N=5154)

	Estimated pre-pregnancy weight	Estimated GWG in early pregnancy[a]	Estimated GWG in mid pregnancy[a]	Estimated GWG in late pregnancy[a]	Absolute GWG across whole pregnancy[b]	Birthweight
Estimated pre-pregnancy weight	1					
Estimated GWG in early pregnancy[a]	-0.28	1				
Estimated GWG in mid pregnancy[a]	-0.08	0.00[b]	1			
Estimated GWG in late pregnancy[a]	0.26	-0.59	0.61	1		
Absolute GWG across whole pregnancy[b]	-0.06	0.08	0.57	0.38	1	
Birthweight	0.26	0.04	0.17	0.12	0.14	1

[a] The exposures – pre-pregnancy weight and GWG are estimated for each woman from the multilevel models using all repeat measurements of gestational weight in each woman. The pregnancy periods defined by multilevel models – early-pregnancy = 0-14 weeks; mid-pregnancy = >14-36 weeks; late-pregnancy = > 36 weeks to delivery; all measured in kg/weeks of gestation

[b] Defined as highest weight during pregnancy minus pre-pregnancy weight (i.e. GWG as used in IOM definitions by pre-pregnancy BMI)

All p-values <0.001 except that marked [c] for which p = 0.78

Web-Table 4: Odds ratio (95%CI) for offspring overweight/obesity per 1kg change in maternal estimated pre-pregnancy weight and 400g/week estimated gestational weight gain (N=5154)

Outcome	Exposure	Model 1[a]			Model 2[a]		
		Low estimated GWG[b] ≤ 0g 0-14 wks ≤250g/week other GWG periods	Medium estimated GWG[b] 0-500g 0-14 wks 250 to 500g other GWG periods	High estimated GWG[b] >500g for all GWG periods	Low estimated GWG[b] ≤ 0g 0-14 wks ≤250g/week other GWG periods	Medium estimated GWG[b] 0-500g 0-14 wks 250 to 500g other GWG periods	High estimated GWG[b] >500g for all GWG periods
Overweight or obesity based on BMI[c]	Pre-pregnancy	1.04 (1.03, 1.05)			1.04 (1.03, 1.05)		
	GWG 0-14 weeks	0.61 (0.45,0.82)	0.92 (0.75,1.14)	1.54 (1.12, 2.11)	1.06 (0.77, 1.47)	1.14 (0.92, 1.42)	1.57 (1.13, 2.18)
	GWG >14-36 weeks	0.20 (0.06,0.69)	0.67 (0.43,1.04)	2.64 (1.93, 3.63)	1.05 (0.28, 4.00)	0.98 (0.62, 1.54)	2.00 (1.43, 2.79)
	GWG after 36 weeks	0.74 (0.52, 1.07)	1.41 (0.97, 2.04)	1.54 (1.28, 1.87)	0.88 (0.57,1.36)	1.02 (0.64,1.61)	1.06 (0.81, 1.39)
Central obesity based on waist circumference[d]	Pre-pregnancy weight	1.04 (1.03, 1.05)			1.04 (1.03, 1.05)		
	GWG 0-14 weeks	0.72 (0.55 , 0.94)	0.99 (0.84, 1.16)	1.44 (1.07, 1.94)	1.16 (0.88, 1.54)	1.22 (1.03, 1.45)	1.50 (1.11, 2.04)
	GWG 14-36 weeks	0.53 (0.17, 1.66)	0.98 (0.69, 1.38)	1.98 (1.50, 2.60)	2.22 (0.67,7.49)	1.22 (0.85, 1.76)	1.54 (1.15, 2.05)
	GWG after 36 weeks	0.85 (0.64, 1.14)	1.35 (1.01, 1.80)	1.41 (1.19,1.67)	0.93 (0.66, 1.32)	0.95 (0.67, 1.37)	1.09 (0.86,1.37)

[a] Model 1: adjusted for age and gender and for fat mass for height and height-squared
Model 2: as model 1 plus additional adjustment for pre-pregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth and mode of delivery

[b] The exposures – pre-pregnancy weight and GWG are estimated for each woman from the multilevel models using all repeat measurements of gestational weight in each woman. Because of strong evidence for non-linear associations with these outcomes for estimated GWG results are presented for subgroups of women in whom magnitudes of associations differ.

[c] Overweight/obese based on BMI using age- and sex-specific thresholds for both child BMI (International Obesity Task Force)[2]

[d] Central obesity based on waist circumference also based on age and sex-specific thresholds and is defined as >=90th percentile[3] based on waist circumference percentile curves derived for British children.[4]

Web-Table 5a: Mean difference (95%CI) in offspring measurements of adiposity per 1kg change in maternal estimated pre-pregnancy weight and 400g/week estimated gestational weight gain – assessing possible mediation of associations by birthweight (N=5154)

Outcome	Exposure	Model 2[a]			Model 3[a]		
		Low estimated GWG[b] ≤ 0g 0-14 wks ≤250g/week other GWG periods	Medium estimated GWG[b] 0-500g 0-14 wks 250 to 500g other GWG periods	High estimated GWG[b] >500g for all GWG periods	Low estimated GWG[b] ≤ 0g 0-14 wks ≤250g/week other GWG periods	Medium estimated GWG[b] 0-500g 0-14 wks 250 to 500g other GWG periods	High estimated GWG[b] >500g for all GWG periods
BMI (kg/m^2)	Pre-pregnancy	0.069 (0.063, 0.075)			0.064 (0.058, 0.071)		
	GWG 0-14 weeks	0.165 (-0.196, 0.525)	0.329 (0.111, 0.547)	0.624 (0.241, 1.007)	0.176 (-0.188, 0.539)	0.265 (0.045, 0.485)	0.592 (0.209, 0.975)
	GWG >14-36 weeks	-0.536 (-2.059, 0.986)	0.386 (-0.069, 0.841)	0.623 (0.257, 0.989)	-0.625 (-2.149, 0.899)	0.233 (-0.229, 0.695)	0.586 (0.215, 0.957)
	GWG > 36 weeks	0.091 (-0.345, 0.526)	-0.031 (-0.483, 0.422)	0.168 (-0.129,0.464)	0.110 (-0.328, 0.548)	-0.013 (-0.469, 0.442)	1.022 (1.015, 1.028)
Waist circ. (cm)	Pre-pregnancy weight	0.183 (0.166, 0.199)			0.170 (0.153, 0.187)		
	GWG 0-14 weeks	0.093 (-0.885,1.071)	0.910 (0.320, 1.500)	1.446 (0.409, 2.484)	0.095 (-0.891, 1.080)	0.744 (0.148, 1.340)	1.342 (0.303, 2.381)
	GWG >14-36 weeks	-1.170 (-5.295, 2.955)	1.105 (-0.129, 2.338)	1.892 (0.900, 2.884)	-1.466 (-5.596, 2.665)	0.739 (-0.512, 1.991)	1.790 (0.785, 2.795)
	GWG > 36 weeks	0.166 (-1.014, 1.345)	-0.028 (-1.255,1.198)	0.722 (-0.081,1.525)	0.248 (-0.939, 1.434)	0.016 (-1.217, 1.249)	0.621 (-0.186, 1.427)

Web-Table 5a: continued

Fat mass (g)	Pre-pregnancy weight	84 (74, 94)			85 (74, 95)		
	GWG 0-14 weeks	-70 (-646, 505)	314 (-33, 662)	1137 (527, 1748)	-36 (-616, 545)	326 (-25, 677)	1164 (552, 1776)
	GWG >14-36 weeks	-717 (-3100, 1713)	6 (-722, 733)	962 (378, 1547)	-665 (-3100, 1769)	43 (-695, 781)	1025 (433, 1617)
	GWG > 36 weeks	447 (-248, 1142)	-172 (-895, 551)	349 (-124, 822)	413 (-287,1112)	-189 (-916, 537)	363 (-112, 838)
SBP (mmHg)	Pre-pregnancy weight	0.108 (0.087, 0.130)			0.112 (0.090, 0.134)		
	GWG 0-14 weeks	0.396 (-0.850, 1.642)	0.459 (-0.293, 1.211)	-0.220 (-1.542, 1.101)	0.390 (-0.866, 1.646)	0.507 (-0.253, 1.266)	-0.151 (-1.476,1.173)
	GWG >14-36 weeks	-3.819 (-9.083, 1.445)	1.704 (0.130, 3.279)	0.861 (-0.405,2.128)	-3.634 (-8.903, 1.635)	1.845 (0.248,3.441)	1.121 (-0.161, 2.403)
	GWG > 36 weeks	0.476 (-1.029, 1.982)	-0.475 (-2.041, 1.090)	0.368 (-0.658, 1.393)	0.405 (-1.109, 1.919)	-0.451 (-2.024, 1.122)	0.358 (-0.671, 1.387)
DBP (mmHg)	Pre-pregnancy weight	0.028 (0.013, 0.043)			0.029 (0.014, 0.045)		
	GWG 0-14 weeks	-0.268 (-1.131, 0.594)	0.393 (-0.128, 0.913)	0.348 (-0.567, 1.264)	-0.301 (-1.171, 0.568)	0.398 (-0.128, 0.924)	0.371 (-0.546, 1.288)
	GWG >14-36 weeks	-4.481 (-8.127, -0.834)	1.004 (-0.087, 2.094)	0.196 (-0.681, 1.073)	-4.325 (-7.974, -0.676)	0.946 (-0.160, 2.052)	0.301 (-0.587, 1.189)
	GWG > 36 weeks	0.486 (-0.557, 1.529)	0.179 (-0.905, 1.264)	0.073 (-0.638, 0.783)	0.418 (-0.630, 1.467)	0.258 (-0.832, 1.348)	0.069 (-0.644, 0.781)

Web-Table 5a: continued

Leptin (geometric mean; null value = 1) N = 3,457	Pre-pregnancy weight	1.012 (1.010, 1.015)			1.013 (1.010, 1.015)		
	GWG 0-14 weeks	0.969 (0.857, 1.096)	1.032 (0.961, 1.109)	1.216 (1.067, 1.386)	0.969 (0.856, 1.097)	1.031 (0.959, 1.108)	1.223 (1.072, 1.395)
	GWG >14-36 weeks	0.718 (0.444, 1.160)	1.079 (0.928, 1.253)	1.246 (1.105, 1.405)	0.728 (0.450, 1.179)	1.086 (0.932, 1.265)	1.257 (1.112, 1.420)
	GWG > 36 weeks	0.974 (0.848, 1.119)	1.006 (0.867, 1.167)	1.026 (0.932, 1.129)	0.969 (0.843, 1.115)	1.002 (0.862, 1.164)	1.026 (0.931, 1.130)

[a] Model 2: identical to model 2 of Table 2 in main paper (confounder adjusted) with adjustment for age, gender, height and height-squared (for fat mass), pre-pregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth and mode of delivery
Model 3: as model 2 plus additional adjustment for birthweight

[b] The exposures – pre-pregnancy weight and GWG are estimated for each woman from the multilevel models using all repeat measurements of gestational weight in each woman. Because of strong evidence for non-linear associations with these outcomes for estimated GWG results are presented for subgroups of women in whom magnitudes of associations differ.

Web-Table 5b: Mean difference (95%CI) in offspring measurements of lipids, apolipoproteins and inflammatory markers per 1kg change in maternal estimated pre-pregnancy weight and 400g/week estimated gestational weight gain – assessing possible mediation of associations by birthweight (N=3457)

Outcome	Exposure period[a]	Model 2[b]	Model 3[b]
HDLc (mmol/l)	Pre-pregnancy weight	-0.002 (-0.003, -0.001)	-0.002 (-0.003, -0.001)
	GWG 0-14 weeks	-0.007 (-0.025, 0.010)	-0.008 (-0.025, 0.010)
	GWG 14-36 weeks	-0.028 (-0.055, -0.002)	-0.027 (-0.054, 0.001)
	GWG after 36 weeks	-0.007 (-0.035, 0.021)	-0.008 (-0.037, 0.020)
non-HDLc (mmol/l)	Pre-pregnancy weight	0.001 (0.000, 0.003)	0.001 (0.000, 0.003)
	GWG 0-14 weeks	-0.033 (-0.118, 0.052)	-0.031 (-0.117, 0.055)
	GWG 14-36 weeks	0.013 (-0.123, 0.150)	-0.011 (-0.153, 0.130)
	GWG after 36 weeks	0.005 (-0.073, 0.082)	-0.007 (-0.086, 0.073)
Apo A1 (mg/dl)	Pre-pregnancy weight	-0.087 (-0.144,-0.031)	-0.062 (-0.119, -0.004)
	GWG 0-14 weeks	-0.872 (-2.004, 0.260)	-0.846 (-1.993, 0.300)
	GWG 14-36 weeks	-1.409 (-3.145, 0.326)	-1.164 (-2.963, 0.636)
	GWG after 36 weeks	-0.387 (-2.214, 1.440)	-0.507 (-2.344, 1.331)
Apo B (mg/dl)	Pre-pregnancy weight	0.041 (0.004, 0.077)	0.040 (0.003, 0.078)
	GWG 0-14 weeks	0.257 (-0.480, 0.993)	0.265 (-0.482, 1.012)
	GWG 14-36 weeks	-0.106 (-1.235, 1.024)	-0.368 (-1.541, 0.805)
	GWG after 36 weeks	-0.667 (-1.855, 0.522)	-0.702 (-1.900, 0.496)
Adiponectin (ng/ml)	Pre-pregnancy weight	-15 (-31, 0)	-18 (-34, -2)
	GWG 0-14 weeks	97 (-220, 414)	17 (-302, 336)
	GWG 14-36 weeks	151 (-334, 637)	47 (-454, 548)
	GWG after 36 weeks	88 (-421, 600)	61 (-450, 573)
Triglycerides (ratio GM[c])	Pre-pregnancy weight	1.002 (1.000, 1.003)	1.001 (1.000, 1.003)
	GWG 0-14 weeks	0.997 (0.972, 1.022)	0.997 (0.972, 1.023)
	GWG 14-36 weeks	1.035 (0.996, 1.075)	1.033 (0.993, 1.074)
	GWG after 36 weeks	1.009 (0.969, 1.050)	1.011 (0.971, 1.052)
CRP (ratio GM[c])	Pre-pregnancy weight	1.009 (1.005, 1.012)	1.009 (1.006, 1.013)
	GWG 0-14 weeks	1.040 (0.972, 1.113)	1.044 (0.974, 1.118)
	GWG 14-36 weeks	1.057 (0.952, 1.174)	1.088 (0.976, 1.213)
	GWG after 36 weeks	1.074 (0.962, 1.199)	1.074 (0.962, 1.200)
IL-6 (ratio GM[c])	Pre-pregnancy weight	1.003 (1.001, 1.006)	1.004 (1.001, 1.006)
	GWG 0-14 weeks	1.023 (0.974, 1.075)	1.030 (0.979, 1.083)
	GWG 14-36 weeks	1.082 (1.003, 1.168)	1.097 (1.014, 1.186)
	GWG after 36 weeks	1.005 (0.928, 1.089)	1.007 (0.929, 1.091)

[a] The exposures – pre-pregnancy weight and GWG are estimated for each woman from the multilevel models using all repeat measurements of gestational weight in each woman

[b] Model 2: identical to model 2 of Table 3 in main paper (confounder adjusted) with adjustment for age, gender, height and height-squared (for fat mass), pre-pregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth and mode of delivery

Model 3: as model 2 plus additional adjustment for birthweight

[c] Results in shaded rows are ratio of geometric means (GM) per 1kg pre-pregnancy weight or per 400g GWG in each period. The null value for these ratios is 1; for all other values the results are mean differences and the null value is 0

Web-Table 5c: Mean difference (95%CI) in offspring adiposity, blood pressure, lipids, apolipoproteins and inflammatory markers by IOM categories of maternal gestational weight gain for BMI – assessing possible mediation of associations by birthweight (N=5154 or 3457 as indicated)

Outcome	IOM category	Model 2[a]	Model 3[a]
BMI (kg/m^2) N = 5154	< recommended	-0.326 (-0.504, -0.148)	-0.213 (-0.393, -0.033)
	= recommended	ref	ref
	> recommended	0.744 (0.552, 0.937)	0.635 (0.441, 0.829)
Waist (cm) N = 5154	< recommended	-0.897 (-1.379, -0.415)	-0.590 (-1.076, -0.104)
	= recommended	ref	ref
	> recommended	1.931 (1.410, 2.452)	1.635 (1.110, 2.159)
Fat mass (g) N = 5154	< recommended	-260 (-540, 21)	-246 (-530, 38)
	= recommended	ref	ref
	> recommended	1075 (773, 1378)	1053 (748, 1359)
SBP (mmHg) N = 5154	< recommended	-0.372 (-0.969, 0.226)	-0.322 (-0.928, 0.284)
	= recommended	ref	ref
	> recommended	1.250 (0.604, 1.896)	1.247 (0.594, 1.901)
HDLc (mmol/l)	< recommended	0.006 (-0.018, 0.030)	0.003 (-0.021,0.027)
	= recommended	ref	ref
	> recommended	-0.029 (-0.055, -0.004)	-0.028 (-0.054, -0.002)
Non-HDLc (mmol/l)	< recommended	-0.04 (-0.09, 0.01)	-0.04 (-0.09, 0.01)
	= recommended	ref	ref
	> recommended	-0.04 (-0.09, 0.01)	-0.04 (-0.09, 0.01)
Apo A1 (mg/dl)	< recommended	-0.167 (-1.726,1.391)	-0.438 (-2.018, 1.143)
	= recommended	ref	ref
	> recommended	-1.649 (-3.327, -0.029)	-1.514 (-3.212, 0.185)
Leptin (ratio GM)[b] N = 3457	< recommended	0.948 (0.893,1.005)	0.952 (0.897,1.011)
	= recommended	ref	ref
	> recommended	1.178 (1.105,1.256)	1.172 (1.098,1.250)
Triglycerides (ratio GM)[b] N = 3457	< recommended	0.977 (0.944, 1.011)	0.981 (0.948, 1.016)
	= recommended	ref	ref
	> recommended	1.020 (0.983, 1.058)	1.016 (0.979, 1.055)
CRP (ratio GM)[b] N = 3457	< recommended	1.012 (0.921,1.111)	1.005 (0.914, 1.106)
	= recommended	ref	ref
	> recommended	1.150 (1.040, 1.273)	1.157 (1.044, 1.282)
IL-6 (ratio GM)[b] N = 3457	< recommended	1.005 (0.939, 1.076)	0.999 (0.932, 1.070)
	= recommended	ref	ref
	> recommended	1.129 (1.050, 1.215)	1.129 (1.049, 1.216)

