Obesity and diabetes mellitus have emerged as enormous public health problems not only in the United States but also globally. In fact, globally, obesity is a bigger health crisis than hunger and is the leading cause of death and disabilities around the world with burdens expected to increase in coming years. In the United States, diabetes mellitus affects ~1 in 10 adults, with a majority (90% to 95%) of the cases being type 2 diabetes mellitus (T2D). Although historically thought to
be an adult disease, increases in body weight among children and adolescents have resulted in an increasing number of T2D cases being diagnosed, especially among black (57.8%) and Hispanic youths (46.1%). The associated costs of obesity and diabetes mellitus are steep. Obese individuals pay on average 42% more for healthcare costs than normal-weight individuals, whereas diabetics pay more than twice (2.3) as much as those without diabetes mellitus. In 2008, the annual medical cost of obesity was estimated to be at $147 billion, whereas the total excess costs related to the current prevalence of adolescent overweight and obesity is estimated to be greater at $254 billion. In 2012, diabetes mellitus cost the US taxpayers $245 billion representing a 41% increase from costs in 2007. The economic burden associated with diagnosed diabetes mellitus, undiagnosed diabetes mellitus, gestational diabetes mellitus, and prediabetes is much higher and exceeded $322 billion in 2012, representing a 48% increase from that of 2007.

Both obesity and diabetes mellitus are related multifactorial, complex diseases, and a large proportion of the cases are preventable. Both conditions significantly raise the risk for cardiovascular disease (CVD) and stroke. In fact, the American Heart Association has identified body mass index (BMI) of <25 kg/m² and a fasting plasma glucose concentration of <100 mg/dL as part of a construct of ideal cardiovascular health. A first step in preventing these costly diseases is an understanding of the reasons behind their unprecedented growth in the past few decades. In this article, we present trends in obesity and diabetes mellitus, explore secular changes in the drivers of this epidemic, and finally evaluate the increased risk of CVD associated with these conditions.

Prevalence and Trends in Obesity

Adult Obesity

Obesity has reached epidemic proportions in the United States. Long-standing and well-established surveys, such as the Behavioral Risk Factor Surveillance System, the National Health Interview Survey, and the National Health and Nutrition Examination Survey (NHANES), have documented the dramatic increases in the prevalence of both overweight and obesity from as early as the 1960s. Data from successive cross-sectional and nationally representative NHANES surveys showed a dramatic increase in the prevalence of obesity from 12.8% to 22.5% between 1960 and 1994 (Figure 1). These upward trends continued between the years 1990 to 2000 and 2009 to 2010 when the prevalence of obesity continued to increase by 17.8%. However, since 2003 to 2004, there have been no significant changes in obesity prevalence among US adults suggesting a leveling off of the obesity epidemic. In examining trend data collected between 1970s and 2004, notable differences were observed in annual increase rates. Overweight and obesity increased much faster in adults than in children and in women than in men. When considering obesity alone, black women had the highest rate of increase (an annual average increase of 0.88%) compared with other ethnic groups. If these secular trends continue, it is estimated that, by 2030, 86.3% of adults will be overweight or obese and 51.1% obese and by the year 2048, all American adults would be either overweight or obese. Similar forecasts were predicted using the Behavioral Risk Factor Surveillance System 1990 to 2008 data where a 33% increase in the prevalence of obesity is forecasted for the next 2 decades. The most recent NHANES data indicate that we are well on our way in reaching these predictions. In 2011 to 2012, the age-adjusted combined prevalence of overweight and obesity among adults,

Nonstandard Abbreviations and Acronyms

<table>
<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<td>CHD</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>HFCS</td>
<td>high-fructose corn syrup</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>MHO</td>
<td>metabolically healthy obesity</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>SSBs</td>
<td>sugar-sweetened beverages</td>
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<td>T2D</td>
<td>type 2 diabetes mellitus</td>
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aged ≥20 years, was ≈70% in women, whereas the prevalence of obesity alone was 35%. Like before, the highest prevalence rates for obesity were seen in non-Hispanic black (56.6%) and Hispanic women (44.4%). Similar disparities were seen for other body composition measures from NHANES. Among men, non-Hispanic blacks had a lower percent of body fat (25.8%) than non-Hispanic whites (28.3%) and Mexican Americans (28.9%). Among women, Mexican Americans had higher mean percent body fat (41.6%) than non-Hispanic whites (39.7%) or blacks (40.9%).