[a] Model 2: identical to model 2 of table 2 in main paper (confounder adjusted) with adjustment for age, gender, height and height-squared (for fat mass), pre-pregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth and mode of delivery

Model 3: as model 2 plus additional adjustment for birthweight

[b] Results in shaded rows are ratio of geometric means (GM) by IOM categories. The null value for these ratios is 1; for all other values the results are mean differences and the null value is 0

Web-Table 6a: Mean difference (95%CI) in offspring measurements of lipids, apolipoproteins and inflammatory markers per 1kg change in maternal estimated pre-pregnancy weight and 400g/week estimated gestational weight gain – assessing possible mediation of associations by fat mass (N=3457)

Outcome	Exposure period[a]	Model 2[b]	Model 4[b]
HDLc (mmol/l)	Pre-pregnancy weight	-0.002 (-0.003, -0.001)	0.000 (-0.001, 0.001)
	GWG 0-14 weeks	-0.007 (-0.025, 0.010)	0.002 (-0.015, 0.019)
	GWG 14-36 weeks	-0.028 (-0.055, -0.002)	-0.016 (-0.042, 0.010)
	GWG after 36 weeks	-0.007 (-0.035, 0.021)	-0.001 (-0.029, 0.026)
non-HDLc (mmol/l)	Pre-pregnancy weight	0.001 (0.000, 0.003)	-0.001 (-0.003, 0.001)
	GWG 0-14 weeks	-0.033 (-0.118, 0.052)	-0.018 (-0.053, 0.017)
	GWG 14-36 weeks	0.013 (-0.123, 0.150)	0.003 (-0.050, 0.057)
	GWG after 36 weeks	0.005 (-0.073, 0.082)	-0.046 (-0.103, 0.010)
Apo A1 (mg/dl)	Pre-pregnancy weight	-0.087 (-0.144,-0.031)	-0.002 (-0.061, 0.057)
	GWG 0-14 weeks	-0.872 (-2.004, 0.260)	-0.467 (-1.590, 0.657)
	GWG 14-36 weeks	-1.409 (-3.145, 0.326)	-0.761 (-2.488, 0.967)
	GWG after 36 weeks	-0.387 (-2.214, 1.440)	-0.225 (-2.034, 1.584)
Apo B (mg/dl)	Pre-pregnancy weight	0.041 (0.004, 0.077)	0.010 (-0.028, 0.048)
	GWG 0-14 weeks	0.257 (-0.480, 0.993)	0.086 (-0.635, 0.808)
	GWG 14-36 weeks	-0.106 (-1.235, 1.024)	-0.023 (-1.133, 1.087)
	GWG after 36 weeks	-0.667 (-1.855, 0.522)	-0.889 (-2.051, 0.272)
Adiponectin (ng/ml)	Pre-pregnancy weight	-15 (-31, 0)	2 (-14, 19)
	GWG 0-14 weeks	97 (-220, 414)	184 (-132, 499)
	GWG 14-36 weeks	151 (-334, 637)	266 (-219, 751)
	GWG after 36 weeks	88 (-421, 600)	123 (-385, 630)
Triglycerides (ratio GM[c])	Pre-pregnancy weight	1.002 (1.000, 1.003)	1.000 (0.998, 1.001)
	GWG 0-14 weeks	0.997 (0.972, 1.022)	0.986 (0.962, 1.010)
	GWG 14-36 weeks	1.035 (0.996, 1.075)	1.024 (0.986, 1.063)
	GWG after 36 weeks	1.009 (0.969, 1.050)	1.001 (0.963, 1.041)
CRP (ratio GM[c])	Pre-pregnancy weight	1.009 (1.005, 1.012)	0.998 (0.995, 1.001)
	GWG 0-14 weeks	1.040 (0.972, 1.113)	0.984 (0.925, 1.046)
	GWG 14-36 weeks	1.057 (0.952, 1.174)	1.002 (0.911, 1.102)
	GWG after 36 weeks	1.074 (0.962, 1.199)	1.030 (0.932, 1.137)
IL-6 (ratio GM[c])	Pre-pregnancy weight	1.003 (1.001, 1.006)	0.999 (0.996, 1.001)
	GWG 0-14 weeks	1.023 (0.974, 1.075)	0.998 (0.951, 1.048)
	GWG 14-36 weeks	1.082 (1.003, 1.168)	1.053 (0.977, 1.134)
	GWG after 36 weeks	1.005 (0.928, 1.089)	0.991 (0.917, 1.071)

[a] The exposures – pre-pregnancy weight and GWG are estimated for each woman from the multilevel models using all repeat measurements of gestational weight in each woman

[b] Model 2: identical to model 2 of table 2 in main paper (confounder adjusted) with adjustment for age, gender, pre-pregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth and mode of delivery

Model 4: as model 2 plus additional adjustment for fat mass, height and height-squared

[c] Results in shaded rows are ratio of geometric means (GM) per 1kg pre-pregnancy weight or per 400g GWG in each period. The null value for these ratios is 1; for all other values the results are mean differences and the null value is 0

Web-Table 6b: Mean difference (95%CI) in offspring blood pressure, lipids, apo-lipoproteins and inflammatory markers by IOM categories of maternal gestational weight gain for BMI – assessing possible mediation of associations by fat mass (N=5154 or 3457 as indicated)

Outcome	IOM category	Model 2[a]	Model 4[a]
SBP (mmHg) N = 5154	< recommended	-0.372 (-0.969, 0.226)	0.173 (-0.365, 0.712)
	= recommended	ref	ref
	> recommended	1.250 (0.604, 1.896)	0.205 (-0.380, 0.789)
HDLc (mmol/l)	< recommended	0.006 (-0.018, 0.030)	0.000 (-0.023, 0.023)
	= recommended	ref	ref
	> recommended	-0.029 (-0.055, -0.004)	-0.007 (-0.032, 0.018)
Apo A1 (mg/dl)	< recommended	-0.167 (-1.726,1.391)	-0.465 (-2.008, 1.077)
	= recommended	ref	ref
	> recommended	-1.649 (-3.327, -0.029)	-0.781 (-2.449, 0.887)
Triglycerides (ratio GM[b]) N = 3457	< recommended	0.977 (0.944, 1.011)	0.983 (0.950,1.016)
	= recommended	ref	ref
	> recommended	1.020 (0.983, 1.058)	0.992 (0.957,1.029)
CRP (ratio GM[b]) N = 3457	< recommended	1.012 (0.921,1.111)	1.031 (0.948, 1.123)
	= recommended	ref	ref
	> recommended	1.150 (1.040, 1.273)	1.000 (0.912, 1.096)
IL-6 (ratio GM[b]) N = 3457	< recommended	1.005 (0.939, 1.076)	1.018 (0.952, 1.087)
	= recommended	ref	ref
	> recommended	1.129 (1.050, 1.215)	1.068 (0.994, 1.147)

[a] Model 2: identical to model 2 of table 3 in main paper (confounder adjusted) with adjustment for age, gender, pre-pregnancy weight and GWG in previous period, head of household social class, parity, maternal smoking in pregnancy, age at birth and mode of delivery

Model 4: as model 2 plus additional adjustment for fat mass, height and height-squared

b Results in shaded rows are ratio of geometric means (GM) by IOM categories. The null value for these ratios is 1; for all other values the results are mean differences and the null value is 0

References for supplementary web material

1. Royston P, Attman DG. Regression using functional polynominals of continuous covariates: Parsimonious parametric modelling. Appl Statist 1994;43:429-467.
2. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-1243.
3. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S. The metabolic syndrome in children and adolescents. Lancet 2007;369:2059-2061.
4. McCarthy HD, Jarrett KV, Crawley HF. The development of waist circumference percentiles in British children aged 5.0-16.9 y. Eur J Clin Nutr 2001;55:902-907

Commentary

Improving Health Outcomes: Future Directions in the Field

XAVIER PI-SUNYER, MD, MPH; P. M. KRIS-ETHERTON, PhD, RD

Obesity has been steadily increasing in the United States for the past 3 decades. At present almost 65% of the population is overweight or obese, with the prevalence higher for minority populations. Obesity now is present in 31% of the population and overweight in 34% (1). Approximately 1% of the adult population is moving into the obese category (body mass index [BMI]>30) every year. A similar increase is being seen among children and adolescents (2). This pattern is not confined to the United States, but is also occurring throughout the world, in both developed and less developed countries (3).

Obesity is associated with several risk factors and diseases. These include insulin resistance, glucose intolerance, type 2 diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, stroke, heart failure, and certain kinds of cancer, as well as earlier mortality (4). This has led to increasing costs. Obesity has been reported to be responsible for 5.5% to 7.8% of all health care costs (5), to lead to a loss of productivity by days lost from work, and to cause a great number of disabilities (6). These disabilities are expensive both financially and with respect to quality of life.

The change in weight of the US population has occurred without changes in the gene pool, suggesting that the root cause of the epidemic is change in lifestyle and environment rather than a biological genetic change in the population. This does not imply that genes are not important. Between 30% and 40% of the variance of weight is genetic (7). There is clearly a gene-environment interaction, with some individuals being more sensitive than others to the "toxic" environment we now experience.

The environmental determinants of weight gain in the population are diet and physical activity. Individuals are eating more and exercising less, and this imbalance between energy intake and energy expenditure leads to a situation in which adults between 20 and 40 years of age in this country gain about 1.8 to 2.0 pounds per year (8).

What are the future directions in the field that could improve health outcomes? It is evident that much remains to be learned about all aspects of obesity, ranging from basic biology to effective intervention programs for prevention and treatment. We have learned a great deal over the years about many important aspects of obesity; nonetheless, we have not been able to translate it to better intervention for prevention and treatment. As mentioned earlier, there is still an alarming increase in overweight and obesity in all population groups.

We need to do everything we can to get people to understand that they are ingesting too many calories. We need to improve nutrition education. This will require a combined effort of nutrition professionals, physicians, health maintenance organizations, insurance companies, government, and industry. We need to alert people to avoid large portion sizes, energy-dense foods, indiscriminate snacking, high intake of caloric beverages, and empty calories. A better understanding of the basis of a sound diet that brings adequate micronutrients without extra calories is required.

We also need to encourage people to be more physically active. This will require public awareness campaigns by the government, the medical profession, voluntary health agencies, and private groups. In addition, we need to improve the environment to create the venues in which physical activity can take place. This includes safe streets and sidewalks, better and safer parks, more and open gymnasiums, and more bike paths and public swimming pools.

Studies to date have shown that relatively small decreases in weight and relatively small increases in exercise can have a profound effect on health. The Diabetes Prevention Program (9) and the Finnish Diabetes Prevention Study (10) have both reported this. A 6% to 7% decrease in weight and a 30-minute per-day increase in physical activity can decrease the conversion of impaired glucose tolerance to diabetes by more than 50%.

We need to get industry to undertake changes that can help to ameliorate the obesity problem. These include, both for food companies and for restaurants, better nutrition labeling, smaller portion sizes, lower energy density, and more low-calorie alternatives. Adolescent obesity tracks to adult obesity, so it is particularly important to attempt to stem the increase in obesity in this group. School-based initiatives should be created to try to develop efficacious and practical programs to prevent and

X. Pi-Sunyer is director, Obesity Research Center, Columbia University, St Luke's-Roosevelt Hospital Center, New York, NY. P. M. Kris-Etherton is a distinguished professor of nutrition, Department of Nutritional Sciences, The Pennsylvania State University, University Park.

Address correspondence to: Xavier Pi-Sunyer, MD, MPH, Director, Obesity Research Center, Department of Medicine, St Luke's-Roosevelt Hospital Center, 1111 Amsterdam Ave, Room 1020, New York, NY 10025. E-mail: fxp1@columbia.edu

0002-8223/05/10505-1012$30.00/0
doi: 10.1016/j.jada.2005.02.027

reverse obesity. More and better nutrition education and physical education are needed in the schools. We are deficient in this regard in the United States.

We have learned a great deal in the last decade about the biology of the regulation of food intake, but we need to know much more. More research funding is needed from the federal government. Research is necessary for understanding how important centers in the gut, the brain, and elsewhere control hunger, satiety, and thermogenesis. We need to understand more about which genes are important in turning food intake on and off and influencing energy expenditure. We need to identify the peptides and other molecules that are important, and we need to understand the mechanisms by which they work. We have to look seriously at the genetic underpinnings of behavior. Little work has been done in this area to date. The fat cell as an endocrine organ must be studied because it produces bioactive molecules that have an influence on inflammation, thrombosis, endothelial function, macronutrient disposal, and energy production. The role that ectopic fat plays in the development of diabetes and cardiovascular disease needs to be better defined and explained. How inflammatory stimuli abet the chronic diseases associated with obesity has to be further explored. The role of vascular reactivity and its relation to products released by excessive and ectopic fat must be defined.

We need to learn more about effective weight-loss diets/programs and how best to counsel patients. This will require more research that is designed to understand dietary patterns (including individual components of the diet) that result in the prevention of weight gain and successful treatment of obesity. This research will need to be in the form of intervention trials that actually test the role of nutrients and their effects. Simply doing observational longitudinal studies is not enough. Observational cross-sectional studies are worse than useless because they are often misleading.

Although our current tools for confronting the obesity epidemic are weak because our knowledge base is still small, we know enough now to make concerted efforts to begin to improve public health. This will require, as mentioned earlier, changes in people's consciousness about the problem, improved education about healthful diets and physical activity, an improved environment, and serious efforts by government and industry to help in the difficult task of turning this epidemic around.

Recent dietary guidelines have addressed the overweight and obesity problem in the United States. The 2005 Dietary Guidelines (11) have stressed for the first time the importance of physical activity. The recommendations take into consideration the growth of obesity in the United States and address the important issues. In addition to the guidelines themselves, an evidence-based report by the Dietary Guidelines Advisory Committee has also been published (12) and is available to all health professionals and the general public. Similarly, the American Heart Association Dietary Guidelines (13) recommend that the major emphasis for weight management should be on avoiding excess total energy intake and following a regular pattern of physical activity. These guidelines are written for the general population. Widespread implementation of these guidelines, though challenging, is necessary. Strategically, the dietetics community is confronted with what to do to lessen the burden of the obesity epidemic. Simply stated, this means developing and implementing effective strategies for treating overweight and obesity on an individual level and in large cohorts at the community, state, and national levels. The magnitude of the obesity epidemic is so serious that, to have a major impact on slowing (and even stopping) the rate of increase and ultimately dramatically reducing the incidence of obesity, dietetics professionals must identify new strategies to deal with this enormous health problem. Although some optimistic observers suggest that the incidence of obesity is plateauing, we see no such evidence to date. Hopefully, some of our remedial suggestions may help to bring this about. The role of the dietetics professional in practice has evolved in response to changing societal needs. When the American Dietetic Association (ADA) was founded in 1917, it was dedicated to helping the government conserve food and improve the public's health and nutrition during World War I. History shows that the early ADA provided valuable assistance to this cause. The nutrition and health needs of the US population are different today than in 1917, with diseases related to overconsumption assuming prominence in health care. In parallel, dietetics practice has changed markedly with the evolution of many different practice emphases (such as private practice, foodservice management, nutrition education, clinical nutrition, and many others) that relate to food behaviors. Thus, with the broad education and training required of dietetics professionals and the diversity of expertise in the ADA membership, the dietetics profession is in a strong position to develop innovative and effective obesity intervention programs.

Traditionally, a model that favors one-on-one counseling approaches has guided medical nutrition therapy. There is much information in the literature about guidelines for the treatment of overweight and obesity summarized in the National Institutes of Health Clinical Guidelines Report (14). The role of the dietetics professional in providing medical nutrition therapy involves assessing nutritional status and planning and recommending food behavior interventions (15). Medical nutrition therapy also involves identifying effective interviewing approaches, treatment plans that involve patients/clients, ideal documentation strategies, suitable follow-up timelines, and appropriate referrals when indicated.

Although there is little dispute that dietitians are experts at delivering medical nutrition therapy using this time-honored approach, the magnitude of the obesity problem argues that the profession must develop new ways to have a substantial impact on the obesity epidemic. The reality is that the health care profession is a long way from where it needs to be if it is to rein in the obesity epidemic. There is no question that innovative and bold new approaches must be developed for the prevention and treatment of obesity. The critically pressing question is: what are they? There is no simple solution. The dietetics profession confronts a complex and challenging problem (16).

What should dietetics practice look like in the future? It must go beyond the traditional in all areas of the profession. The future paradigm will involve population-based obesity interventions that will require the full cooperation of the entire health care community. Moreover, it

will require coordinated integration of the expertise represented by different health care disciplines with the diversity of skills to develop innovative ways to tackle the obesity problem. The magnitude of the problem is such that the food industry and government also must be active participants in planning and implementing solutions. Active cooperation of the health care community, the private sector, and policymakers is essential if we are to make marked progress.

The expertise and diversity of skills of the dietetics profession offers much for a bold initiative to battle obesity. A major effort will be required to meaningfully reduce the incidence of obesity in the population at large. First, new education efforts are needed to overcome the rampant public misunderstanding about what lifestyle strategies are effective for weight loss. The importance of a balanced diet for lifetime health has to be at the forefront of our effort. Given the public's perceptions about the efficacy of unbalanced diets, this will be a major challenge. Dietetics professionals are well positioned to lead this nutrition education effort. It is essential that dietetics professionals continue their legacy of implementing practice guidelines for the treatment of overweight and obesity. This will continue to make an impact at the individual level.

Dietetics professionals must emphasize sound weight-management approaches in all counseling sessions. Repeated messages about a healthful diet and physical activity patterns for achieving and maintaining a goal weight will reinforce important messages about preventing overweight and obesity, and even preventing small weight changes that occur slowly over time. A dietetics professional and patient partnership that defines reasonable changes and expectations is important to set the stage for smaller, permanent changes. By implementing state-of-the-art counseling skills, dietetics professionals will have a long-term impact on the weight-management efforts of individual clients. With advances in pharmacotherapy for obesity, it is important for dietetics professionals to work with physicians in implementing medication use within the context of lifestyle change.

On a grander scale, dietetics professionals should be encouraged to participate in nutrition advocacy at the local, state, and federal levels with policymakers and the private sector, and to encourage healthful eating and lifestyle behaviors, including developing public information campaigns (17). Importantly, they must spearhead nutrition efforts to promote healthful eating behaviors at the grassroots level. Collectively, the dietetics community must participate in the public and scientific discussions at all levels to identify solutions and sensible and effective government policies to catalyze a new framework that makes substantive strides in reducing obesity in the United States.

References

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA.* 2002;288:1723-1727.
2. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA.* 2002;288:1728-1732.
3. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation on Obesity. Geneva, Switzerland, 3-5 June, 1997. Geneva, Switzerland: World Health Organization; 1998. WHO Technical Report Series, No. 894.
4. Pi-Sunyer FX. Medical hazards of obesity. *Ann Intern Med.* 1993;119:655-660.
5. Kortt M, Langley P, Cox E. A review of cost-of-illness studies on obesity. *Clin Ther.* 1998;20:772-779.
6. Wolf A, Colditz G. Current estimates of the economic cost of obesity in the United States. *Obes Res.* 1998; 6:97-106.
7. Bouchard C, Perusse L, Rice T, Rao DC. Genetics of human obesity. In: Bray G, Bouchard C, eds. *Handbook of Obesity*. New York, NY: Marcel Dekker; 2004
8. Hill J, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: Where do we go from here? *Science.* 2003;299:853-855.
9. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2003; 346:393-403.
10. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344: 1343-1350.
11. US Department of Health and Human Services and US Department of Agriculture. Dietary Guidelines for Americans 2005. Available at: http://www.healthierus.gov/dietaryguidelines. Accessed January 12, 2005.
12. United States Department of Agriculture. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. USDA; Agricultural Research Service, 2005.
13. Krauss RM, Eckel RH, Howard B, Appel LJ, Daniels SR, Deckelbaum RJ, Erdman JW Jr, Kris-Etherton P, Goldberg IJ, Kotchen TA, Lichtenstein AH, Mitch WE, Mullis R, Robinson K, Wylie-Rosett J, St Jeor S, Suttie J, Tribble DL, Bazzarre TL. AHA Dietary Guidelines—Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Stroke.* 2000;31: 2751-2766.
14. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report*. Bethesda, MD: National Institutes of Health. National Heart, Lung, and Blood Institute; 1998.
15. *Medical Nutrition Therapy Across the Continuum of Care*. 2nd ed. Chicago, IL: American Dietetic Association; 1998.
16. American Dietetic Association. Position of the American Dietetic Association: Weight Management. *J Am Diet Assoc.* 2002;102:1145-1155.
17. North American Association for the Study of Obesity. National Nutrition Summit Position Paper. Available at: http://www.naaso.org/nutsummit.htm. Accessed October 2002.

Metabolic Implications of Menopause

Hanah N. Polotsky, M.D., F.A.C.P.,[1] and Alex J. Polotsky, M.D., F.A.C.O.G.[2]

ABSTRACT

The incidence of metabolic syndrome increases substantially during perimenopause and early menopause. Postmenopausal women are at a higher risk of hypertension, proatherogenic lipid changes, diabetes, and severe cardiovascular disease as compared with their premenopausal counterparts. Whether or not menopause has a causative contribution to the deteriorating metabolic profile that is independent of chronological aging has been a subject of many studies. Menopausal transition is associated with significant weight gain (2 to 2.5 kg over 3 years on average), which is not dissimilar to that in premenopausal women of like age. Concomitantly, there is an increase in abdominal adiposity and a decrease in energy expenditure, phenomena that have been postulated to explain the higher risk of metabolic syndrome and increases in cholesterol and triglycerides. Hypertension and diabetes become more prevalent with age and should be timely diagnosed and treated. Lifestyle changes including moderately decreased caloric intake and aerobic exercise could prevent proatherogenic changes and weight gain observed with aging. Accurate prediction of cardiovascular risk in midlife women is essential to help identify the subset of women who are likely to benefit from intensive management of metabolic risk factors. This review focuses on metabolic changes associated with menopausal transition, specifically alterations in weight, waist circumference, body fat distribution, energy expenditure, and circulating biomarkers including adipokines.

KEYWORDS: Menopause, obesity, metabolic syndrome, cardiovascular risk

Connection between body habitus and health had been contemplated since antiquity as illustrated by a treatise on "drawbacks of excessive obesity" written by Avicenna (980–1037) in his "Canon in Medicine."[1] For women, postmenopausal status has been traditionally regarded as a cardiovascular risk factor.[2] Incidence of heart disease increases with age in both genders, yet it occurs a decade later in women, largely after menopause.[3] Increase in heart disease risk was observed in women following surgical and natural menopause.[4] Estrogen deficiency has been posited as a cause of this increase. However, trials of hormone therapy for primary and secondary prevention of cardiovascular disease (CVD) in postmenopausal women demonstrated an unexpected increase in CVD with estrogen supplementation.[5] An increase in prevalence of heart disease at midlife could be related to a multitude of metabolic and hormonal changes occurring during the menopausal transition and early postmenopause.[6,7] The effect of menopausal transition on anthropometric parameters, blood pressure, lipids, insulin sensitivity, and metabolic syndrome has been a subject of several recent studies. Postmenopausal heart disease may be related to an observed increase in the incidence of metabolic

[1]Weill-Cornell Medical Center and Memorial Sloan-Kettering Cancer Center; and [2]Division of Reproductive Endocrinology and Infertility, Albert Einstein College of Medicine, Bronx, New York.

Address for correspondence and reprint requests: Hanah N. Polotsky, M.D., F.A.C.P., Fellow in Endocrinology, Diabetes and Metabolism, Weill-Cornell Medical Center and Memorial Sloan-Kettering Cancer Center, 525 East 68th Street, Baker 20, New York, NY 10065 (e-mail: hpolotsky@yahoo.com).

Menopause: Demystifying Management of Common Clinical Challenges; Guest Editor, Lubna Pal, M.B.B.S., M.R.C.O.G., M.S.

Semin Reprod Med 2010;28:426–434.

DOI: http://dx.doi.org/10.1055/s-0030-1262902.
ISSN 1526-8004.

syndrome. Reductions in estrogen levels observed in the perimenopause and postmenopause are concomitantly accompanied by an androgen-dominated metabolic environment.[8] An association between increasing age and cardiometabolic risk markers has been observed in both men and women.[9] Changes in weight and lipids observed during the menopausal transition were independent of age in some studies[10,11] but not others.[12,13] This review focuses on studies researching the metabolic and cardiovascular risks of menopause.

Table 1 Overweight and Obesity as Defined by the World Health Organization[77]

Category	Body Mass Index
Normal	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obesity class I	30–34.9 kg/m^2
Obesity class II	35–39.9 kg/m^2
Obesity class III	≥40 kg/m^2

Body mass index = weight (kg)/height^2 (m^2).

DEFINITION AND TERMINOLOGY OF MENOPAUSE

Menopause involves the transition from reproductive competence to postmenopause and is best thought of as a dynamic process that takes place over several years. It involves many hormonal and physiological changes including but not limited to increased follicle-stimulating hormone (FSH) production by the pituitary, changes in the length and regularity of menstrual cycles with eventual attainment of amenorrhea, decreases in hepatic sex hormone-binding globulin (SHBG) and serum levels of estradiol (E2), and minimal decline in circulating androgens. In contradistinction, alterations in nonreproductive hormones produced by thyroid, parathyroid, and pancreas that are noticeable postmenopause are thought to be related to chronological aging without a significant relationship to menopause.[14–16] Knowledge and investigation of the menopausal physiology and timeline were greatly facilitated by the development of staging systems of reproductive aging. The following terminology, adopted from the Stages of Reproductive Aging Workshop,[17] is used in this review:

- Menopause: A state after 12 months of amenorrhea following the final menstrual period (FMP); note the retrospective nature of this definition.
- Menopausal transition: Early (stage 2) or late (stage 1) includes changes in menstrual regularity and increases in FSH that culminates in the FMP.
- Perimenopause: Menopausal transition plus 1 year after FMP.
- Postmenopause: Early (stage + 1) includes 5 years after FMP and late (stage + 2) until death.

CHANGES IN PHENOTYPE, ENERGY EXPENDITURE, AND METABOLIC MILIEU WITH REPRODUCTIVE AGING

Obesity, as defined by World Health Organization (Table 1), is more prevalent in women than in men. The latest National Health and Nutrition Examination Survey data estimate that approximately two thirds of women 40 to 60 years of age are overweight or obese.[18] Body weight increases with age, irrespective of the baseline weight in normal and obese individuals alike. Weight gain during menopausal transition has been scrutinized as a major contributing factor to midlife body weight. The Healthy Women Study demonstrated an average weight gain of 2.5 kg over a 3-year-period during the menopausal transition, a significant finding that was nonetheless similar to the observed change of control women who remained premenopausal during the study period.[13] In contrast to the observational studies,[19,20] weight gain appeared more pronounced in women on hormone therapy (HT). Yet the wide range of weight changes made it difficult to reach generalizable conclusions because some women gained up to 32 kg and others lost close to 15 kg.[13] No baseline characteristics, including initial body mass index (BMI), were predictive of the degree of weight gain.[13] Similarly, the Study of Women's Health across the Nation (SWAN) demonstrated no difference in the BMI between premenopausal women and those who experienced natural menopause, with an average weight gain of 2.1 kg related to chronological aging but not to menopause per se.[11,21] Likewise, in a longitudinal study from Scotland, women gained weight independent of their menopausal status or hormone replacement therapy use.[22]

Weight gain at midlife is partially attributed to the reduction in energy expenditure (EE). Lovejoy et al demonstrated a larger decrease in EE in women who underwent menopause compared with the premenopausal controls at 4-year follow-up.[23] Several explanations were proposed to rationalize this observed decline in EE including a reduction in leisure time physical activity, loss of lean body mass causing basal EE decline as well as a loss of the luteal phase increases in EE described in the premenopausal years.[24,25] Changes in waist circumference, visceral adipose tissue (VAT), and body fat distribution has been ascribed to both chronological aging and menopause.[26,27] In SWAN, chronological aging was a contributing factor to the increase in weight and waist circumference, whereas menopausal status was not.[21] Using computed tomography (CT), Lovejoy et al demonstrated an increase in subcutaneous adipose tissue with age, independent of menopausal status, whereas VAT and total body fat increased only in women who became postmenopausal during the

4 years of follow-up.[23] This change in visceral adiposity was accompanied by a decrease in circulating estradiol and increase in FSH and was attributed by the authors to influences of estrogen on lipoprotein lipase activity and lipolysis.[23] A smaller study by Franklin et al used magnetic resonance imaging to study total abdominal, visceral, and subcutaneous adiposity in eight healthy women before and after menopause; the authors demonstrated an overall increase in the absolute adiposity, without evidence of fat redistribution from the subcutaneous to visceral sites. Of note, BMI and waist circumference did not change in this study.[28]

VAT is thought to play an important role in the production of inflammatory adipocytokines: monocyte-chemotactic protein(MCP)-1), tissue plasminogen activator inhibitor (tPA), tumor necrosis factor-α, and interleukin-6.[29] Patients with increased abdominal adiposity have been demonstrated to have higher levels of leptin and C-reactive protein (CRP) and lower levels of adiponectin.[30] Associations between inflammatory cytokines and increased risk of postmenopausal coronary artery disease, metabolic syndrome, and diabetes have been reported.[29,31] During menopausal transition Lee et al demonstrated a positive correlation between intra-abdominal fat and changes in leptin, tPA, MCP-1, and CRP; and a negative correlation with adiponectin.[32]

METABOLIC SYNDROME AND MENOPAUSE

Metabolic syndrome (MetS) is a cluster of cardiovascular disease and diabetes risk factors (Table 2) that was recognized in the1990s as a major risk factor for cardiovascular morbidity and mortality.[33] Although the terminology and diagnostic criteria of MetS have been a subject of debate and controversy,[34] most experts agree that each individual component of the purported syndrome constitutes an independent risk for CVD.[35] Recently, a joint statement of several international organizations published unified criteria of MetS with waist circumference measurements based on regional or national data (Table 2).[36] By this definition, approximately a quarter of the U.S. population is affected by the metabolic syndrome at midlife.[37] Menopause is associated with a 60% increased risk of MetS, a relationship that is described as being independent of age, BMI, and physical activity.[38] Beyond the defined clinical features of MetS, (i.e., central adiposity and hypertension), a proatherogenic and a proinflammatory environment and insulin resistance describe the metabolic milieu of MetS.[39] Further, a close relationship between abdominal adiposity and insulin resistance is recognized.[40] Increased visceral adiposity during menopausal transition is thought to be associated with the worsening insulin resistance, elevated free fatty acid levels as well as decreased adiponectin. Low circulating SHBG levels were linked to MetS in postmenopausal women in the Women's Health Study.[41] In SWAN, prevalence of MetS prior to the FMP was 32.7% with an additional 13.7% of the cohort developing incident MetS at the time of FMP. The incidence of MetS had been demonstrated to increase progressively during the menopausal transition and in the 6 years following menopause.[42] An increase in the bioavailable testosterone and a decrease in SHBG observed in SWAN were both associated with the development of MetS, whereas changes in estradiol and total testosterone were not. A relative excess of androgens rather than estrogen deficiency was found to be related to the risk of developing MetS in the SWAN cohort, independent of age or other cardiovascular risk factors.[43]

Taken together, the studies suggest that prevalence of MetS increases substantially during menopausal transition and is independent of age, body mass, and physical activity. Changes in the androgens-to-estrogens ratio after menopause appears to be related to an

Table 2 Criteria for Clinical Diagnosis of the Metabolic Syndrome*

Measure	Categorical Cut Points	
Elevated waist circumference	Male	Female
US/Canada/European†	≥102 cm	≥88 cm
White, Middle Eastern, Mediterranean, Sub-Saharan African‡	≥94 cm	≥80 cm
Asian, ethnic Central and South American‡	≥90 cm	≥80 cm
Elevated triglycerides or drug treatment for elevated triglycerides	≥150 mg/dL (1.7 mmol/L)	
Reduced high-density lipoprotein-cholesterol (HDL-C) or drug treatment for decreased HDL-C	<40 mg/dL (1.0 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women	
Elevated blood pressure or antihypertensive treatment	Systolic ≥130 and/or diastolic ≥85 mm Hg	
Elevated fasting glucose or drug treatment of elevated glucose	≥100 mg/dL	

*Adopted from a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and the International Association for the Study of Obesity, Circulation, 2009.[36]
†Adult Treatment Panel III, Health Canada, European Cardiovascular Societies.
‡International Diabetes Federation, World Health Organization.

Table 3 Prediabetes and Diabetes Definitions

Glucose Metabolism Abnormalities	Blood Glucose Level (Two Measurements)
Impaired fasting glucose (IFG)	Fasting glucose 100–125 mg/dL
Impaired glucose tolerance (IGT)	2-hour 75-g postchallenge 140–199 mg/dL
Diabetes	Fasting glucose ≥126 mg/dL 2-hour 75-g postchallenge ≥200 mg/dL

Adopted from the American Diabetes Association Clinical Practice Recommendations 2009. Diabetes Care 2009;32(Suppl 1):62–67.[45b]

observed rise in the deposition of intra-abdominal fat mediating insulin resistance and detrimental lipid changes observed in the MetS.