Childhood and Adolescent Obesity

In children and adolescents, aged 2 to 19 years, overweight is defined as a BMI between the 85th and 95th percentile of the Centers for Disease Control and Prevention sex-specific BMI for age growth charts released in the year 2000. Obesity is defined as a BMI >95th percentile. On the basis of the Centers for Disease Control and Prevention growth charts, in 2012, ≈17% of children and adolescents were obese and ≈32% were overweight or obese. Although these percentages were not significantly different from 2009 to 2010, trend analyses during a 14-year period showed a significant increase in obesity prevalence from 14.5% in 1999 to 2000 to 17.3% in 2009 to 2010. The greatest increases were seen for class 2 (defined as BMI≥120% of the 95th percentile or BMI≥35; 3.8%–5.9%) and class 3 obesity (defined as BMI≥140% of the 95th percentile or BMI≥40; 0.9%–2.1%; Figure 2). Prevalence rates of overweight, obesity, and class 2 obesity increased significantly among Hispanic females and black males. Although the overall proportion of children with obesity seems to be somewhat leveling off, the rates of severe obesity in children continue to rise, particularly in select ethnic groups. Given the high prevalence rates of childhood obesity and that a significant proportion of obese adolescents grow up to be obese adults, it is imperative to address the obesity epidemic. In fact, in 2010, the White House has rightfully established the first-ever Task Force on Childhood Obesity to end the problem of childhood obesity within a generation, and the 1-year report indicates significant progress in communities across the nation.

Abdominal Obesity

Abdominal obesity is a known risk factor for CVD independent of BMI and is thought to affect disease risk through increased insulin resistance. Waist circumference is a simple and reliable measure of abdominal obesity and is particularly useful as a marker of disease among patients who are categorized as normal or overweight. Using nationally representative data during a 40-year period from NHANES, Okosun et al found that mean waist circumference increased progressively and significantly in the US population from 1960 to 1962 to 1999 to 2000 (9.9 cm in men and 23.2 cm in women). Most importantly, these upward trends were observed in normal weight, overweight, and obese categories. More recent trend data from 1999 to 2012 continued to show concerning upward trends in waist circumference. The age-adjusted mean waist circumference increased from 95.5 cm in 1999 to 2000 to 98.5 cm in 2011 to 2012. Likewise, the overall age-adjusted prevalence of abdominal obesity increased significantly from 46.4% in 1999 to 2000 to 54.2% in 2011 to 2012. Significant increases were found in both sexes, non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. Across all years, prevalence was higher in men than in women (Figure 3A). Non-Hispanic black women (76.9%) and Mexican American women (71.6%) had the highest prevalence rates compared with other ethnic groups (Figure 3B). Of note, increases in waist circumference have occurred independent of changes in BMI, suggesting that abdominal obesity continues its upward trend despite a plateauing in general obesity. Between 1999 to 2000 and 2011 to 2012, independent of BMI, mean waist circumference increased by 0.2 cm in men and 2.4 cm in women. These concerning trend data indicate the need for continuous measurement of waist circumference.
circumference in clinical care and for policies aimed at curbing abdominal obesity.

In children and adolescents, aged 2 to 18 years, the age- and sex-specific 90th percentile values of waist circumference in NHANES III were used as cutoff values to identify those with abdominal obesity.\(^2\) Waist/height ratio of \(\geq 0.5\) is another metric for defining abdominal obesity in youth, aged 6 to 18 years, because this cutoff may overestimate prevalence of abdominal obesity in children aged <6 years.\(^1\) Upward trends in abdominal obesity among children and adolescents were much steeper than those in adults. Between 1988 to 1994 and 1999 to 2004, prevalence of abdominal obesity in children and adolescents increased by 65.4% (from 10.5% to 17.4%) for boys and by 69.4% (from 10.5% to 17.8%) for girls.\(^2\) However, unlike their adult counterparts, abdominal obesity (using waist/height ratio as a metric) remained stable between 2003 to 2004 and 2011 to 2012 in all age, sex, and ethnic groups except for non-Hispanic whites whose prevalence in 2011 to 2012 (35.2%) was significantly lower than that in the years 2003 to 2004 (30.6%; Figure 4A and 4B). Still, prevalence rates in 2011 to 2012 continued to remain high with \(\approx 20\%\) of children and adolescents being abdominally obese using waist circumference as the defining criteria.\(^2\) Mexican American children had consistently higher prevalence rates than other ethnic groups (Figure 4A and 4B).

**Prevalence and Trends in Diabetes Mellitus**

Obesity is a major risk factor for T2D,\(^2\)\(^-\)\(^3\) and trends in prevalence and incidence of T2D have closely mirrored those of obesity. The most recent Centers for Disease Control and Prevention report shows that from 1980 to 2014, the age-adjusted incidence of diagnosed diabetes mellitus nearly doubled from 3.5 to 6.6 per 1000 population. Between 1990 and 2008, rates more than doubled from 3.8 to 8.5 per 1000, and increases were seen in both sexes. However, from 2008 to 2014, age-adjusted incidence significantly declined from 8.5 to 6.6 per 1000. Yet, racial disparities continued to persist such that incidence rates were lower among whites than among blacks or Hispanics. However, from 1997 to 2014, age-adjusted incidence did not significantly change among blacks. Among whites, the numbers significantly increased from 1997 to 2008 and significantly decreased from 2008 to 2014 (Figure 5).\(^3\)

In examining trends in prevalence data from 1988 to 1994 to 2011 to 2012, diabetes mellitus increased significantly over time in all age groups, in both sexes, in every racial/ethnic group, and in all education categories \((P<0.05)\). Increases
were particularly steep among non-Hispanic blacks (16.3% to 20.6%) and Mexican Americans (17.5% to 20.5%). On the contrary, the proportion of people with undiagnosed diabetes mellitus significantly decreased. However, when trends were examined by BMI categories, diabetes mellitus only increased among those who were obese (18.0% to 20.1%), suggesting that much of the increase in the prevalence of diabetes mellitus is because of the increasing prevalence of obesity. In fact, 85.2% of people with T2D are overweight or obese. If present trends continue, it is estimated that 1 in 3 Americans will have diabetes mellitus by 2050. Of particular concern is the high prevalence of diabetes mellitus among Asians who despite having a lower BMI are 30% to 50% more likely to develop diabetes mellitus than their white counterparts. In fact,
prospective data from Kaiser Permanente confirm that Pacific Islanders, South Asians, and Filipinos have the highest prevalence (18.3%, 15.9%, and 16.1%, respectively) of diabetes mellitus among all racial/ethnic groups, including minorities traditionally considered high risk such as black, Latinos, and Native Americans.38

Prediabetes (defined as hemoglobin A1c of 5.7 to <6.5% or fasting glucose 100 to ≤126 mg/dL) is associated with an increased risk of developing T2D. The most recent NHANES 2011 to 2012 survey data indicate that the prevalence of prediabetes was 36.5% among adults, aged ≥20 years. Highest prevalence rates were seen among those aged 65 years (54.6%) and among men (39.1%) compared with women (33.8%). Although no significant differences were seen across race/ethnic groups, non-Hispanic blacks had the highest prevalence numbers (38.8%).32 Between 1999 to 2002 and 2007 to 2010, concomitant with secular changes in diabetes mellitus, prevalence of prediabetes increased from 29.2% to 36.2%,37 highlighting the need for initiating prevention efforts much before the start of the disease process.

In recent years, T2D has emerged as a pediatric problem and accounts for ≤45% of new cases in children and adolescents.38 Among youth aged 10 to 19 years, the overall prevalence of T2D increased by 35% from 0.34 per 1000 in 2001 to 0.46 per 1000 in 2009. As with adults, significant increases were seen in both sexes, and in whites, blacks, and Hispanics. Although no increases were observed among American Indians, prevalence rates were high (1.20 per 1000 in 2009).39 Despite reports of a significant decline in incidence, prevalence rates continue to remain high and policy efforts to curb the diabetes mellitus epidemic should focus on high-risk minority groups and in children and adolescents.

Major Drivers of the Obesity and Diabetes Mellitus Epidemics

Although obesity has traditionally been considered to be a disease of energy imbalance, its pathogenesis is highly complex and involves interplay among genetic, environmental, physiological, behavioral, social, and economic factors. As obesity is a primary risk factor for T2D and because both diseases share common causes, we discuss below how secular changes in the major risk factors contributed to the diabetes epidemic.