DIABETES RISK, DIABETES, AND MENOPAUSE

Approximately 10 million women live with diabetes in the United States based on the Centers for Disease Control and Prevention statistics.[44] The risk of diabetes increases with age in women and men.[45a] A role of menopause as a risk factor for diabetes, independent of age and excess BMI, had been suggested but remains unproven. Impaired glucose tolerance (Table 3) has been observed in patients with increased abdominal adiposity.[46,47] The incidence of MetS, but not type 2 diabetes, had been described to rise with menopausal transition.[39] The increased free testosterone and decreased SHBG described in the context of menopause are implicated in the pathophysiology of the observed greater risk of type 2 diabetes and impaired fasting glucose in postmenopausal women.[48] A cross-sectional study by Muscelli et al found no difference in insulin sensitivity, fasting glucose, or insulin levels between premenopausal and postmenopausal women matched for age and body mass.[49] A 6-year longitudinal study from Australia by Soriguer et al failed to show an appreciable change in impaired glucose tolerance or type 2 diabetes in women during or after menopausal transition. In this study, the women progressively gained weight during follow-up, yet no changes in waist circumference, abdominal adiposity, or other cardiovascular risk parameters were observed.[50] Of note, most studies of women treated with HT, including a secondary analysis of the Women's Health Initiative, found a decreased incidence type 2 diabetes in women on HT. A combination therapy of estrogen and progesterone had a greater effect on type 2 diabetes incidence reduction than estrogen alone. These observational studies mostly used fasting glucose, and not 2-hour oral glucose tolerance testing, to diagnose diabetes.[48] Some studies[51,52] but not others[53] demonstrated that women with diabetes, type 1 and type 2 alike, undergo menopausal transition at a younger age. Women with type 1 diabetes may be preferentially at a higher risk for ovarian failure based on a shared predisposition for autoimmune pathogenesis of both entities. The earlier time of menopause observed in women with type 2 diabetes may likely be related to obesity per se and not diabetes itself.[54] Increased free androgens observed in diabetes are most likely related to lower levels of SHBG caused by hyperinsulinemia and not necessarily to menopausal status.[55]

Unlike MetS, no independent increase in the risk for diabetes had been demonstrated in studies during menopausal transition or menopause. Patients treated with HT, however, had a significant decrease in the incidence of type 2 diabetes in some studies. Further research is needed to elucidate the precise relationship of reproductive hormone dynamics and diabetes risk during menopausal transition.

LIPID CHANGES AND MENOPAUSE

Multiple studies demonstrated an association between postmenopausal status and increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), lipoprotein(a), and decreased levels of high-density lipoprotein-cholesterol (HDL-C).[39] These lipid changes are attributed to an increase in abdominal adiposity, especially visceral (omental and mesenteric) adiposity occurring during menopausal transition, rather than to reproductive senescence per se. Androgen and estrogen receptors are found in adipocytes from subcutaneous fat with high density of androgen receptors isolated in the visceral fat. Higher amount of free fatty acids (FFA) produced by the VAT contributes to decreases in degradation of apolipoprotein B (apoB) in the liver that leads to increase production of small very low density lipoproteins particles and triglycerides. Increases in FFA lead to increased activity of the hepatic lipase with subsequent increases in production of smaller and denser LDL-C and HDL-C particles, which are more atherogenic. FFAs are also implicated in worsening insulin resistance, especially in the skeletal muscle, mediated through inhibition of glucose transport.[56] In the SWAN population, proatherogenic lipid changes occurred during the late peri- and early postmenopausal period.[12] On one hand, higher E2 levels of during the menopausal transition predicted lower levels of total cholesterol, LDL-C, and triglycerides, whereas on the other, women with higher FSH levels tended to have higher levels of HDL-C. Of interest is the relationship between HDL-C and reproductive stage that exhibited an inverted "U"-shaped relationship as HDL-C was observed to peak during perimenopause with a subsequent decline in postmenopause compared with premenopausal levels. Triglycerides increased progressively across the menopausal transition, and this change was independent of age. Women with the highest BMI demonstrated the

smallest changes in total cholesterol and LDL-C, which was attributed to higher levels of E2 in this subgroup. Thinnest women experienced the greatest changes in lipids during the menopausal transition.[12] In concert with these findings, an elegant study of premenopausal and postmenopausal twin pairs reported higher levels of total cholesterol, triglycerides, and apoB after menopause, independent of age.[57] LDL-C levels increased by 10–20% with menopause.[2] Density of LDL particles decreased significantly during the menopausal transition with more atherogenic small, dense LDL-C reported in postmenopause then prior to menopause. Women with a predominance of small dense LDL-C versus large LDL-C have been reported to have a threefold increase in cardiovascular risk and higher coronary calcium scores demonstrated by CT.[58] Further, triglycerides increase significantly across the menopausal transition, peaking in the early postmenopausal period.[39] Although the prevalence of triglyceridemia increases significantly at midlife in both genders, this finding appears to be more predictive of an increased risk of heart disease in women.[59]

Preponderance of data thus demonstrate attainment of a more proatherogenic lipid profile concomitant with reproductive aging. Of interest is the appreciation that increases in total cholesterol, triglycerides, and LDL-C, and a decrease in HDL-C with menopause were more pronounced in the thinnest women as compared with their overweight and obese counterparts. Increases in FFA with subsequent production of more atherogenic smaller and denser LDL-C and HDL-C particles could partially explain the increased incidence and severity of heart disease observed in postmenopausal women. These proatherogenic lipid changes appear to be independent of age and are likely related to a shift in body fat preferentially to intra-abdominal deposits during and following menopause.

BLOOD PRESSURE AND MENOPAUSE

Studies of the relationship between menopause and hypertension have produced mixed results. An increase in systolic and diastolic blood pressure has been associated with menopause independent of age and BMI in many cross-sectional and some prospective studies; other prospective studies, however, demonstrate no associated between menopause, blood pressure, and cardiovascular risk independent of age.[60] A deteriorating cardiovascular risk profile is known to ensue within weeks of surgical menopause, in the absence of estrogen replacement; the latter phenomena appear to be independent of age.[61] Differences in blood pressure may be underestimated because many more women are treated for hypertension postmenopausally compared with in premenopausal years. In some studies, the onset of menopause at a younger age and longer duration of postmenopause existence were associated with higher blood pressure levels.[62] Menopause has been associated with a considerable decrease in estradiol and the estradiol-to-testosterone ratio, creating an androgen dominant milieu that is theorized to be of pathogenic significance in the causation of blood pressure elevation. Indeed, such a profile is well described in women diagnosed with polycystic ovarian syndrome (PCOS) who demonstrate a higher risk of hypertension and CVD. The effects of the hormonal changes seen in PCOS and menopause are difficult to differentiate from other cardiovascular risk factors contributing to hypertension including obesity, age, insulin resistance, inflammatory milieu, and dyslipidemia.[63] Several mechanisms can contribute toward the development of hypertension in postmenopausal women. Certainly, endothelial dysfunction, inappropriate activation of the renin angiotensin and sympathetic systems, oxidative stress, dyslipidemia, and inflammatory mediators are all identified as contributory to postmenopausal blood pressure elevations.[60,63] However, it remains uncertain whether these physiological changes are caused by menopausal transition or are related to chronological aging.

To date, few studies have evaluated the relationship between changes in blood pressure and menopause in a way that allowed researchers to study the independent effects of age, body composition, insulin resistance, and dyslipidemia on blood pressure. Women experiencing surgical menopause or premature ovarian failure may have a more pronounced effect of the estrogen- deficient state on blood pressure compared with those experiencing natural and age-appropriate menopause. The scientific evidence for the relationship between blood pressure and menopause thus remains scarce and requires further investigation.

CARDIOVASCULAR DISEASE AND MENOPAUSE

Although premenopausal women are at a lower risk of heart disease compared with men, a twofold increase in risk for CVD follows menopause.[64] After surgical menopause without estrogen therapy, a significant increase in cardiovascular events risk is observed. This effect has been attributed to changes in estrogen levels occurring at and following menopause.[65] The contributions of multiple cardiovascular risk factors observed in the context of menopause and aging render the relationship complex; a "cause-and-effect" relationship for the individual risks is difficult to tease apart from contributions of aging per se. Increase in hypertension observed with aging is closely related to the increased risk of cardiovascular events. Dyslipidemia, exacerbated by menopausal transition and related to an increased abdominal adiposity, is a modifiable risk factor. Increases in LDL-C and triglycerides and decreases in HDL-C are independent contributors to risk for cardiovascular morbidity and mortality.

Primary prevention studies using statins to lower LDL-C demonstrated considerable reductions in cardiovascular events.[66] Prevalence of diabetes increases with age and the incidence of MetS increases with menopause independent of age, both exacerbating cardiovascular risk in aging women. Increase in abdominal visceral adiposity is a significant risk factor for heart disease in both men and women. Decrease in EE and leisurely physical activity observed following menopause, in addition to the progressive weight gain concomitant with aging, all contribute to a detrimental metabolic environment that is contributory to the observed higher CVD events in the postmenopausal population.[67] A significant increase in total peripheral resistance and cardiac wall thickness with a concomitant decrease in cardiac index was reported after menopause; importantly this was independent of hypertension.[49]The authors postulate a direct effect of estrogens on the myocardium, with low estrogen exerting a negative inotropic effect and hence resulting in impaired systolic function. Diurnal variations in blood pressure are described in the premenopausal years, and cyclic reduction in the blood pressure has been attributed to positive effects of estrogen on mediating arterial vasodilatation; blunting of this latter phenomenon is described after menopause and could contribute to the postmenopausal increase in blood pressure and worsening left ventricular strain. Increases in blood viscosity with decreases in circulating volume and left ventricular size are also mentioned in relation to menopause.[68]

In summary, menopause is associated with increased prevalence and severity of CVD. The androgenic hormonal milieu observed in menopause is associated with worsening of abdominal adiposity accompanied by proatherogenic lipid changes, increases in incidence of insulin resistance, and MetS that may contribute to heart disease. Further studies are warranted to investigate the independent effects of menopause on cardiac function and vasculature independent of weight, lipids, and insulin resistance.

CONCLUSIONS AND PUBLIC HEALTH PERSPECTIVE

Increases in BMI, in measures of central adiposity and a preferential increase in visceral fat, accompany the transgression of reproductive stages toward and into menopause. The incidence of MetS goes up considerably in the aging female population, and the metabolic profile becomes more proatherogenic and proinflammatory. Although the prevalence of hypertension increases with age, many hypertensive postmenopausal women remain underdiagnosed and undertreated.[60] Because CVD is the leading cause of death in women, it is critical from a public health standpoint to identify risk factors and implement strategies to minimize the metabolic detriment that accompanies the menopause transition and menopause.

Identification of risk factors and establishing overall cardiovascular risk in perimenopausal women would help timely implementation of strategies that can mitigate end organ damage and prevent cardiovascular morbidity and mortality in the future. Recognition and treatment of established CVD in perimenopausal and postmenopausal women are critical to the success of secondary preventive strategies.[67] Until recently most of the global cardiovascular risk scores used in women were based on the Framingham study done 40 years ago that used age, hypertension, smoking, diabetes, and hyperlipidemia in calculation of the risk.[69] Cardiovascular risk assessment scores specific for women would be more helpful because 20% of women experience coronary events even in the absence of classic coronary risk factors.[70] Many women with high risk scores based on the Framingham study do not experience cardiovascular-adverse events.[70] The Reynolds Risk Score, a recently developed and validated assessment tool, incorporates measures of HDL-C and high-sensitivity CRP.[71] Body composition and hormonal changes occurring during the menopausal transition may need to be included in future risk calculators to help account for biological differences in heart disease presentation between men and women. The menopause transition should be perceived as a time for more stringent routine health-care assessments, and women in menopausal transition should have regular medical visits with monitoring of BMI, waist circumference, lipid profile, fasting glucose, and blood pressure. Women diagnosed with MetS should be treated aggressively to improve individual metabolic risks in efforts to decrease the overall risk of CVD that is recognized as associated with a diagnosis of MetS.

Exercise has been shown to attenuate the deteriorating metabolic profile of menopause. Cuff et al demonstrated mitigation in insulin resistance and a decrease in abdominal adiposity in postmenopausal diabetic women with exercise.[72] Bergström et al demonstrated a statistically significant decrease in waist circumference with moderate physical exercise program in postmenopausal women.[73] Weight loss through dietary intervention and exercise should be a mainstay of management women across all reproductive stages, in those who manifest features of MetS or who exhibit a high CVD risk profile, as well as in healthy women going through menopause to minimize the metabolic detriment of menopause. The Women's Healthy Lifestyle Project followed 535 healthy premenopausal women across the menopausal transition for 5 years. Half of the women were treated with a lifestyle intervention that included a 1300 kcal/day diet (25% total fat, 7% saturated fat, 100 mg dietary cholesterol) with a moderate increase in physical activity equivalent of brisk walking 10 to 15 miles per week and weight loss goal of

5 to 15 lb depending on the baseline BMI. Women in the intervention group maintained their weight compared with the control group that gained an average of 2.5 kg consistent with age-dependent weight gain observed in other studies.[11,13,21] Lifestyle intervention significantly reduced increases in LDL-C, triglycerides, blood glucose, and insulin occurring during the menopausal transition that were observed in the control group.[74,75] Likewise, the Diabetes Prevention Program Study demonstrated a significant decrease in the incidence of diabetes and MetS with a similar lifestyle intervention regimen.[76] Medical treatment of elevated blood pressure, glucose, and hyperlipidemia in addition to lifestyle changes are needed to combat heart disease in at-risk perimenopausal and menopausal women.[39] Educational efforts should focus on lifestyle changes including a healthy diet with moderately decreased calorie intake, regular moderate aerobic exercise, smoking cessation, and decreased alcohol consumption that decrease the weight gain, the central obesity, and the accompanying deterioration in metabolic profile observed during and beyond the menopausal transition. Weight maintenance and weight reduction would benefit overall health and likely decrease the cardiovascular morbidity and mortality observed in postmenopausal women.

REFERENCES

1. Abdel-Halim RE. Obesity: 1000 years ago. Lancet 2005; 366(9481):204
2. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321(10):641–646
3. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease. The Framingham Study. Ann Intern Med 1978;89(2):157–161
4. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986;111(2):383–390
5. Kannel WB, Levy D. Menopause, hormones, and cardiovascular vulnerability in women. Arch Intern Med 2004;164(5): 479–481
6. Guthrie JR, Taffe JR, Lehert P, Burger HG, Dennerstein L. Association between hormonal changes at menopause and the risk of a coronary event: a longitudinal study. Menopause 2004;11(3):315–322
7. Matthews KA, Santoro N, Lasley B, et al. Relation of cardiovascular risk factors in women approaching menopause to menstrual cycle characteristics and reproductive hormones in the follicular and luteal phases. J Clin Endocrinol Metab 2006;91(5):1789–1795
8. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health across the Nation. Arch Intern Med 2008; 168(14):1568–1575
9. Janssen I. Influence of age on the relation between waist circumference and cardiometabolic risk markers. Nutr Metab Cardiovasc Dis 2009;19(3):163–169
10. Pasquali R, Casimirri F, Labate AM, et al; The VMH Collaborative Group. Body weight, fat distribution and the menopausal status in women. Int J Obes Relat Metab Disord 1994;18(9):614–621
11. Matthews KA, Abrams B, Crawford S, et al. Body mass index in mid-life women: relative influence of menopause, hormone use, and ethnicity. Int J Obes Relat Metab Disord 2001;25(6):863–873
12. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health across the Nation. Am J Epidemiol 2009;169(11):1352–1361
13. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga PL. Weight gain at the time of menopause. Arch Intern Med 1991;151(1):97–102
14. Sherman BM, West JH, Korenman SG. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. J Clin Endocrinol Metab 1976;42(4):629–636
15. Weinberg ME, Manson JE, Buring JE, et al. Low sex hormone-binding globulin is associated with the metabolic syndrome in postmenopausal women. Metabolism 2006; 55(11):1473–1480
16. Chahal HS, Drake WM. The endocrine system and ageing. J Pathol 2007;211(2):173–180
17. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Fertil Steril 2001;76(5):874–878
18. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295(13):1549–1555
19. Espeland MA, Stefanick ML, Kritz-Silverstein D, et al; Postmenopausal Estrogen-Progestin Interventions Study Investigators. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. J Clin Endocrinol Metab 1997;82(5):1549–1556
20. Kritz-Silverstein D, Barrett-Connor E. Long-term postmenopausal hormone use, obesity, and fat distribution in older women. JAMA 1996;275(1):46–49
21. Sternfeld B, Wang H, Quesenberry CP Jr, et al. Physical activity and changes in weight and waist circumference in midlife women: findings from the Study of Women's Health across the Nation. Am J Epidemiol 2004;160(9):912–922
22. Macdonald HM, New SA, Campbell MK, Reid DM. Longitudinal changes in weight in perimenopausal and early postmenopausal women: effects of dietary energy intake, energy expenditure, dietary calcium intake and hormone replacement therapy. Int J Obes Relat Metab Disord 2003; 27(6):669–676
23. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond) 2008; 32(6):949–958
24. Lovejoy JC. Weight gain in women at midlife: the influence of menopause. Obesity Management 2009;5:52–56
25. Polotsky AJ, Santoro N. Menopause and cardiovascular disease: endogenous reproductive hormone exposure affects risk factors. Menopause Manage 2007;16(2):21–25
26. Shimokata H, Andres R, Coon PJ, Elahi D, Muller DC, Tobin JD. Studies in the distribution of body fat. II. Longitudinal effects of change in weight. Int J Obes 1989; 13(4):455–464

27. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr 1992;55(5):950–954
28. Franklin RM, Ploutz-Snyder L, Kanaley JA. Longitudinal changes in abdominal fat distribution with menopause. Metabolism 2009;58(3):311–315
29. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res 2005;96(9):939–949
30. Winzer C, Wagner O, Festa A, et al. Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. Diabetes Care 2004; 27(7):1721–1727
31. Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2007;27(11):2276–2283
32. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab 2009;94(4):1104–1110
33. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab 2007;92(2): 399–404
34. Kahn R, Buse J, Ferrannini E, Stern M; American Diabetes Association; European Association for the Study of Diabetes. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28(9):2289–2304
35. Nilsson PM. Cardiovascular risk in the metabolic syndrome: fact or fiction? Curr Cardiol Rep 2007;9(6):479–485
36. Alberti KGMMF, Eckel RHMDF, Grundy SMMDPF et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120(16):1640–1645
37. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. Diabetes Care 2004;27(10):2444–2449
38. Bauersachs R, Lindhoff-Last E. Anticoagulation of pregnant women with mechanical heart valves using low-molecular-weight heparin. Arch Intern Med 2003;163(22):2788–2789
39. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88(6): 2404–2411
40. Frayn KN. Visceral fat and insulin resistance—causative or correlative? Br J Nutr 2000;83(Suppl 1):S71–S77
41. Weinberg ME, Manson JE, Buring JE, et al. Low sex hormone-binding globulin is associated with the metabolic syndrome in postmenopausal women. Metabolism 2006; 55(11):1473–1480
42. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health across the Nation. Arch Intern Med 2008; 168(14):1568–1575
43. Torréns JI, Sutton-Tyrrell K, Zhao X, et al. Relative androgen excess during the menopausal transition predicts incident metabolic syndrome in midlife women: study of Women's Health across the Nation. Menopause 2009;16(2): 257–264
44. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990–1998. Diabetes Care 2000;23(9):1278–1283
45a. Department of Health ad Human Services Centers for Disease Control and Prevention. National diabetes fact sheet 2007. Available at: http://www.cdc.gov/diabetes/pubs/factsheet07.htm. Accessed July 22, 2010
45b. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2009;32(Suppl 1): 62–67
46. Sites CK, Calles-Escandón J, Brochu M, Butterfield M, Ashikaga T, Poehlman ET. Relation of regional fat distribution to insulin sensitivity in postmenopausal women. Fertil Steril 2000;73(1):61–65
47. Campbell AJ, Busby WJ, Horwath CC, Robertson MC. Relation of age, exercise, anthropometric measurements, and diet with glucose and insulin levels in a population aged 70 years and over. Am J Epidemiol 1993;138(9):688–696
48. Szmuilowicz ED, Stuenkel CA, Seely EW. Influence of menopause on diabetes and diabetes risk. Nat Rev Endocrinol 2009;5(10):553–558
49. Muscelli E, Kozàkovà M, Flyvbjerg A, et al; RISC investigators. The effect of menopause on carotid artery remodeling, insulin sensitivity, and plasma adiponectin in healthy women. Am J Hypertens 2009;22(4):364–370
50. Soriguer F, Morcillo S, Hernando V, et al. Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: longitudinal study. Menopause 2009;16(4):817–821
51. Dorman JS, Steenkiste AR, Foley TP, et al; Familial Autoimmune and Diabetes (FAD) Study. Menopause in type 1 diabetic women: is it premature? Diabetes 2001; 50(8):1857–1862
52. Malacara JM, Huerta R, Rivera B, Esparza S, Fajardo ME. Menopause in normal and uncomplicated NIDDM women: physical and emotional symptoms and hormone profile. Maturitas 1997;28(1):35–45
53. López-López R, Huerta R, Malacara JM. Age at menopause in women with type 2 diabetes mellitus. Menopause 1999;6(2):174–178
54. Verhaeghe J. Menopause care for obese and diabetic women. Facts Views Vision Obgyn 2009;1(2):142–152
55. Korytkowski MT, Krug EI, Daly MA, Deriso L, Wilson JW, Winters SJ. Does androgen excess contribute to the cardiovascular risk profile in postmenopausal women with type 2 diabetes? Metabolism 2005;54(12):1626–1631
56. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000; 21(6):697–738
57. Middelberg RP, Spector TD, Swaminathan R, Snieder H. Genetic and environmental influences on lipids, lipoproteins, and apolipoproteins: effects of menopause. Arterioscler Thromb Vasc Biol 2002;22(7):1142–1147
58. Mackey RH, Kuller LH, Sutton-Tyrrell K, Evans RW, Holubkov R, Matthews KA. Lipoprotein subclasses and coronary artery calcium in postmenopausal women from the healthy women study. Am J Cardiol 2002;90(8A, 8A): 71i–76i

59. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3(2):213–219
60. Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension: an age-old debate. Hypertension 2008; 51(4):952–959
61. Stampfer MJ, Colditz GA, Willett WC. Menopause and heart disease. A review. Ann N Y Acad Sci 1990;592:193–203, discussion 257–262
62. Izumi Y, Matsumoto K, Ozawa Y, et al. Effect of age at menopause on blood pressure in postmenopausal women. Am J Hypertens 2007;20(10):1045–1050
63. Barton M, Meyer MR. Postmenopausal hypertension: mechanisms and therapy. Hypertension 2009;54(1): 11–18
64. Kannel WB. Metabolic risk factors for coronary heart disease in women: perspective from the Framingham Study. Am Heart J 1987;114(2):413–419
65. Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Porcellati C. Early cardiac changes after menopause. Hypertension 1998;32(4):764–769
66. Byington RP, Davis BR, Plehn JF, et al. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. Circulation 2001;103(3):387–392
67. Collins P, Rosano G, Casey C, et al. Management of cardiovascular risk in the peri-menopausal woman: a consensus statement of European cardiologists and gynaecologists. Eur Heart J 2007;28(16):2028–2040
68. Guthrie JR, Taffe JR, Lehert P, Burger HG, Dennerstein L. Association between hormonal changes at menopause and the risk of a coronary event: a longitudinal study. Menopause 2004;11(3):315–322
69. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease—six year follow-up experience. The Framingham Study. Ann Intern Med 1961;55:33–50
70. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290(7):898–904
71. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007;297(6):611–619
72. Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. Diabetes Care 2003;26(11):2977–2982
73. Bergström I, Lombardo C, Brinck J. Physical training decreases waist circumference in postmenopausal borderline overweight women. Acta Obstet Gynecol Scand 2009;88(3): 308–313
74. Kuller LH, Simkin-Silverman LR, Wing RR, Meilahn EN, Ives DG. Women's Healthy Lifestyle Project: a randomized clinical trial: results at 54 months. Circulation 2001;103(1): 32–37
75. Simkin-Silverman LR, Wing RR, Boraz MA, Kuller LH. Lifestyle intervention can prevent weight gain during menopause: results from a 5-year randomized clinical trial. Ann Behav Med 2003;26(3):212–220
76. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393–403
77. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults–the evidence report. Obes Res 1998; 6(Suppl 2):51S–209S

Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults

THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE EXPERT PANEL ON THE IDENTIFICATION, EVALUATION, AND TREATMENT OF OVERWEIGHT AND OBESITY IN ADULTS[1]

An estimated 97 million adults in the United States are overweight or obese, a condition that substantially raises their risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Obese individuals may also suffer from social stigmatization and discrimination. As a major contributor to preventive death in the United States today, overweight and obesity pose a major public health challenge.

Overweight is here defined as a body mass index (BMI, calculated as kg/m^2) of 25 to 29.9 and obesity as a BMI of ≥ 30. However, overweight and obesity are not mutually exclusive, since obese persons are also overweight. A BMI of 30 is about 30 lb overweight and equivalent to 221 lb in a 6'0"person and to 186 lb in one 5'6". The number of overweight and obese men and women has risen since 1960; in the last decade the percentage of people in these categories has increased to 54.9% of adults age 20 years or older. Overweight and obesity are especially evident in some minority groups, as well as in those with lower incomes and less education.

Obesity is a complex multifactorial chronic disease that develops from an interaction of genotype and the environment. Our understanding of how and why obesity develops is incomplete, but involves the integration of social, behavioral, cultural, physiological, metabolic, and genetic factors.

While there is agreement about the health risks of overweight and obesity, there is less agreement about their management. Some have argued against treating obesity because of the difficulty in maintaining long-term weight loss and of potentially negative consequences of the frequently seen pattern of weight cycling in obese subjects. Others argue that the potential hazards of treatment do not outweigh the known hazards of being obese. The intent of these guidelines is to provide evidence for the effects of treatment on overweight and obesity. The guidelines focus on the role of the primary care practitioner in treating overweight and obesity.

EVIDENCE-BASED GUIDELINES

To evaluate published information and to determine the most appropriate treatment strategies that would constitute evidence-based clinical guidelines on overweight and obesity for physicians and associated health professionals in clinical practice, health care policy makers, and clinical investigators, the National Heart, Lung, and Blood Institute's Obesity Education Initiative in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases convened the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults in May 1995. The guidelines are based on a systematic review of the published scientific literature found in MEDLINE from January 1980 to September 1997 of topics identified by the panel as key to extrapolating the data related to the obesity evidence model. Evidence from approximately 394 randomized controlled trials (RCTs) was considered by the panel.

The panel is comprised of 24 members, 8 ex-officio members, and a methodologist consultant. Areas of expertise contributed to by panel members included primary care, epidemiology, clinical nutrition, exercise physiology, psychology, physiology, and pulmonary disease. There were 5 meetings of the full panel and 2 additional meetings of the executive committee comprised of the panel chair and 4 panel members.

The San Antonio Cochrane Center assisted the panel in the literature abstraction and in organizing the data into appropriate evidence tables. The center pretested and used a standardized 25-page form or "Critical Review Status Sheet" for the literature abstraction. Ultimately, 236 RCT articles were abstracted and the data were then compiled into individual evidence tables developed for each RCT. The data from these RCTs served as the basis for many of the recommendations contained in the guidelines.

[1]A complete list of the members of the Expert Panel is found at the end of this article.

Editor's note: The Executive Summary was first published in the *Archives of Internal Medicine*, September 28, 1998. Reprinted with permission.

Table 1
Evidence categories

Evidence category	Sources of evidence	Definition
A	Randomized controlled trials (RCTs) (rich body of data)	Evidence is from endpoints of well-designed RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A therefore requires substantial numbers of studies involving substantial numbers of participants.
B	RCTs (limited body of data)	Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
C	Nonrandomized trials; observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment	Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature and/or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the above-listed criteria. This category is used only in cases where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C).

The panel determined the criteria for deciding on the appropriateness of an article. At a minimum, studies had to have a time frame from start to finish of at least 4 months. The only exceptions were a few 3-month studies related to dietary therapy and pharmacotherapy. To consider the question of long-term maintenance, studies with outcome data provided at approximately 1 year or longer were examined. Excluded were studies in which self-reported weights by subjects were the only indicators used to measure weight loss. No exclusions of studies were made by study size. The panel weighed the evidence based on a thorough examination of the threshold or magnitude of the treatment effect. Each evidence statement (other than those with no available evidence) and each recommendation is categorized by a level of evidence which ranges from A to D. Table 1 summarizes the categories of evidence by their source and provides a definition for each category.

■ **Who is at risk?** All overweight and obese adults (age 18 years of age or older) with a BMI of ≥ 25 are considered at risk for developing associated morbidities or diseases such as hypertension, high blood cholesterol, type 2 diabetes, coronary heart disease, and other diseases. Individuals with a BMI of 25 to 29.9 are considered overweight, while individuals with a BMI ≥ 30 are considered obese. Treatment of overweight is recommended only when patients have 2 or more risk factors. It should focus on altering dietary and physical activity patterns to prevent development of obesity and to produce moderate weight loss. Treatment of obesity should focus on producing substantial weight loss over a prolonged period. The presence of comorbidities in overweight and obese patients should be considered when deciding on treatment options.

■ **Why treat overweight and obesity?** Obesity is clearly associated with increased morbidity and mortality. There is strong evidence that weight loss in overweight and obese individuals reduces risk factors for diabetes and cardiovascular disease (CVD). Strong evidence exists that weight loss reduces blood pressure in both overweight hypertensive and nonhypertensive individuals; reduces serum triglycerides and increases high-density lipoprotein (HDL)-cholesterol; and generally produces some reduction in total serum cholesterol and low-density lipoprotein (LDL)-cholesterol. Weight loss reduces blood glucose levels in overweight and obese persons without diabetes; and weight loss also reduces blood glucose levels and HbA_{1c} in some patients with type 2 diabetes. Although there have been no prospective trials to show changes in mortality with weight loss in obese patients, reductions in risk factors would suggest that development of type 2 diabetes and CVD would be reduced with weight loss.

■ **What treatments are effective?** A variety of effective options exist for the management of overweight and obese patients, including dietary therapy approaches such as low-calorie diets and lower-fat diets; altering physical activity patterns; behavior therapy techniques; pharmacotherapy[2]; surgery; and combinations of these techniques.

CLINICAL GUIDELINES

Treatment of the overweight or obese patient is a 2-step process: assessment and treatment management. Assessment requires determination of the degree of overweight and overall risk status. Management includes both reducing excess body weight and instituting other measures to control accompanying risk factors.

Assessment

When assessing a patient for risk status and as a candidate for weight loss therapy, consider the patient's BMI, waist circumference, and overall risk status. Consideration also needs to be given to the patient's motivation to lose weight.

[2]As of September 1997, the Food and Drug Administration (FDA) requested the voluntary withdrawal from the market of dexfenfluramine and fenfluramine due to a reported association between valvular heart disease and the use of dexfenfluramine or fenfluramine alone or combined with phentermine. The use of these drugs for weight reduction, therefore, is not recommended in this report. Sibutramine is approved by FDA for long-term use. It has limited but definite effects on weight loss and can facilitate weight loss maintenance. (Note: FDA approval for orlistat is pending a resolution of labeling issues and results of Phase III trials.)

Table 2
Classification of overweight and obesity by body mass index[a] (BMI)

	Obesity class	BMI
Underweight		<18.5
Normal		18.5-24.9
Overweight		25.0-29.9
Obesity	I	30.0-34.9
	II	35.0-39.9
Extreme obesity	III	≥40

[a]Calculated as kg/m^2.

■ **Body mass index** The BMI, which describes relative weight for height, is significantly correlated with total body fat content. The BMI should be used to assess overweight and obesity and to monitor changes in body weight. In addition, measurements of body weight alone can be used to determine efficacy of weight loss therapy. BMI is calculated as weight (kg)/height squared (m^2). To estimate BMI using pounds and inches, use: [weight (pounds)/height (inches)^2] × 703. Weight classifications by BMI, selected for use in this report, are shown in Table 2. A conversion table of heights and weights resulting in selected BMI units is provided in Table 3.

■ **Waist circumference** The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and morbidity. Waist circumference is positively correlated with abdominal fat content. It provides a clinically acceptable measurement for assessing a patient's abdominal fat content before and during weight loss treatment. The following sex-specific cutoffs can be used to identify increased relative risk for the development of obesity-associated risk factors in most adults with a BMI of 25 to 34.9:

High Risk
Men > 102 cm (> 40 in)
Women > 88 cm (> 35 in)

These waist circumference cutpoints lose their incremental predictive power in patients with a BMI ≥35 because these patients will exceed the cutpoints noted above. Table 4 adds the disease risk of increased abdominal fat to the disease risk of BMI. These categories denote *relative* risk, not *absolute* risk; that is, relative to risk at normal weight. They should not be equated with absolute risk, which is determined by a summation of risk factors. They relate to the need to institute weight loss therapy and do not directly define the required intensity of modification of risk factors associated with obesity.

■ **Risk Status** Assessment of a patient's absolute risk status requires examination for the presence of:

Disease conditions: established coronary heart disease (CHD), other atherosclerotic diseases, type 2 diabetes, and sleep apnea; patients with these conditions are classified as being at very high risk for disease complications and mortality.

Other obesity-associated diseases: gynecological abnormalities, osteoarthritis, gallstones and their complications, and stress incontinence.

Cardiovascular risk factors: cigarette smoking, hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or the patient is taking antihypertensive agents), high-risk LDL-cholesterol (≥160 mg/dL[3]), low HDL-cholesterol (< 35 mg/dL), impaired fasting glucose (fasting plasma glucose of 110 to 125 mg/dL[4]), family history of premature CHD (definite myocardial infarction or sudden death at or before 55 years of age in father or other male first-degree relative, or at or before 65 years of age in mother or other female first-degree relative), and age (men ≥ 45 years and women ≥ 55 years or postmenopausal). Patients can be classified as being at high absolute risk if they have 3 of the aforementioned risk factors. Patients at high absolute risk usually require clinical management of risk factors to reduce risk.

Patients who are overweight or obese often have other cardiovascular risk factors. Methods for estimating *absolute risk* status for developing cardiovascular disease based on these risk factors are described in detail in the National Cholesterol Education Program's *Second Report of the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (NCEP's ATP II) and the *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI). The intensity of intervention for cholesterol disorders or hypertension is adjusted according to the absolute risk status estimated from multiple risk correlates. These include both the risk factors listed above and evidence of end-organ damage present in hypertensive patients. Approaches to therapy for cholesterol disorders and hypertension are described in ATP II and JNC VI, respectively. In overweight patients, control of cardiovascular risk factors deserves equal emphasis as weight reduction therapy. Reduction of risk factors will reduce the risk for CVD whether or not efforts at weight loss are successful.