Changes in Agricultural Policies

In recent years, changes in US agricultural policies may have played a role in the obesity epidemic. In particular, the US farm bill that was created to subsidize farmers’ income and provide a secure food supply for Americans has morphed into a system that may have directly contributed to the obesity epidemic. For example, 70% to 80% of all farm subsidies are directed toward 8 commodity crops (corn, wheat, cotton, soybeans, rice, barley, oats, and sorghum) and farmers growing specialty crops such as fruits and vegetables are penalized if they receive federal farm payments for these crops. As a result, commodity crops cover ~70% of US cropland, and their abundance has undoubtedly contributed to their low cost. This in turn has changed corporate behavior and consumer consumption patterns toward those that favor the obesity and diabetes mellitus epidemic.50,51 For example, the overabundance of corn has led to the emergence of inexpensive corn-based sweeteners such as high-fructose corn syrup (HFCS) which comprises ~55% fructose and ~45% sucrose (as opposed to table sugar that is 50% sucrose and 50% fructose). In the past few decades, HFCS has slowly replaced sucrose, and it now represents >40% of caloric sweeteners added to foods and is the sole caloric sweetener in carbonated beverages in the United States. Indeed, food consumption data from the United States Department of Agriculture indicate that consumption of HFCS increased >1000% between 1970 and 1990. The average daily consumption of HFCS exceeds 130 kcal for all Americans aged ≥22 years, and the top 20% of consumers of caloric sweeteners ingest 316 kcal from HFCS per day. This increased consumption has mirrored the rapid increase in obesity in the United States.42 Moreover, countries with larger availability of HFCS have a higher prevalence of diabetes mellitus that is independent of obesity.43

Changes in Physical Activity and Sleep

Regular physical activity has been shown to be associated with decreased risk for obesity and other chronic diseases such as CVD and T2D among adults, irrespective of their sex or ethnicity.44 Physical activity trend data have shown marginal improvements during the years. National estimates of leisure-time physical activity during 1990 to 1998 using data obtained from Behavioral Risk Factor Surveillance System show that the proportion of adults reporting no physical activity decreased from 30.7% in 1990 to 28.7% in 1998.46 Although 40% of adults engaged in no leisure-time physical activity in 1997, only 1 in 3 adults reported doing so in 2013 meeting the 2020 target of 32.6%.46 However, the picture remains unpromising for youth. Recent data from national surveys and longitudinal studies indicate that active commuting, high school physical education, and outdoor play (in 3–12-year olds) has declined over time. At the same time, in 2013, more than one-third (41.3%) of children reported spending ≥3 hours per day on an average school day playing video or computer games or used a computer for something that was not school work.47 Increases in time spent watching television (per hour per day) are independently associated with weight gain (0.31 lb).48 Furthermore, use of an electronic device has been known to be disruptive to sleep.49 It is noteworthy that among racial/ethnic minority children, the presence of a bedroom television alone, irrespective of screen time, was associated with shorter sleep from infancy to mid-childhood.50 Sleep, in turn, is a recognized risk factor for T2D. In a meta-analysis of prospective studies representing a total of 18,443 incident T2D cases and 482,502 participants, compared with 7-hour sleep duration per day, each 1-hour shorter sleep duration was associated with a 9% higher risk (95% confidence interval [CI], 4%–15%) for T2D among individuals who slept ≤7 hours per day.51 Most recently, in the Nurses’ Health Study, we observed that compared with women who had no change, decreases in sleep duration were adversely associated with changes in diet quality and physical activity, whereas increases were associated with greater weight gain.52 The low levels of physical activity combined with increases in screen time and the accompanying sleep debt contribute to a higher risk of T2D both directly and indirectly through their effects on body weight.
Changes in Diet and the Food Environment

Diet is an important modifiable risk factor for the prevention of noncommunicable diseases, including obesity, CVD, T2D, and certain cancers. In fact, in the United States, dietary risks account for 26% of deaths and 14% of disability-adjusted life years. Therefore, improvement in diet represents a huge potential for disease reduction either directly or indirectly through improvements in intermediate risk factors, such as blood pressure, fasting glucose, and weight gain. The top dietary risk factors in the United States are diets low in fruits, low in nuts and seeds, high in sodium, high in processed meats, low in vegetables, and high in trans fats. Similar to physical activity, an examination of dietary trends in the past century has shown that the US diet has been slowly improving. Using the Diet Quality Index as an overall metric of diet quality in a nationally representative sample of US adults, Popkin et al found that overall dietary quality improved during a quarter century between 1965 and 1989 to 1991 in all socioeconomic and racial/ethnic groups. More recently, to capture the effect of changes in the food supply, national economy, and food policy on diet quality, Wang et al applied the Alternate Healthy Eating Index-2010 scores for fruit, vegetables, whole grains, nuts and legumes, and long-chain omega-3 fatty acids, the top dietary risk factors in the United States, consumption remained low. In fact, more than half of the gain in diet quality was because of a large reduction in consumption of trans fat which was the result of several policy changes during that period. The authors estimated that improvements in dietary quality between 1999 and 2012 prevented 1.1 million premature deaths and resulted in 12.6% fewer T2D cases and 8.6% fewer CVD cases.

Increasing consumption of fruits and vegetables among the US population is especially important given strong evidence that healthy dietary patterns such as those rich in fruits and vegetables are associated with less long-term weight gain, whereas those characterized by meat and fried foods are associated with greater weight gain. A more recent analysis from US health professionals pointed that 4-year weight change was positively and strongly associated with increased daily servings of potato chips, potatoes, sugar-sweetened beverages (SSBs), unprocessed red meats, and processed meats and inversely associated with intake of vegetables, whole grains, fruits, nuts, and yogurt. In addition, to specific foods, poor carbohydrate quality also seems to influence subsequent weight gain and T2D risk. A considerable amount of attention has focused on added sugar intake primarily because of their caloric contributions to the diet. Data from the Minnesota Heart Survey indicate that added sugar increased by 54% in women between 1980 to 1982 and 2000 to 2002 but declined somewhat in 2007 to 2009 with men following a similar pattern. Concurrent with these increases, BMI increased in both sexes and all age and weight groups. SSBs are the single largest source of added sugar intake and the top source of energy intake in the US diet. A quantitative synthesis of the literature has shown that they are implicated in weight gain in both adults and children. Most recently, we showed that SSB consumption was associated with a higher risk of T2D, independent of its effect on weight gain. Although national trends indicate that consumption of SSBs has reduced in the past decade, youth and adults continue to consume ≈150 kcal/d on average from these beverages. At the same time, consumption of nontraditional SSBs such as sports/energy drinks has increased. These trends can largely be attributed to changes in the food environment. Although diet and physical activity are the primary determinants of obesity, the built environment can determine the level of exposure to these risk factors. Over the past few decades, the food landscape has changed to an obesogenic one with increased availability of energy-dense foods and larger portion sizes. In the past 30 years (between 1977 and 2003–2006), total energy intake increased by 570 kcal/d among US adults, aged ≥2 years. Although the number of daily eating occasions did increase during this period (+1.1), increases in total energy intake were primarily because of increases in portion sizes (15 kcal/d/yr). Similar increases in total energy intake (108 kcal/d) and eating out occasions (+1.2) were noted among children between 1977 and 2005–2010. When examining trends by age and race/ethnicity, Piernas and Popkin found that adolescents were more susceptible to increased portion sizes than younger children. For example, among children aged 7–18 years, higher energy intakes at meals coincided with larger portion sizes of SSBs, French fries, or salty snacks. Adults living in neighborhoods with a high density of fast-food restaurants or food deserts were nearly twice (odds ratio=1.89; 95% CI, 1.01–3.50) as likely to be obese compared with those in areas with a low density of fast-food restaurants. As a result, the White House Task Force on Childhood Obesity Report to the President identified access to healthy, affordable food and reducing food deserts as key to solving the childhood obesity epidemic. To achieve this, the Healthy Food Financing Initiative was launched in 2010 as a key part of the Let’s Move! initiative. With a goal of eliminating food deserts across the country for the next 7 years, this multimillion-dollar initiative aims to expand access to nutritious food in food deserts through the establishment of healthy food retail outlets, including developing and equipping grocery stores, small retailers, corner stores, and farmers markets selling healthy food. Taken together, these data underscore the urgent need for not only improving dietary quality but also changing the food landscape such that making the healthy choice the easy choice. To achieve this, it is crucial for legislators and policy makers to adopt a holistic approach in curbing the existing diabetes epidemic.