Other risk factors: physical inactivity and high serum triglycerides (> 200 mg/dL[5]). When these factors are present, patients can be considered to have incremental absolute risk above that estimated from the preceding risk factors. Quantitative risk contribution is not available for these risk factors, but their presence heightens the need for weight reduction in obese persons.

■ **Patient Motivation** When assessing the patient's motivation to enter weight loss therapy, the following factors should be evaluated: reasons and motivation for weight reduction; previous history of successful and unsuccessful weight loss attempts; family, friends, and worksite support; the patient's understanding of the causes of obesity and how obesity contributes to several diseases; attitude toward physical activity; capacity to engage in physical activity; time availability for weight loss intervention; and financial considerations. In addition to considering these issues, the health care practitioner needs to heighten a patient's motivation for weight loss and prepare the patient for treatment. This can be done by enumerating the dangers accompanying persistent obesity and by describing the strategy for clinically assisted weight reduction.

[3]To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. Cholesterol of 5.00 mmol/L = 193 mg/dL.
[4]To convert mmol/L glucose to mg/dL, multiply mmol/L by 18.0. To convert mg/dL glucose to mmol/L, multiply mg/dL by 0.0555. Glucose of 6.0 mmol/L = 108 mg/dL.
[5]To convert mmol/L triglyceride to mg/dL, multiply mmol/L by 88.6. To convert mg/dL triglyceride to mmol/L, multiply mg/dL by 0.0113. Triglyceride of 1.80 mmolL = 159 mg/dL.

Table 3
Selected body mass index[a] (BMI) units categorized by inches (cm) and pounds (kg)

Height in inches (cm)	Body weight in lb (kg)		
	BMI 25	BMI 27	BMI 30
58 (147.32)	119 (53.98)	129 (58.51)	143 (64.86)
59 (149.86)	124 (56.25)	133 (60.33)	148 (67.13)
60 (152.40)	128 (58.06)	138 (62.60)	153 (69.40)
61 (154.94)	132 (59.87)	143 (64.86)	158 (71.67)
62 (157.48)	136 (61.69)	147 (66.68)	164 (74.39)
63 (160.02)	141 (63.96)	152 (68.95)	169 (76.66)
64 (162.56)	145 (65.77)	157 (71.21)	174 (78.93)
65 (165.10)	150 (68.04)	162 (73.48)	180 (81.65)
66 (167.64)	155 (70.31)	167 (75.75)	186 (84.37)
67 (170.18)	159 (72.12)	172 (78.02)	191 (86.64)
68 (172.72)	164 (74.39)	177 (80.29)	197 (89.36)
69 (175.26)	169 (76.66)	182 (82.56)	203 (92.08)
70 (177.80)	174 (78.93)	188 (85.28)	207 (93.89)
71 (180.34)	179 (81.19)	193 (87.54)	215 (97.52)
72 (182.88)	184 (83.46)	199 (90.27)	221 (100.25)
73 (185.42)	189 (85.73)	204 (92.53)	227 (102.97)
74 (187.96)	194 (88.00)	210 (95.26)	233 (105.69)
75 (190.50)	200 (90.72)	216 (97.98)	240 (108.86)
76 (193.04)	205 (92.99)	221 (100.25)	246 (111.58)

[a]Metric conversion formula for BMI=weight (kg)/height $(m)^2$. For example, a person who weighs 78.93 kg and is 177-cm tall has a BMI of 25: weight (78.93 kg)/height $(1.77\ m)^2=25$.

Nonmetric conversion formula for BMI=weight (lb)/height $(in)^2 \times 703$. For example, a person who weighs 164 lb and is 68 in (or 5 ft 8 in) tall has a BMI of 25: weight (164 lb)/height $(68\ in)^2 \times 703=25$.

Table 4
Classification of overweight and obesity by body mass index[a] (BMI), waist circumference, and associated disease risk

	BMI	Obesity class	Disease risk[b] relative to normal weight and waist circumference	
			Men≤102 cm (≤40 in) or Women ≤88 cm (≤35 in)	Men>102 cm (>40 in) or Women >88 cm (>35 in)
Underweight	<18.5		. . .	. . .
Normal[c]	18.5-24.9		. . .	. . .
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very high
	35.0-39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

[a]Calculated as kg/m^2.
[b]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.
[c]Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Reviewing the patients' past attempts at weight loss and explaining how the new treatment plan will be different can encourage patients and provide hope for successful weight loss.

Evaluation and Treatment

The general goals of weight loss and management are: (1) at a minimum, to prevent further weight gain; (2) to reduce body weight; and (3) to maintain a lower body weight over the long term. The overall strategy for the evaluation and treatment of overweight and obese patients is presented in the Treatment Algorithm (see the Figure). This algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not include any initial overall assessment for cardiovascular risk factors or diseases that are indicated. Each step (designated by a box) in this process is described.

Box 1: Patient Encounter A patient encounter is defined as any interaction between a health care practitioner (generally a physician, nurse practitioner or physician's assistant) that provides the opportunity to assess a patient's weight status and provide advice, counseling, or treatment.

Box 2: History of Overweight or Recorded BMI ≥ 25 The practitioner must seek to determine whether the patient has ever been overweight. While a technical definition is provided, a simple question such as "Have you ever been overweight?" will accomplish the same goal. Questions directed towards weight history, dietary habits, physical activities, and medications may provide useful information about the origins of obesity in particular patients.

Box 3: BMI Measured in Past 2 Years For those who have not been overweight, a 2-year interval is appropriate for the reassessment of BMI. While this time span is not evidence-based, it is believed to be a reasonable compromise between the need to identify weight gain at an early stage and the need to limit the time, effort, and cost of repeated measurements.

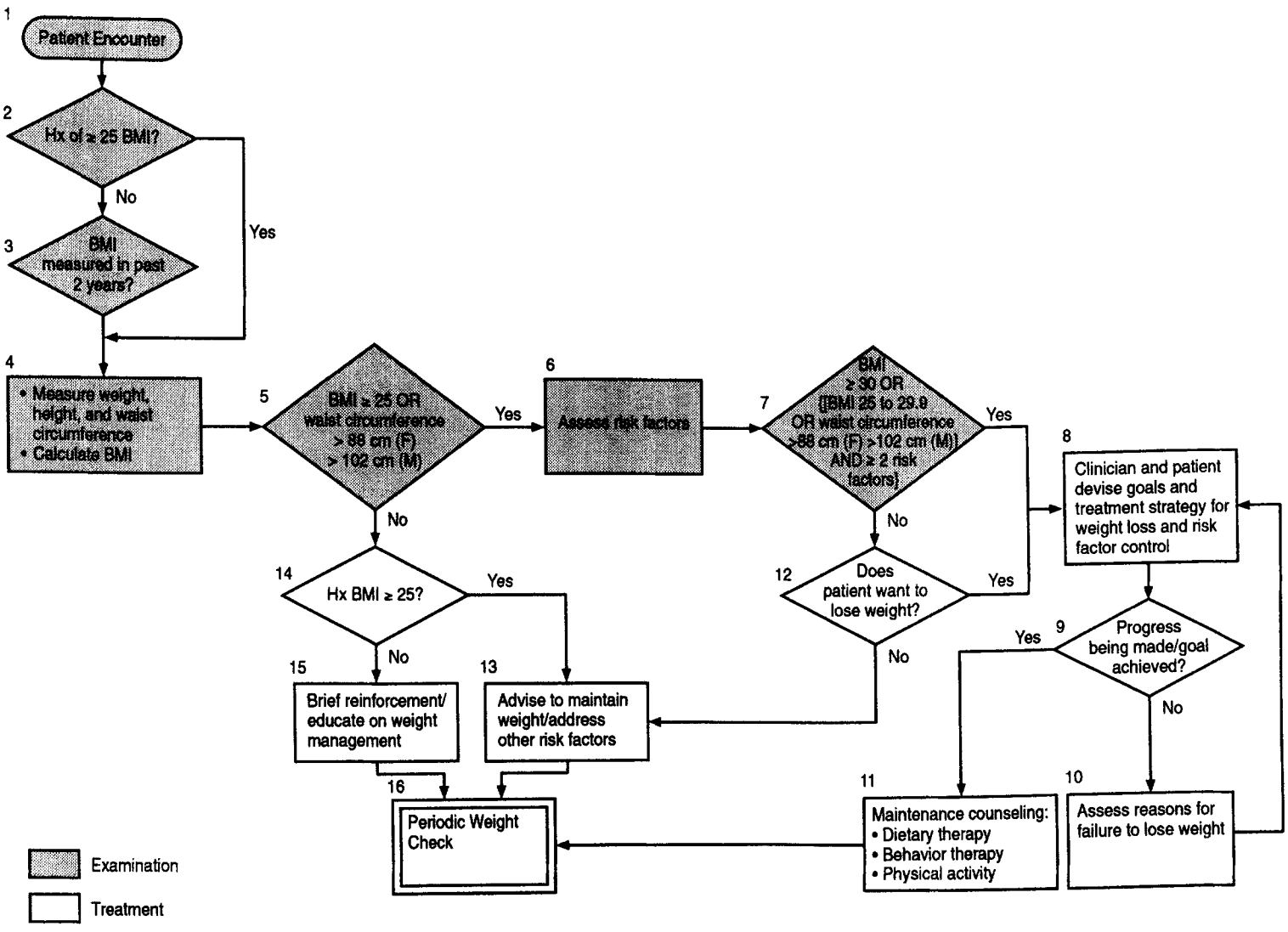
Box 4: Measure Weight, Height, Waist Circumference; Calculate BMI Weight must be measured so that the BMI can be calculated. Most charts are based on weights obtained with the patient wearing undergarments and no shoes. BMI can be manually calculated (kg/[height in meters]^2), but is more easily obtained from a nomogram. Waist circumference is important because evidence suggests that abdominal fat is a particularly strong determinant of cardiovascular risk in those with a BMI of 25 to 34.9. Increased waist circumference can also be a marker of increased risk even in persons of normal weight. A nutrition assessment will also help to assess the diet and physical activity habits of overweight patients.

Box 5: BMI ≥ 25, OR Waist Circumference > 88 (F) or > 102 cm (M) These cutpoints divide overweight from normal weight and are consistent with other national and international guidelines. The relation between weight and mortality is J-shaped, and evidence suggests that the right side of the "J" begins to rise at a BMI of 25. Waist circumference is incorporated as an "or" factor because some patients with BMI lower than 25 will have disproportionate abdominal fat, and this increases their cardiovascular risk despite their low BMI. These abdominal circumference values are not necessary for patients with a BMI ≥ 35.

Box 6: Assess Risk Factors Risk assessment for CVD and diabetes in a person with evident obesity will include special considerations for the history, physical examination, and laboratory examination. Of greatest urgency is the need to detect existing CVD or end-organ damage. Since the major risk of obesity is indirect (obesity elicits or aggravates hypertension, dyslipidemias, and diabetes, which cause cardiovascular complications), the management of obesity should be implemented in the context of these other risk factors. While there is no direct evidence demonstrating that addressing risk factors increases weight loss, treating the risk factors through weight loss is a recommended strategy.

Box 7: BMI ≥ 30, OR ([BMI 25 to 29.9 OR Waist Circumference > 88 or > 102 cm] AND ≥ 2 risk factors) The panel recommends that all patients meeting these criteria attempt to lose weight. However, it is important to ask the patient whether or not they want to lose weight. Those with BMIs between 25 and 29.9 who have one or no risk factors should work on maintaining their current weight rather than embark on a weight reduction program. The panel recognizes that the decision to lose weight must be made in the context of other risk factors (eg, quitting smoking is more important than losing weight) and patient preferences.

Box 8: Clinician and Patient Devise Goals The decision to lose weight must be made jointly between the clinician and patient. Patient involvement and investment is crucial to success. The patient may choose not to lose weight but rather to



Treatment Algorithm. Note: The algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not include any initial overall assessment for cardiovascular risk factors or diseases that are indicated.

prevent further weight gain as a goal. The panel recommends as an initial goal the loss of 10% of baseline weight, to be lost at a rate of 1 to 2 lb/week, establishing an energy deficit of 500 to 1,000 kcal/day. For individuals who are overweight, a deficit of 300 to 500 kcal/day may be more appropriate, providing a weight loss of about ½ lb/week. Also, there is evidence that an average of 8% of weight can be lost in a 6-month period. Since the observed average 8% weight loss includes people who do not lose weight, an individual goal of 10%t is reasonable. After 6 months, most patients will equilibrate (caloric intake balancing energy expenditure) and will require adjustment of energy balance if they are to lose more weight.

The 3 major components of weight loss therapy are dietary therapy, increased physical activity, and behavior therapy. Lifestyle therapy should be tried for at least 6 months before considering pharmacotherapy. In addition, pharmacotherapy should be considered as an adjunct to lifestyle therapy in patients with a BMI ≥ 30 with no concomitant obesity-related risk factors or diseases, or for patients with a BMI ≥ 27 with concomitant obesity-related risk factors or diseases. The risk factors or diseases considered important enough to warrant pharmacotherapy at a BMI of 27 to 29.9 are hypertension, dyslipidemia, CHD, type 2 diabetes, and sleep apnea. However, sibutramine, the only FDA-approved drug for long-term use, should not be used in patients with a history of hypertension, CHD, congestive heart failure, arrhythmias, or history of stroke. Certain patients may be candidates for weight loss surgery. Each component of weight loss therapy can be introduced briefly. The selection of weight loss methods should be made in the context of patient preferences, analysis of past failed attempts, and consideration of the available resources.

Box 9: Progress Being Made/Goal Achieved During the acute weight loss period and at 6-month and 1-year follow-up visits, the patients should be weighed, BMI calculated, and progress assessed. If at any time it appears that the program is failing, a reassessment should take place to determine the reasons (see Box 10). If pharmacotherapy is being used, appropriate monitoring for side effects is recommended. If a patient can achieve the recommended 10% reduction in body weight in 6 months to 1 year, this change in weight can be considered good progress. The patient can then enter the phase of weight maintenance and long-term monitoring. It is important for the practitioner to recognize that some persons are more apt to lose or gain weight on a given regimen and that this phenomenon cannot always be attributed to degree of compliance. However, if significant obesity remains and absolute risk from obesity-associated risk factors remains high, at some point an effort should be made to reinstitute weight loss therapy to achieve further weight reduction. Once a limit of weight loss has been obtained, the practitioner is responsible for long-term monitoring of risk factors and for encouraging the patient to maintain a reduced weight level.

Box 10: Assess Reasons for Failure to Lose Weight If a patient fails to achieve the recommended 10% reduction in body weight in 6 months or 1 year, a reevaluation is required. A critical question is whether the level of motivation is high enough to continue clinical therapy. If motivation is high, revise the goals and strategies (see Box 8). If motivation is not high, clinical therapy should be discontinued, but the patient should be encouraged to embark on efforts to lose weight or to at least avoid further weight gain. Even if weight loss therapy is stopped, risk factor management must be continued.

Failure to achieve weight loss should prompt the practitioner to investigate energy intake (dietary recall including alcohol intake, daily intake logs), energy expenditure (physical activity diary), attendance at behavior therapy group meetings, recent negative life events, family and societal pressures, or evidence of detrimental psychiatric problems (depression, binge eating disorder). If attempts to lose weight have failed, and the BMI is ≥ 40, surgical therapy should be considered.

Box 11: Maintenance Counseling Evidence suggests that over 80% of persons who lose weight will gradually regain it. Patients who continue on weight maintenance programs have a greater chance of keeping weight off. Maintenance consists of continued contact with the health care practitioner for continued education, support, and medical monitoring.

Box 12: Does the Patient Want to Lose Weight? All patients who are overweight (BMI 25 to 29.9), or do not have a high waist circumference, and have few (0 to 1) cardiovascular risk factors and do not want to lose weight, should be counseled regarding the need to keep their weight at or below its present level. Patients who wish to lose weight should be guided per Boxes 8 and 9. The justification for offering these overweight patients the option of maintaining (rather than losing) weight is that their health risk, while higher than that of persons with a BMI < 25, is only moderately increased.

Box 13: Advise to Maintain Weight/Address Other Risk Factors Those who have a history of overweight and are now at appropriate weight, and those who are overweight and not obese but wish to focus on maintenance of their current weight, should be provided with counseling and advice so that their weight does not increase. An increase in weight increases their health risk and should be prevented. The physician should actively promote prevention strategies including enhanced attention by the patient to diet, physical activity, and behavior therapy. For addressing other risk factors, see Box 6, because even if weight loss cannot be addressed, other risk factors should be covered.

Box 14: History of BMI ≥25 This box differentiates those who are not overweight now and never have been from those with a history of overweight; see Box 2.

Box 15: Brief Reinforcement Those who are not overweight and never have been should be advised of the importance of staying in this category.

Box 16: Periodic Weight, BMI, and Waist Circumference Check Patients should receive periodic monitoring of their weight, BMI, and waist circumference. Patients who are not overweight or have no history of overweight should be screened for weight gain every 2 years. This time span is a reasonable compromise between the need to identify weight gain at an early stage and the need to limit the time, effort, and the cost of repeated measurements.