Genetics and Gene–Environment Interactions

It is no surprise that obesity has an underlying genetic component. Recent genome-wide association studies have identified 97 BMI-associated loci which together account for 2.7% of
BMI variation. When the cumulative effect of the 97 loci were constructed into a genetic-susceptibility score, there was an average modest increase of 0.1 kg/m² per BMI-increasing allele or 260 to 320 g higher body weight in adults of 160 to 180 cm in height.17 Given these modest increases, variations in these genes alone cannot explain the dramatic increases in obesity prevalence. However, changes in the environment have dictated how disease risk is modified in individuals with different genetic makeup. Accordingly, a bulk of the literature has rightfully focused on gene–environment interactions. For example, in children and adolescents, lower dietary protein intake was found to attenuate the association between fat mass and obesity-associated genotype and adiposity.72 In another recent study, Qi et al.73 documented an interaction between fried food consumption and a genetic risk score based on 32 BMI-associated variants on BMI. Compared with consumption of fried foods less than once per week, the likelihood of obesity per 10 risk alleles was 3-fold (odds ratio=2.72; 95% CI, 2.12–3.48) for fried food consumption ≥4 times a week. Using the same genetic risk score, for every increment of 10 risk alleles, the authors noted a 5-fold higher risk of obesity among those consuming ≥1 servings of SSBs per day.74 These results indicate that unhealthy dietary habits may amplify genetic effects of obesity.

In addition to gene–environment interactions, a substantial body of evidence supports the role of early life exposures to famine,75 maternal malnutrition (including both undernutrition and overweight), maternal smoking status,76 maternal diabetes mellitus before pregnancy,79 gestational diabetes mellitus,80 and maternal obesity81 in influencing offspring’s subsequent risk of obesity and T2D, through mechanisms often referred to as developmental programming. These programs can result in permanent structural changes of various organs and tissues, alter responses to environmental stimuli, and induce epigenetic changes in gene expression.82 The importance of the early life environment in determining obesity and diabetes mellitus risk later in life presents a unique opportunity for intervention and prevention of these costly diseases.83

### Obesity and Cardiovascular Disease

Obesity is a chronic metabolic disease that has a substantial influence on the cardiovascular system.84 Obesity produces a variety of structural and functional adaptations to the cardiovascular system, including lower cardiac output, increased peripheral resistance, increased left ventricular mass, left ventricular wall thickness, internal dimension, and poorer left ventricular systolic function.85 Obesity is also known to influence coronary risk indirectly through its effect on related comorbidities, such as dyslipidemia, hypertension, glucose intolerance, endothelial dysfunction, and inflammation.86,87 National secular trends in CVD risk factors show that although marginal improvements have occurred in all weight groups, risk factors continue to be higher in obese and overweight individuals.88,89 In addition to its indirect effects on CVD risk, early epidemiological evidence from the Framingham Heart Study,90 the Nurses’ Health Study,91 and the Manitoba study92 established obesity as an independent risk factor for CVD.

In the Nurses’ Health Study, obesity was associated with a 2-fold higher risk (relative risk=1.9; 95% CI, 1.3–2.6) of coronary heart disease (CHD) even after adjustment for hypertension, diabetes mellitus, high serum cholesterol, and parental history of myocardial infarction. Such independent associations were observed in both men and women and even with small increases in BMI.94 In a recent systematic review and meta-analysis of 1.2 million participants and 37488 incident CHD cases, each unit increment in BMI (kg/m²) was associated with a higher risk of CHD in women (hazard ratio [HR]=1.04; 95% CI, 1.03–1.05) and men (HR=1.05; 95% CI, 1.04–1.07). Compared with people of a normal weight, obesity was associated with a 60% higher CHD (HR=1.61; 95% CI, 1.42–1.82 in women; HR=1.60; 95% CI, 1.43–1.79 in men).93 From a pathophysiological standpoint, several mechanisms underlie obesity-induced atherosclerosis.94

As reviewed by Lovren et al.,95 these include an adipokine imbalance because of release of proinflammatory adipokines by the visceral adipose tissue, increased oxidative stress because of elevation in free radicals production by the adipose tissue, impaired autophagy, endothelial dysfunction, and activation of adipose tissue macrophages, T cells, and B cells within fat deposits all of which lead to fibrous plaques and lesions. Most recently, gut microbiota found in obese individuals were found to induce low-grade chronic inflammation in the host, thereby suggesting a novel link between the microbiome and atherosclerotic risk.