GOALS OF WEIGHT LOSS AND MANAGEMENT

The *initial goal* of weight loss therapy is to reduce body weight by approximately 10% from baseline. If this goal is achieved, further weight loss can be attempted, if indicated through further evaluation.

A *reasonable time line* for a 10% reduction in body weight is 6 months of therapy. For overweight patients with BMIs in the typical range of 27 to 35, a decrease of 300 to 500 kcal/day will result in weight losses of about ½ to 1 lb/week and a 10% loss in 6 months. For more severely obese patients with BMIs > 35, deficits of up to 500 to 1,000 kcal/day will lead to weight

losses of about 1 to 2 lb/week and a 10% weight loss in 6 months. Weight loss at the rate of 1 to 2 lb/week (calorie deficit of 500 to 1,000 kcal/day) occurs safely for up to 6 months. After 6 months, the rate of weight loss usually declines and weight plateaus because of a lesser energy expenditure at the lower weight.

Experience reveals that lost weight usually will be regained unless a weight maintenance program consisting of dietary therapy, physical activity, and behavior therapy is continued indefinitely.

After 6 months of weight loss treatment, efforts to maintain weight loss should be put in place. If more weight loss is needed, another attempt at weight reduction can be made. This will require further adjustment of the diet and physical activity prescriptions.

For patients unable to achieve significant weight reduction, prevention of further weight gain is an important goal; such patients may also need to participate in a weight management program.

STRATEGIES FOR WEIGHT LOSS AND WEIGHT MAINTENANCE

Dietary Therapy

A diet that is individually planned and takes into account the patient's overweight status in order to help create a deficit of 500 to 1,000 kcal/day should be an integral part of any weight loss program. A patient may choose a diet of 1,000 to 1,200 kcal/day for women and 1,200 to 1,500 kcal/day for men. Depending on the patient's risk status, the low-calorie diet (LCD) recommended should be consistent with the NCEP's Step I or Step II Diet. Besides decreasing saturated fat, total fats should be 30% or less of total calories. Reducing the percentage of dietary fat alone will not produce weight loss unless total calories are also reduced. Isocaloric replacement of fat with carbohydrates will reduce the percentage of calories from fat but will not cause weight loss. Reducing dietary fat, along with reducing dietary carbohydrates, usually will be needed to produce the caloric deficit needed for an acceptable weight loss. When fat intake is reduced, priority should be given to reducing saturated fat to enhance lowering of LDL-cholesterol levels. Frequent contacts with the practitioner during dietary therapy help to promote weight loss and weight maintenance at a lower weight.

Physical Activity

An increase in physical activity is an important component of weight loss therapy, although it will not lead to substantially greater weight loss over 6 months. Most weight loss occurs because of decreased caloric intake. Sustained physical activity is most helpful in the prevention of weight regain. In addition, it has a benefit in reducing cardiovascular and diabetes risks beyond that produced by weight reduction alone. For most obese patients, exercise should be initiated slowly, and the intensity should be increased gradually. The exercise can be done all at one time or intermittently over the day. Initial activities may be walking or swimming at a slow pace. The patient can start by walking 30 minutes for 3 days a week and can build to 45 minutes of more intense walking at least 5 days a week. With this regimen, an additional expenditure of 100 to 200 kcal per day can be achieved. All adults should set a long-term goal to accumulate at least 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week. This regimen can be adapted to other forms of physical activity, but walking is particularly attractive because of its safety and accessibility. Patients should be encouraged to increase "every day" activities such as taking the stairs instead of the elevator. With time, depending on progress and functional capacity, the patient may engage in more strenuous activities. Competitive sports, such as tennis and volleyball, can provide an enjoyable form of exercise for many, but care must be taken to avoid injury. Reducing sedentary time is another strategy to increase activity by undertaking frequent, less strenuous activities.

Behavior Therapy

Strategies, based on learning principles such as reinforcement, that provide tools for overcoming barriers to compliance with dietary therapy and/or increased physical activity are helpful in achieving weight loss and weight maintenance. Specific strategies include self-monitoring of both eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring, and social support.

Combined Therapy

A combined intervention of behavior therapy, an LCD, and increased physical activity provides the most successful therapy for weight loss and weight maintenance. This type of intervention should be maintained for at least 6 months before considering pharmacotherapy.

Pharmacotherapy

In carefully selected patients, appropriate drugs can augment LCDs, physical activity, and behavior therapy in weight loss. Weight loss drugs that have been approved by the FDA for long-term use can be useful adjuncts to dietary therapy and physical activity for some patients with a BMI of ≥ 30 with no concomitant risk factors or diseases, and for patients with a BMI of ≥ 27 with concomitant risk factors or diseases. The risk factors and diseases considered important enough to warrant pharmacotherapy at a BMI of 27 to 29.9 are hypertension, dyslipidemia, CHD, type 2 diabetes, and sleep apnea. Continual assessment by the physician of drug therapy for efficacy and safety is necessary.

At the present time, sibutramine is available for long-term use. (Note: FDA approval of orlistat is pending a resolution of labeling issues and results of Phase III trials.) It enhances weight loss modestly and can help facilitate weight loss maintenance. Potential side effects with drugs, nonetheless, must be kept in mind. With sibutramine, increases in blood pressure and heart rate may occur. Sibutramine should not be used in patients with a history of hypertension, CHD, congestive heart failure, arrhythmias, or history of stroke. With orlistat, fat soluble vitamins may require replacement because of partial malabsorption. All patients should be carefully monitored for these side effects.

Weight Loss Surgery

Weight loss surgery is one option for weight reduction in a limited number of patients with clinically severe obesity, ie, BMIs ≥ 40 or ≥ 35 with comorbid conditions. Weight loss surgery should be reserved for patients in whom efforts at medical therapy have failed and who are suffering from the complications of extreme obesity. Gastrointestinal surgery (gastric restriction [Vertical gastric banding] or gastric bypass [Roux-en Y]) is an intervention weight loss option for motivated subjects with acceptable operative risks. An integrated program must be in place to provide guidance on diet, physical activity, and behavioral and social support both prior to and after the surgery.

ADAPT WEIGHT LOSS PROGRAMS TO MEET THE NEEDS OF DIVERSE PATIENTS

Standard treatment approaches for overweight and obesity must be tailored to the needs of various patients or patient

groups. Large individual variation exists within any social or cultural group; furthermore, substantial overlap among subcultures occurs within the larger society. There is, therefore, no "cookbook" or standardized set of rules to optimize weight reduction with a given type of patient. However, to be more culturally sensitive and to incorporate patient characteristics in obesity treatment programs: consider and adapt the setting and staffing for the program; consider how the obesity treatment program integrates into other aspects of patient health care and self care; and expect and allow for program modifications based on patient responses and preferences.

The issues of weight reduction after age 65 involve such questions as: does weight loss reduce risk factors in older adults; are there risks associated with obesity treatment that are unique to older adults; and does weight reduction prolong the lives of older adults? Although there is less certainty about the importance of treating overweight at older ages than at younger ages, a clinical decision to forego obesity treatment in older adults should be guided by an evaluation of the potential benefit of weight reduction and the reduction of risk for future cardiovascular events.

In the obese patient who smokes, smoking cessation is a major goal of risk factor management. Many well-documented health benefits accompany smoking cessation, but a major obstacle to cessation has been the attendant weight gain observed in about 80% of quitters. This weight gain averages 4.5 to 7 lb, but in 13% of women and 10% of men, weight gain exceeds 28 lb. Weight gain that accompanies smoking cessation has been quite resistant to most dietary, behavioral, or physical activity interventions.

The weight gained with smoking cessation is less likely to produce negative health consequences than would continued smoking. For this reason, smoking cessation should be strongly advocated regardless of baseline weight. Prevention of weight gain through diet and physical activity should be stressed. For practical reasons, it may be prudent to avoid initiating smoking cessation and weight loss therapy simultaneously. If weight gain ensues after smoking cessation, it should be managed vigorously according to the guidelines outlined in this report. Although short-term weight gain is a common side effect of smoking cessation, this gain does not rule out the possibility of long-term weight control.

SUMMARY OF EVIDENCE-BASED RECOMMENDATIONS

Advantages of Weight Loss

The recommendation to treat overweight and obesity is based not only on evidence that relates obesity to increased mortality but also on RCT evidence that weight loss reduces risk factors for disease. Thus, weight loss may not only help control diseases worsened by obesity, it may also help decrease the likelihood of developing these diseases. The panel reviewed RCT evidence to determine the effect of weight loss on blood pressure and hypertension, serum/plasma lipid concentrations, and fasting blood glucose and fasting insulin. Recommendations focusing on these conditions underscore the advantages of weight loss.

Blood pressure To evaluate the effect of weight loss on blood pressure and hypertension, 76 articles reporting RCTs were considered for inclusion in these guidelines. Of the 45 accepted articles, 35 were lifestyle trials and 10 were pharmacotherapy trials. There is strong and consistent evidence from these lifestyle trials in both overweight hypertensive and nonhypertensive patients that weight loss produced by lifestyle modifications reduces blood pressure levels. Limited evidence exists that decreases in abdominal fat will reduce blood pressure in overweight nonhypertensive individuals, although not independent of weight loss, and there is considerable evidence that increased aerobic activity to increase cardiorespiratory fitness reduces blood pressure (independent of weight loss). There is also suggestive evidence from randomized trials that weight loss produced by most weight loss medications, except for sibutramine, in combination with adjuvant lifestyle modifications will be accompanied by reductions in blood pressure. Based on a review of the evidence from the 45 RCT blood pressure articles, the panel makes the following recommendation:

Weight loss is recommended to lower elevated blood pressure in overweight and obese persons with high blood pressure. Evidence Category A.

Serum/plasma lipids Sixty-five RCT articles were evaluated for the effect of weight loss on serum/plasma concentrations of total cholesterol, LDL-cholesterol, very low-density lipoprotein (VLDL)-cholesterol, triglycerides, and HDL-cholesterol. Studies were conducted on individuals over a range of obesity and lipid levels. Of the 22 articles accepted for inclusion in these guidelines, 14 RCT articles examined lifestyle trials while the remaining 8 articles reviewed pharmacotherapy trials. There is strong evidence from the 14 lifestyle trials that weight loss produced by lifestyle modifications in overweight individuals is accompanied by reductions in serum triglycerides and by increases in HDL-cholesterol. Weight loss generally produces some reductions in serum total cholesterol and LDL-cholesterol. Limited evidence exists that a decrease in abdominal fat correlates with improvement in lipids, although the effect may not be independent of weight loss, and there is strong evidence that increased aerobic activity to increase cardiorespiratory fitness favorably affects blood lipids, particularly if accompanied by weight loss. There is suggestive evidence from the 8 randomized pharmacotherapy trials that weight loss produced by weight loss medications and adjuvant lifestyle modifications, including caloric restriction and physical activity, does not result in consistent effects on blood lipids. The following recommendation is based on the review of the data in these 22 RCT articles:

Weight loss is recommended to lower elevated levels of total cholesterol, LDL-cholesterol, and triglycerides, and to raise low levels of HDL-cholesterol in overweight and obese persons with dyslipidemia. Evidence Category A.

Blood Glucose To evaluate the effect of weight loss on fasting blood glucose and fasting insulin levels, 49 RCT articles were reviewed for inclusion in these guidelines. Of the 17 RCT articles accepted, 9 RCT articles examined lifestyle therapy trials and 8 RCT articles considered the effects of pharmacotherapy on weight loss and subsequent changes in blood glucose. There is strong evidence from the 9 lifestyle therapy trials that weight loss produced by lifestyle modification reduces blood glucose levels in overweight and obese persons without diabetes, and weight loss reduces blood glucose levels and HbA_{1c} in some patients with type 2 diabetes. There is

suggestive evidence that decreases in abdominal fat will improve glucose tolerance in overweight individuals with impaired glucose tolerance, although not independent of weight loss; and there is limited evidence that increased cardiorespiratory fitness improves glucose tolerance in overweight individuals with impaired glucose tolerance or diabetes, although not independent of weight loss. In addition, there is suggestive evidence from randomized trials that weight loss induced by weight loss medications does not appear to improve blood glucose levels any better than weight loss through lifestyle therapy in overweight persons both with and without type 2 diabetes. Based on a full review of the data in these 17 RCT articles, the panel makes the following recommendation:

Weight loss is recommended to lower elevated blood glucose levels in overweight and obese persons with type 2 diabetes. Evidence Category A.

Measurement of Degree of Overweight and Obesity

Patients should have their BMI and levels of abdominal fat measured not only for the initial assessment of the degree of overweight and obesity, but also as a guide to the efficacy of weight loss treatment. Although there are no RCTs that review measurements of overweight and obesity, the panel determined that this aspect of patient care warranted further consideration and that this guidance was deemed valuable. Therefore, the following four recommendations that are included in the Treatment Guidelines were based on nonrandomized studies as well as clinical experience.

BMI to assess overweight and obesity There are a number of accurate methods to assess body fat (eg, total body water, total body potassium, bioelectrical impedance, and dual-energy x-ray absorptiometry), but no trial data exist to indicate that one measure of fatness is better than any other for following overweight and obese patients during treatment. Since measuring body fat by these techniques is often expensive and is not readily available, a more practical approach for the clinical setting is the measurement of BMI; epidemiological and observational studies have shown that BMI provides an acceptable approximation of total body fat for the majority of patients. Because there are no published studies that compare the effectiveness of different measures for evaluating changes in body fat during weight reduction, the panel bases its recommendation on expert judgment from clinical experience:

Practitioners should use the BMI to assess overweight and obesity. Body weight alone can be used to follow weight loss, and to determine efficacy of therapy. Evidence Category C.

BMI to estimate relative risk In epidemiological studies, BMI is the favored measure of excess weight to estimate relative risk of disease. BMI correlates both with morbidity and mortality; the relative risk for CVD risk factors and CVD incidence increases in a graded fashion with increasing BMI in all population groups. Moreover, calculating BMI is simple, rapid, and inexpensive, and can be applied generally to adults. The panel, therefore, makes this recommendation:

The BMI should be used to classify overweight and obesity and to estimate relative risk of disease compared to normal weight. Evidence Category C.

Assessing abdominal fat For the most effective technique for assessing abdominal fat content, the panel considered measures of waist circumference, waist-to-hip ratio (WHR), magnetic resonance imaging (MRI), and computed tomography. Evidence from epidemiological studies shows waist circumference to be a better marker of abdominal fat content than WHR, and that it is the most practical anthropometric measurement for assessing a patient's abdominal fat content before and during weight loss treatment. Computed tomography and MRI are both more accurate but impractical for routine clinical use. Based on evidence that waist circumference is a better marker than WHR—and taking into account that the MRI and computed tomography techniques are expensive and not readily available for clinical practice—the panel makes the following recommendation:

The waist circumference should be used to assess abdominal fat content. Evidence Category C.

Sex-specific measurements Evidence from epidemiological studies indicates that a high waist circumference is associated with an increased risk for type 2 diabetes, dyslipidemia, hypertension, and CVD. Therefore, the panel judged that sex-specific cutoffs for waist circumference can be used to identify increased risk associated with abdominal fat in adults with a BMI in the range of 25 to 34.9. These cutpoints can be applied to all adult ethnic or racial groups. On the other hand, if a patient is very short, or has a BMI above the 25 to 34.9 range, waist cutpoints used for the general population may not be applicable. Based on the evidence from nonrandomized studies, the panel makes this recommendation:

For adult patients with a BMI of 25 to 34.9, sex-specific waist circumference cutoffs should be used in conjunction with BMI to identify increased disease risks. Evidence Category C.

Goals for Weight Loss

The general goals of weight loss and management are to reduce body weight, to maintain a lower body weight over the long term, and to prevent further weight gain. Evidence indicates that a moderate weight loss can be maintained over time if some form of therapy continues. It is better to maintain a moderate weight loss over a prolonged period than to regain from a marked weight loss.

Initial Goal of Weight Loss from Baseline There is strong and consistent evidence from randomized trials that overweight and obese patients in well-designed programs can achieve a weight loss of as much as 10% of baseline weight. In the diet trials, an average of 8% of baseline weight was lost. Since this average includes persons who did not lose weight, an individualized goal of 10% is reasonable. The panel, therefore, recommends that:

The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. Evidence Category A.

Amount of weight loss Randomized trials suggest that weight loss at the rate of 1 to 2 lb/week (calorie deficit of 500 to 1,000 kcal/day) commonly occurs for up to 6 months.

Weight loss should be about 1 to 2 lb/week for a period of 6 months, with the subsequent strategy based on the amount of weight lost. Evidence Category B.

How to Achieve Weight Loss

The panel reviewed relevant treatment strategies designed for weight loss that can also be used to foster long-term weight control and prevention of weight gain. The consequent recommendations emphasize the potential effectiveness of weight control using multiple interventions and strategies, including dietary therapy, physical activity, behavior therapy, pharmacotherapy, and surgery, as well as combinations of these strategies.