### Metabolically Healthy Obesity: The Fat-but-Fit Hypothesis

Despite the widely established metabolic effects of obesity at the population level, substantial heterogeneity exists in individual responses to obesity. Findings from epidemiological studies indicate that a subgroup of obese individuals present with a normal metabolic profile, have a substantially lower risk of metabolic complications than other obese individuals, or are not at a higher risk of CVD than their nonobese counterparts. This group has been described as having metabolically healthy obesity (MHO). Although the definition of MHO varies considerably in the literature, accepted criteria include absence of abdominal obesity, absence of metabolic syndrome components, insulin sensitivity, and a high level of cardiorespiratory fitness.95 The proportion of population considered to be MHO varies on the basis the criteria used to define it. National estimates from NHANES indicate that the proportion of US adults who are obese yet have a high cardiovascular fitness level (fat but fit) was 8.9%, whereas another 17.4% were overweight and high fit (defined as age- and sex-specific cutoffs of VO₂ max ≥60th percentile of the Aerobics Center Longitudinal Study).96 Data from the 1999 to 2004 NHANES survey indicate that among US adults, aged ≥20 years, ≈16 million adults (or 23.5%) of normal weight were metabolically abnormal (defined as ≥2 cardiometabolic abnormalities), whereas ≈36 million (51.3%) of overweight adults and ≈20 million (31.7%) obese adults were metabolically healthy.97 Significant ethnic disparities exist in the prevalence of the MHO phenotype such that non-Hispanic blacks (38.9%) have a higher prevalence than non-Hispanic whites (30.8%).97 Nearly one-third of obese children and adolescents...
(BMI > 85th percentile), aged 8 to 17 years, can be classified as MHO. 
Accumulating evidence from prospective cohort studies show that although individuals with the MHO phenotype have a higher risk of incident CVD and T2D compared with those who are normal weight, they are at a lower risk than their metabolically unhealthy counterparts. Still, those with MHO have a greater prevalence of subclinical markers of disease progression, including greater intima–media thickness and coronary artery calcification, than normal weight metabolic healthy individuals. Data from animal and human studies point to several potential mechanisms that underlie the development of the MHO phenotype. These include preserved insulin sensitivity, increased adipogenesis in subcutaneous adipose tissue, lower amount of lipid deposition in the liver, a metabolically beneficial adipokine pattern, and decreased mitochondrial iron transport into the mitochondrial matrix. From a clinical and public health standpoint, it is critical to understand if the MHO phenotype is fixed or if it represents a transient state where the metabolic function of MHO individuals may change into that of a metabolically high-risk individual over time. Prospective data indicate that the MHO is, in fact, a dynamic concept and that over time, a significant proportion progresses into a metabolically at-risk profile and are more likely to develop T2D, CVD, and chronic kidney disease. Because of the transient nature of this subphenotype, prevention strategies that result in moderate weight loss may reverse disease progression from MHO to healthy normal weight. Finally, the existence of MHO phenotype underscores the need for clinicians to consider other metabolic markers in addition to BMI alone. Genetic association studies of large cohorts of individuals with the MHO phenotype and those who are metabolically at risk for obesity could provide insights about protective genes.

**Diabetes Mellitus and Cardiovascular Disease Epidemiological Evidence**

Cardiovascular disease is the leading cause of morbidity and mortality among individuals with T2D accounting for 68% of all diabetic deaths. Between 1997 and 2005, National Health Interview Survey data indicate that the number of people aged ≥ 35 years with diagnosed diabetes mellitus who reported having CVD increased 36%. However, the age-adjusted prevalence decreased 11%, indicating an increase in the number of patients diagnosed with diabetes mellitus that exceeded the increase in CVD prevalence. This excess risk disproportionately affects women such that diabetes mellitus completely eliminates or attenuates the advantages of being female. In 2 quantitative summaries of data from 64 cohort studies, women with diabetes mellitus were found to have a 44% greater risk of incident CHD and 27% greater risk of stroke compared with men with diabetes mellitus. Among women, the risk of incident CHD events associated with diabetes mellitus was 2.82 (95% CI, 2.35–3.38), whereas the corresponding risk estimates were 2.16 (95% CI, 1.82–2.56) in men. For stroke associated with diabetes mellitus, the pooled maximum-adjusted relative risk was 2.28 (95% CI, 1.93–2.69) in women and 1.83 (1.60–2.08) in men. Diabetes mellitus also raises the risk of other vascular end points. Evidence from case–control studies and prospective data indicate that diabetes mellitus is associated with a higher risk of venous thromboembolism (pooled HR = 1.35; 95% CI, 1.17–1.55) and sudden cardiac death (HR = 2.18; 95% CI, 1.89–2.52) with risk estimates being similar in men and women. In a meta-analysis of 7 prospective studies comprising >1.6 million participants, diabetes mellitus was associated with a 24% higher risk of atrial fibrillation (95% CI, 6% to 44%) and the population attributable fraction of atrial fibrillation caused by diabetes mellitus was 2.5%. In the Emerging Risk Factors Collaboration, diabetes mellitus was associated with >2-fold risk (HR = 2.32; 95% CI, 2.11–2.56) of death from vascular causes. However, rates of diabetes mellitus–related complications have substantially declined in the past 2 decades (between 1990 and 2010) with acute myocardial infarctions and stroke declining by more than half. Still, the burden of diabetes mellitus continues to be enormous because of its high prevalence.

**Lifestyle and Dietary Determinants of Cardiovascular Disease Among Those With Type 2 Diabetes Mellitus**

Despite advances in pharmacotherapy, diet, and lifestyle remaining the cornerstone in preventing cardiovascular complications among those with T2D. A recent meta-analysis of 16 randomized controlled trials found that lifestyle interventions (such as increased physical activity, reduced caloric intake, dietary education, and counseling and education on treatment adherence or disease monitoring) had favorable effects on various CVD risk factors. The standardized difference in means of change from baseline significantly favored the intervention for BMI (−0.29; 95% CI, −0.52 to −0.06), hemoglobin A1c (−0.37; 95% CI, −0.59 to −0.14), systolic blood pressure (−0.16; 95% CI, −0.29 to −0.03), and diastolic blood pressure (−0.27; 95% CI, −0.41 to −0.12). However, no differences between the intervention and control groups in high-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentrations were documented. In another meta-analysis of 20 randomized controlled trials, walking as a form of physical activity was found to significantly decrease hemoglobin A1c by 0.50% (95% CI, −0.78% to −0.21%), BMI by 0.91 kg/m² (95% CI, −1.22 to −0.59), and diastolic blood pressure by 1.97 mm Hg (−3.94 to −0.0). However, like before, no effects were noted for systolic blood pressure, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol. Taken together, these quantitative summaries suggest that interventions that focus on weight reduction and improvements in physical activity have beneficial effects on glycemic control and improve the cardiometabolic profile. In fact, in the landmark Look AHEAD (Action for Health in Diabetes) trial, an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity produced greater reductions in hemoglobin A1c and improvements in fitness and all CVD risk factors, except for low-density lipoprotein cholesterol among overweight or obese adults with T2D. Despite these improvements, a median follow-up of 9.6 years, the intervention did not significantly reduce the rate of CVD events, the primary outcome of the trial. On the contrary, in the Prevención con Dieta Mediterránea (PREDIMED) trial, a Mediterranean diet supplemented with extravirgin olive oil...
Reduced the incidence of major CVD events by 31% (95% CI, 3%–50%) among those with diabetes mellitus. Similarly, in the Da Qing Diabetes Prevention Study, a 6-year lifestyle intervention (of diet and exercise) lowered CVD mortality by 41% (HR=0.59; 95% CI, 0.36–0.96) after 23-year follow-up among Chinese adults with impaired glucose tolerance. Altogether, these results suggest that even short-term lifestyle changes have long-term consequences in the prevention of chronic disease and provide justification for implementing public health policies that focus on risk factor control early on.

Conclusions

Although the most recent national data for obesity and diabetes mellitus are somewhat encouraging, their high prevalence combined with their gigantic costs highlight the urgent need for comprehensive measures in preventing these diseases. Obesity and T2D are complex diseases. Such complexity calls for a multipronged solution that ranges from cellular and metabolic investigations to community-level interventions to curb their increases. At a cellular level, recent advances in systems levels tools and omics technologies have enabled researchers to understand the underlying biological pathways in disease progression. In particular, the field of metabolomics offers a unique opportunity to not only explore how complex interactions between modifiable risk factors and the human organism affect future disease risk but also identify new targets for disease prevention. At the community level, successful studies such as the Shape Up Somerville have demonstrated that a comprehensive approach that engages all sectors and levels of the community, focuses on engaging at-risk populations, and increases access to healthy food and physical activity opportunities has lasting effects in curbing the obesity epidemic. Finally, policy measures such as a tax on SSBs could prevent thousands of new cases of obesity and diabetes mellitus and save considerable medical costs. Clearly, no single approach will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. Obesity (Silver Spring). 2008;16:2322–2330. doi: 10.1038/oby.2008.351.

Disclosures

None.

Sources of Funding

Drs Bhupathiraju and Hu are supported by grant P30 DK46200 from the National Institutes of Health.


Epidemiology of Obesity and Diabetes and Their Cardiovascular Complications
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Circ Res. 2016;118:1723-1735
doi: 10.1161/CIRCRESAHA.115.306825
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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