Dietary therapy The panel reviewed 86 RCT articles to determine the effectiveness of diets on weight loss (including LCDs, very low-calorie diets [VLCDs], vegetarian diets, American Heart Association dietary guidelines, the NCEP's Step I diet with caloric restriction, and other low-fat regimens with varying combinations of macronutrients). Of the 86 articles reviewed, 48 were accepted for inclusion in these guidelines. These RCTs indicate strong and consistent evidence that an average weight loss of 8% of initial body weight can be obtained over 3 to 12 months with an LCD and that this weight loss effects a decrease in abdominal fat; and, although lower-fat diets without targeted caloric reduction help promote weight loss by producing a reduced caloric intake, lower-fat diets with targeted caloric reduction promote greater weight loss than lower-fat diets alone. Further, VLCDs produce greater initial weight losses than LCDs (over the long term of >1 year, weight loss is not different than that of the LCDs). In addition, randomized trials suggest that no improvement in cardiorespiratory fitness as measured by Vo_2max appears to occur in obese adults who lose weight on LCDs alone without physical activity. The following recommendations are based on the evidence extracted from the 48 accepted articles:

LCDs are recommended for weight loss in overweight and obese persons. Evidence Category A. Reducing fat as part of an LCD is a practical way to reduce calories. Evidence Category A.

Reducing dietary fat alone without reducing calories is not sufficient for weight loss. However, reducing dietary fat, along with reducing dietary carbohydrates, can facilitate caloric reduction. Evidence Category A.

A diet that is individually planned to help create a deficit of 500 to 1,000 kcal/day should be an integral part of any program aimed at achieving a weight loss of 1 to 2 lb/week. Evidence Category A.

Physical Activity

Effects of physical activity on weight loss Twenty-three RCT articles were reviewed to determine the effect of physical activity on weight loss, abdominal fat (measured by waist circumference), and changes in cardiorespiratory fitness (Vo_2 max). Thirteen of these articles were accepted for inclusion in these guidelines. A review of these articles reveals strong evidence that physical activity alone, ie, aerobic exercise, in obese adults results in modest weight loss and that physical activity in overweight and obese adults increases cardiorespiratory fitness, independent of weight loss. Randomized trials suggest that increased physical activity in overweight and obese adults reduces abdominal fat only modestly or not at all, and that regular physical activity independently reduces the risk for CVD. The panel's recommendation on physical activity is based on the evidence from these 13 articles:

Physical activity is recommended as part of a comprehensive weight loss therapy and weight control program because it: (1) modestly contributes to weight loss in overweight and obese adults (Evidence Category A), (2) may decrease abdominal fat (Evidence Category B), (3) increases cardiorespiratory fitness (Evidence Category A), and (4) may help with maintenance of weight loss (Evidence Category C).

Physical activity should be an integral part of weight loss therapy and weight maintenance. Initially, moderate levels of physical activity for 30 to 45 minutes, 3 to 5 days a week, should be encouraged. All adults should set a long-term goal to accumulate at least 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week. Evidence Category B.

Effects of Physical Activity and Diet on Weight Loss (Combined Therapy) Twenty-three RCT articles were reviewed to determine the effects on body weight of a combination of a reduced-calorie diet with increased physical activity. Fifteen of these articles were accepted for inclusion in the guidelines. These articles contain strong evidence that the combination of a reduced-calorie diet and increased physical activity produces greater weight loss than diet alone or physical activity alone, and that the combination of diet and physical activity improves cardiorespiratory fitness as measured by Vo_2max in overweight and obese adults when compared to diet alone. The combined effect of a reduced calorie diet and increased physical activity seemingly produced modestly greater reductions in abdominal fat than either diet alone or physical activity alone, although it has not been shown to be independent of weight loss. The panel's following recommendations are based on the evidence from these articles:

The combination of a reduced calorie diet and increased physical activity is recommended since it produces weight loss that may also result in decreases in abdominal fat and increases in cardiorespiratory fitness. Evidence Category A.

Behavior Therapy

Thirty-six RCTs were reviewed to evaluate whether behavior therapy provides additional benefit beyond other weight loss approaches, as well as to compare various behavioral techniques. Of the 36 RCTs reviewed, 22 were accepted. These RCTs strongly indicate that behavioral strategies to reinforce changes in diet and physical activity in obese adults produce weight loss in the range of 10% over 4 months to 1 year. In addition, no one behavior therapy appeared superior to any other in its effect on weight loss; multimodal strategies appear to work best and those interventions with the greatest intensity appear to be associated with the greatest weight loss. Long-term follow-up of patients undergoing behavior therapy shows a return to baseline weight for the great majority of subjects in the absence of continued behavior intervention. Randomized trials suggest that behavior therapy, when used in combination with other weight loss approaches, provides additional benefits in assisting patients to lose weight short-term, ie, 1 year (no additional benefits are found at 3 to 5 years). The panel found little evidence on the effect of behavior therapy on cardiorespiratory fitness. Evidence from these articles provided the basis for the following recommendation:

Behavior therapy is a useful adjunct when incorporated into treatment for weight loss and weight maintenance. Evidence Category B.

There is also suggestive evidence that patient motivation is a key component for success in a weight loss program. The panel, therefore, makes the following recommendation:

Practitioners need to assess the patient's motivation to enter weight loss therapy; assess the readiness of the patient to implement the plan and then take appropriate steps to motivate the patient for treatment. Evidence Category D.

Summary of Lifestyle Therapy

There is strong evidence that combined interventions of an LCD, increased physical activity, and behavior therapy provide the most successful therapy for weight loss and weight maintenance. The panel makes the following recommendation:

Weight loss and weight maintenance therapy should employ the combination of LCDs, increased physical activity, and behavior therapy. Evidence Category A.

Pharmacotherapy

A review of 44 pharmacotherapy RCT articles provides strong evidence that pharmacological therapy (which has generally been studied along with lifestyle modification, including diet and physical activity) using dexfenfluramine, sibutramine, orlistat, or phentermine/fenfluramine results in weight loss in obese adults when used for 6 months to 1 year. Strong evidence also indicates that appropriate weight loss drugs can augment diet, physical activity, and behavior therapy in weight loss. Adverse side effects from the use of weight loss drugs have been observed in patients. As a result of the observed association of valvular heart disease in patients taking fenfluramine and dexfenfluramine alone or in combination, these drugs have been withdrawn from the market. Weight loss drugs approved by the FDA for long-term use may be useful as an adjunct to diet and physical activity for patients with a BMI of ≥30 with no concomitant obesity-related risk factors or diseases, as well as for patients with a BMI of ≥27 with concomitant risk factors or diseases; moreover, using weight loss drugs singly (not in combination) and starting with the lowest effective doses can decrease the likelihood of adverse effects. Based on this evidence, the panel makes the following recommendation:

Weight loss drugs approved by the FDA may be used as part of a comprehensive weight loss program, including dietary therapy and physical activity for patients with a BMI of ≥30 with no concomitant obesity-related risk factors or diseases, and for patients with a BMI of ≥27 with concomitant obesity-related risk factors or diseases. Weight loss drugs should never be used without concomitant lifestyle modifications. Continual assessment of drug therapy for efficacy and safety is necessary. If the drug is efficacious in helping the patient to lose and/or maintain weight loss and there are no serious adverse effects, it can be continued. If not, it should be discontinued. Evidence Category B.

Weight Loss Surgery

The panel reviewed 14 RCTs that examined the effect of surgical procedures on weight loss; 8 were deemed appropriate. All of the studies included individuals who had a BMI of 40 or above, or a BMI of 35 to 40 with comorbidity. These trials provide strong evidence that surgical interventions in adults with clinically severe obesity, ie, BMIs ≥ 40 or ≥ 35 with comorbid conditions, result in substantial weight loss, and suggestive evidence that lifelong medical surveillance after surgery is necessary. Therefore, the panel makes the following recommendation:

Weight loss surgery is an option for carefully selected patients with clinically severe obesity (BMIs ≥ 40 or ≥ 35 with comorbid conditions) when less invasive methods of weight loss have failed and the patient is at high risk for obesity-associated morbidity or mortality. Evidence Category B.

GOALS FOR WEIGHT LOSS MAINTENANCE

Once the goals of weight loss have been successfully achieved, maintenance of a lower body weight becomes the challenge. Whereas studies have shown that weight loss is achievable, it

is difficult to maintain over a long period of time (3 to 5 years). In fact, the majority of persons who lose weight, once dismissed from clinical therapy, frequently regain it—so the challenge to the patient and the practitioner is to maintain the weight loss. Successful weight reduction thus depends on continuing a maintenance program on a long-term basis. In the past, obtaining the goal of weight loss has been considered the end of weight loss therapy. Observation, monitoring, and encouragement of patients who have successfully lost weight should be continued long term. The panel's recommendations on weight loss maintenance are derived from RCT evidence as well as nonrandomized and observational studies.

Weight Maintenance Phase

RCTs from the Behavior Therapy section above suggest that lost weight usually will be regained unless a weight maintenance program consisting of dietary therapy, physical activity, and behavior therapy is continued indefinitely. Drug therapy in addition may be helpful during the weight maintenance phase. The panel also reviewed RCT evidence that considered the rate of weight loss and the role of weight maintenance. These RCTs suggest that after 6 months of weight loss treatment, efforts to maintain weight loss are important. Therefore, the panel recommends the following:

After successful weight loss, the likelihood of weight loss maintenance is enhanced by a program consisting of dietary therapy, physical activity, and behavior therapy, which should be continued indefinitely. Drug therapy can also be used. However, drug safety and efficacy beyond 1 year of total treatment have not been established. Evidence Category B.

A weight maintenance program should be a priority after the initial 6 months of weight loss therapy. Evidence Category B.

Strong evidence indicates that better weight loss results are achieved with dietary therapy when the duration of the intervention is at least 6 months. Suggestive evidence also indicates that during dietary therapy, frequent contacts between professional counselors and patients promote weight loss and maintenance. Therefore, the panel recommends the following:

The literature suggests that weight loss and weight maintenance therapies that provide a greater frequency of contacts between the patient and the practitioner and are provided over the long term should be utilized whenever possible. This can lead to more successful weight loss and weight maintenance. Evidence Category C.

SPECIAL TREATMENT GROUPS

The needs of special patient groups must be addressed when considering treatment options for overweight and obesity. The guidelines focus on three such groups including smokers, older adults, and diverse patient populations.

Smokers

Cigarette smoking is a major risk factor for cardiopulmonary disease. Because of its attendant high risk, smoking cessation is a major goal of risk-factor management. This aim is especially important in the overweight or obese patient, who usually carries excess risk from obesity-associated risk factors. Thus, smoking cessation in these patients becomes a high priority for risk reduction. Smoking and obesity together apparently compound cardiovascular risk, but fear of weight gain upon smoking cessation is an obstacle for many patients. Therefore, the panel recommends that:

All smokers, regardless of their weight status, should quit smoking. Evidence Category A. Prevention of weight gain should be encouraged and if weight gain does occur, it should be treated through dietary therapy, physical activity, and behavior therapy, maintaining the primary emphasis on the importance of abstinence from smoking. Evidence Category C.

Older Adults

The general nutritional safety of weight reduction at older ages is of concern because restrictions on overall food intake due to dieting could result in inadequate intake of protein or essential vitamins or minerals. In addition, involuntary weight loss indicative of occult disease might be mistaken for success in voluntary weight reduction. These concerns can be alleviated by providing proper nutritional counseling and regular body weight monitoring in older persons for whom weight reduction is prescribed. A review of several studies indicates that age alone should not preclude treatment for obesity in adult men and women. In fact, there is evidence from RCTs that weight reduction has similar effects in improving cardiovascular disease risk factors in older and younger adults. Therefore, in the panel's judgment:

A clinical decision to forego obesity treatment in older adults should be guided by an evaluation of the potential benefits of weight reduction for day-to-day functioning and reduction of the risk of future cardiovascular events, as well as the patient's motivation for weight reduction. Care must be taken to ensure that any weight reduction program minimizes the likelihood of adverse effects on bone health or other aspects of nutritional status. Evidence Category D.

Diverse Patient Populations

Standard obesity treatment approaches should be tailored to the needs of various patients or patient groups. It is, however, difficult to determine from the literature how often this occurs, how specific programs and outcomes are influenced by tailoring, and whether it makes weight loss programs more effective. After reviewing 2 RCTs, 4 cross-sectional studies, and 4 intervention studies, as well as additional published literature on treatment approaches with diverse patient populations, the panel recommends the following:

The possibility that a standard approach to weight loss will work differently in diverse patient populations must be considered when setting expectations about treatment outcomes. Evidence Category B.

CLOSING

The clinical guidelines evidence report was reviewed by 115 health experts at major medical and professional societies. It has been endorsed by members of the coordinating committees of the National Cholesterol Education Program and the National High Blood Pressure Education Program, the North American Association for the Study of Obesity, and the National Institute of Diabetes and Digestive and Kidney Diseases National Task Force on the Prevention and Treatment of Obesity. These groups represent 54 professional societies, government agencies, and consumer organizations. An abbreviated practical guide based on the evidence report will be distributed to primary care physicians in the United States as well as to other interested health care practitioners. *The Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report* is published as the September 1998 supplement to the *Journal of Obesity Research* and is available on the NHLBI website—http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm or by writing to the NHLBI Information Center, PO Box 30105, Bethesda, MD 20824-0105.

The following persons served on the National Heart, Lung, and Blood Institute Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

Expert Panel members: *F. Xavier Pi-Sunyer, MD, MPH, Chair of the Expert Panel, chief of Endocrinology, Diabetes, and Nutrition, and director of the Obesity Research Center, St Luke's/Roosevelt Hospital Center, and professor of Medicine, Columbia University College of Physicians and Surgeons, New York, NY; Diane M. Becker, ScD, MPH, director of the Center for Health Promotion and associate professor of the Department of Medicine, The Johns Hopkins University, Baltimore, Md; Claude Bouchard, PhD, professor of Exercise Physiology, Physical Activity Sciences Laboratory, Laval University, Sainte Foy, Quebec, Canada; Richard A. Carleton, MD, professor of Medicine with the Brown University School of Medicine, Pawtucket, RI; Graham A. Colditz, MD, DrPH, associate professor of Medicine with the Harvard Medical School, Channing Laboratory, Boston, Mass; William H. Dietz, MD, PhD, director of the Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Ga; John P. Foreyt, PhD, professor of Medicine and director of the Nutrition Research Clinic, Baylor College of Medicine, Houston, Tex; Robert J. Garrison, PhD, associate professor with the Department of Preventive Medicine, University of Tennessee, Memphis; Scott M. Grundy, MD, PhD, director of the Center for Human Nutrition, University of Texas, Southwestern Medical Center at Dallas; Barbara C. Hansen, PhD, professor of Physiology and director of the Obesity and Diabetes Research Center, University of Maryland School of Medicine, Baltimore; Millicent Higgins, MD, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor; James O. Hill, PhD, associate director of Research for the Center for Human Nutrition, University of Colorado Health Sciences Center, Denver; Barbara V. Howard, PhD, president of Medlantic Research Institute, Washington, DC; Robert J. Kuczmarski, DrPH, RD, nutrition analyst with the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md; Shiriki Kumanyika, PhD, RD, MPH, professor and head, Department of Human Nutrition and Dietetics, The University of Illinois at Chicago; R. Dee Legako, MD, Prime Care Canyon Park Family Physicians, Inc, Edmond, Okla; T. Elaine Prewitt, DrPH, RD, assistant professor, Department of Preventive Medicine and Epidemiology, Loyola University Medical Center, Maywood, Ill; Albert P. Rocchini, MD, chief of Cardiology, University of Michigan Medical Center, Ann Arbor; Philip L. Smith, MD, professor of Medicine, Division of Pulmonary and Critical Care Medicine, The Johns Hopkins Asthma and Allergy Center, Baltimore, Md; Linda G. Snetselaar, PhD, RD, associate professor and head of Preventive Nutrition Education, Department of Preventive Medicine, University of Iowa, Iowa City; James R. Sowers, MD, professor of Medicine and Physiology and director of the Division of Endocrinology, Metabolism, and Hypertension, Wayne State University School of Medicine, University Health Center, Detroit, Mich; Michael Weintraub, MD, director of the Office of Drug Evaluation V, Food and Drug Administration, Rockville, Md; David F. Williamson, PhD, MS, epidemiologist, Division of Diabetes Translation (K-10), Centers for Disease Control and Prevention, Atlanta, Ga; G. Terence Wilson, PhD, Oscar K. Buros Professor of Psychology and director of the Rutgers Eating Disorders Clinic, Piscataway, NJ.*

Ex-officio members: *Clarice D. Brown, MS, project manager, CODA Research, Inc, Silver Spring, Md; Karen A. Donato, MS, RD[6], executive director of Expert Panel and coordinator of the NHLBI Obesity Education Initiative, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Nancy Ernst, PhD, RD[6], nutrition coordinator, Office of the Director, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; D. Robin Hill, PhD[6], social science analyst, Behavioral Medicine Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Michael J. Horan, MD, ScM[6], director of the NIH Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Van S. Hubbard, MD, PhD, director of the NIH Division of Nutrition Research Coordination, and chief of the Nutritional Sciences Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md; James P. Kiley, PhD[6], director of the Airway Biology and Disease Program, Division of Lung Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Eva Obarzanek, PhD, RD, MPH[6], research nutritionist, Prevention Scientific Research Group, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.*

Consultant: *David Schriger, MD, MPH, FACEP, associate professor, UCLA Emergency Medicine Center, University of California at Los Angeles, School of Medicine, Los Angeles.*

San Antonio Cochrane Center: *Elaine Chiquette, PharmD, V.A. Cochrane Center at San Antonio, Audie L. Murphy Memorial Veterans Hospital, San Antonio, Tex.*

[6]Member of the National Heart, Lung, and Blood Institute (NHLBI) Obesity Initiative Task Force.